**PLEURAL EFFUSION**

Pleural effusion is defined as an abnormal accumulation of fluid in the pleural space. Excess fluid results from the disruption of the equilibrium that exists across pleural membranes.

In terms of anatomy, the pleural space is bordered by parietal and visceral pleura. Parietal pleurae cover the inner surface of the thoracic cavity, including the mediastinum, diaphragm, and ribs. Visceral pleurae envelop all surfaces of the lungs, including the interlobar fissures. This lining is absent at the hilus, where pulmonary vessels, bronchi, and nerves enter the lung tissue. The mediastinum completely separates the right and left pleural spaces.

Both parietal and visceral membranes are smooth, glistening, and semitransparent. Despite these similarities, the two membranes have unique differences in anatomic architecture, innervation, pain fibers, blood supply, lymphatic drainage, and function. For example, the visceral pleurae contain no pain fibers and have a dual blood supply (bronchial and pulmonary).

**Frequency**

In the US: Pleural effusion affects 1.3 million individuals each year. Approximate annual incidences of pleural effusions are based on major underlying disease processes, as follows: congestive heart failure, 500,000; bacterial pneumonia, 300,000 (uncomplicated, 270,000; complicated, 30,000); malignancy, 200,000; pulmonary embolus, 150,000; cirrhosis with ascites, 50,000; pancreatitis, 20,000; collagen vascular disease, 6,000; and tuberculosis, 2,500.

Internationally: The relative annual incidence of pleural effusion is estimated to be 320 per 100,000 people in industrialized countries. When extrapolating these figures to apply to other countries, the distribution and incidence of pleural effusion causes are dependent on the population studied. For instance, in areas where tuberculosis (TB) is prevalent, a higher percentage of pleural effusions from TB is possible. Congestive heart failure, pneumonia, malignancy, and pulmonary emboli account for most pleural effusions.

Morbidity and mortality of pleural effusions are directly related to cause, stage of disease at the time of presentation, and biochemical findings in the pleural fluid.

Morbidity and mortality rates of patients with pneumonia and pleural effusions are higher than those of patients with pneumonia alone.

Development of a malignant pleural effusion is associated with a poor prognosis. The average life expectancy of a patient after a diagnosis of malignant pleural effusion is 3-6 months.

In general, the incidence is equal between the sexes; however, certain causes have a sex predilection. About two-thirds of malignant pleural effusions occur in women. Malignant pleural effusions are significantly associated with breast and gynecologic malignancies.

**Causes**

Four main types of fluids in the pleural space are serous fluid (hydrothorax), blood (hemothorax), lipid (chylothorax), and pus (pyothorax or empyema). Classification of pleural effusion is based on the mechanism of fluid formation and pleural fluid chemistry. Generally, pleural effusions are categorized into transudative or exudative effusions; however, with some causes, the pleural fluid may have either transudative or exudative characteristics. The etiologic spectrum of pleural effusion is extensive; however, pleural effusions are caused by congestive heart failure, pneumonia, malignancy, or pulmonary emboli.

With transudative pleural effusions, systemic factors that govern formation of fluid include increased systemic and/or pulmonary capillary hydrostatic pressure (elevated pulmonary capillary wedge pressure of 10 cm H2O or higher), decreased colloid osmotic pressure in the systemic circulation, or both. Pleural membranes are intact and not involved in pathogenesis of the fluid formation. The permeability of pleural capillaries to proteins is normal.

With exudative pleural effusions, local factors governing formation of fluid include altered permeability of pleural membranes, increased capillary wall permeability or vascular disruption, and decreased or complete obstruction of lymphatic drainage of pleural space. Pleural membranes are involved in pathogenesis of the fluid formation. Permeability of pleural capillaries to proteins is high, resulting in an elevated protein content.

Hemothorax is present when the pleural fluid hematocrit level is 50% greater than that of peripheral blood. A late complication of moderate or large hemothoraces is fibrothorax, which is characterized by gradual deposition of a thick layer of fibrous tissue on the visceral pleura.

Chyliform or pseudochylous pleural effusion grossly resembles chylothorax. However, this effusion contains no chylomicrons, and pathogenesis does not involve the thoracic duct. High lipid levels (cholesterol crystals or lecithin-globulin complexes) are present and cause a milky white appearance. Pseudochylous pleural effusions commonly occur with long-standing (mean, 5 y) pleural effusions associated with rheumatoid pleuritis, tuberculosis, and paragonimiasis worm infection.

Neoplastic disease causes 13-40% of all pleural effusions. Pleural effusion develops in nearly one half of all patients with metastatic cancer. The most common tumors that cause malignant pleural effusions are adenocarcinoma and other carcinomas of the lung, breast cancer, lymphoma, and leukemia. These malignancies, combined, account for approximately 75% of all malignant pleural effusions. Other relatively common malignancies associated with pleural effusion are ovarian carcinoma, stomach cancer, and sarcomas (including melanoma).

Pleural effusion develops in 30-40% of patients with bacterial pneumonia. Those with bacterial pneumonia, especially that caused by Streptococcus pneumoniae, have a high predilection for complications. These complications can include bacteremia, multilobar involvement, and pleural effusion. Pleural effusions are relatively uncommon in patients with acquired immunodeficiency syndrome; however, Kaposi sarcoma, bacterial pneumonia, and TB are among the most common causes of pleural effusion in this population.

A well-known risk factor for benign inflammatory exudative pleural effusion is asbestos exposure. Asbestos also is implicated in the pathogenesis of diffuse malignant mesothelioma. Other pleural reactions associated with asbestos exposure include pleural plaques, pleural calcifications, diffuse pleural fibrosis and/or thickening, and rounded atelectasis (subpleural focus of airless lung).

**Pathophysiology**

Pleural effusion is an indicator of a pathologic process that may be of primary pulmonary origin or of an origin related to another organ system or to systemic disease. It may occur in the setting of acute or chronic disease and is not a diagnosis in itself.

Normal pleural fluid has the following characteristics: clear ultrafiltrate of plasma, pH 7.60-7.64, protein content less than 2% (1-2 g/dL), fewer than 1000 WBCs per cubic millimeter, glucose content similar to that of plasma, lactate dehydrogenase (LDH) level less than 50% of plasma and sodium, and potassium and calcium concentration similar to that of the interstitial fluid.

The principal function of pleural fluid is to provide a frictionless surface between the two pleurae in response to changes in lung volume with respiration. The following mechanisms play a role in the formation of pleural effusion:

Altered permeability of the pleural membranes (eg, inflammatory process, neoplastic disease, pulmonary embolus)

Reduction in intravascular oncotic pressure (eg, hypoalbuminemia, hepatic cirrhosis)

Increased capillary permeability or vascular disruption (eg, trauma, neoplastic disease, inflammatory process, infection, pulmonary infarction, drug hypersensitivity, uremia, pancreatitis)

Increased capillary hydrostatic pressure in the systemic and/or pulmonary circulation (eg, congestive heart failure, superior vena caval syndrome)

Reduction of pressure in pleural space; lung unable to expand (eg, extensive atelectasis, mesothelioma)

Inability of the lung to expand (eg, extensive atelectasis, mesothelioma)

Decreased lymphatic drainage or complete blockage, including thoracic duct obstruction or rupture (eg, malignancy, trauma)

Increased fluid in peritoneal cavity, with migration across the diaphragm via the lymphatics (eg, hepatic cirrhosis, peritoneal dialysis)

Movement of fluid from pulmonary edema across the visceral pleura

Persistent increase in pleural fluid oncotic pressure from an existing pleural effusion, causing accumulation of further fluid

Iatrogenic causes (eg, central line misplacement)

**CLINICAL**

**History**

The clinical manifestations of pleural effusion are variable and often are related to the underlying disease process.

The most commonly associated symptoms are progressive dyspnea, cough (typically nonproductive), and pleuritic chest pain.

* Dyspnea

Dyspnea is the most common clinical symptom at presentation.

It indicates a large effusion (usually not <500 mL).

It is reported to occur in 50% of patients with malignant pleural effusions.

However, other factors (eg, underlying lung disease, cardiac dysfunction, anemia) also may contribute to the development of dyspnea.

* Chest pain

Chest pain may be mild or severe; it typically is described as sharp or stabbing, is exacerbated with deep inspiration, and is pleuritic.

Pain may be localized to the chest wall or referred to the ipsilateral shoulder or upper abdomen (frequently seen with malignant mesothelioma), usually because of diaphragmatic involvement.

It often diminishes in intensity as the pleural effusion increases in size.

Chest pain signifies pleural irritation, which can aid in the diagnosis of the cause of the effusion, since most transudative effusions do not cause direct pleural irritation.

* Other signs and symptoms

Increasing lower extremity edema, orthopnea, and paroxysmal nocturnal dyspnea all may occur with congestive heart failure.

Night sweats, fever, hemoptysis, and weight loss may occur with TB.

An acute febrile episode, purulent sputum production, and pleuritic chest pain may occur in patients with an effusion associated with aerobic bacterial pneumonia.

**Physical**

Physical findings are variable and depend on the volume of the pleural effusion. Generally, findings are undetectable for effusions smaller than 300 mL. With an effusion larger than 300 mL, physical findings often may include the following:

* Dullness or decreased resonance to percussion
* Diminished or inaudible breath sounds
* Decreased tactile fremitus
* Egophony (“e” to “a” changes) at the most superior aspect of the pleural effusion (This finding signifies atelectasis and consolidation caused by compression of lung parenchyma with subsequent decrease in gas content per unit volume.)
* Pleural friction rub
* Present throughout respiratory cycle and loudest at end inspiration and early expiration
* Seldom present, but when present, best heard over the area of pleural inflammation, over posterior inferior aspect of thoracic cage, or over inferior lateral anterior surface of thoracic cage
* Described as a rubbing or grating (eg, leather rubbing on leather), harsh, dry, and scratchy sound that disappears with breath holding
* Asymmetric expansion of thoracic cage, with lagging expansion on the affected side (ie, Hoover sign)
* Mediastinal shift
* Seen only with massive effusions (usually >1000 mL)
* Noted on chest radiographs as displacement of the trachea and mediastinum to the contralateral side of the pleural effusion (In contrast with complete atelectasis of the ipsilateral lung, the trachea deviates toward the side of the effusion and is most commonly seen with complete obstruction of ipsilateral mainstem bronchus caused by bronchogenic carcinoma.)

**Other important findings that provide clues to the cause of the pleural effusion**

Anasarca

Cutaneous changes of chronic liver disease

Distended neck veins

S3 gallop rhythm

Clubbing of the fingers

Breast nodule or intraabdominal mass

**Lab Studies**

The initial step in analyzing pleural fluid is to determine whether the effusion is a transudate or an exudate. For the purpose, the following Light criteria are most accurate: Pleural fluid is exudative if one or more of the following conditions is met; it is transudative if none are met: ratio of pleural fluid and serum protein levels is greater than 0.5, ratio of pleural fluid and serum LDH levels is greater than 0.6, and pleural fluid LDH level is more than two thirds of the upper limit for serum LDH levels.

The criteria are less accurate for transudates caused by congestive heart failure, especially in patients who have undergone diuresis. The longer diuretic therapy lasts, the more likely the fluid will have exudative characteristics. Diuretic therapy less than 48 hours rarely changes the characteristics of pleural fluid to those of exudative effusion. If the criteria are not satisfied despite of high suspicion that congestive heart failure is the cause of the pleural effusion, examine the serum-to–pleural fluid albumin gradient (serum level minus pleural fluid level). A gradient of less than 1.2 g/dL indicates exudative effusion; one greater than 1.2 g/dL, transudative effusion.

The clinical presentation should direct the biochemical and microbiological studies of pleural fluid. The minimal amount of pleural fluid needed for basic diagnostic purposes is 20 mL; if possible, 60 mL should be obtained for potential diagnostic studies.

If the clinical presentation is highly suggestive of transudative effusion, protein and LDH levels should be determined initially. If the patient has undergone diuretic therapy, the pleural albumin level should be determined simultaneously. Concomitant serum total protein; LDH; and, if indicated, serum albumin levels should be measured. If transudative effusion is diagnosed, no further tests are needed.

Exudative effusions require further laboratory investigation. In the ED, the pleural fluid should be analyzed for the following:

* Cell count with differential
* Total protein level
* Glucose level
* LDH level
* Amylase level
* pH
* Cytologic analysis

Cytologic analysis(strongly recommended for patients with history of undiagnosed exudative effusions, suspected malignancy or Pneumocystis carinii infection, or exudative effusions with normal fluid glucose and amylase levels)

In the appropriate clinical setting the following may be helpful: Gram staining, acid-fast bacilli staining, fungal (KOH) staining, culturing and sensitivity testing for aerobic and anaerobic organisms and fungi

* Blood culturing (2 tests, preferably from different sites and one-half hour apart)

The containers necessary for pleural fluid tests are listed in Table 1.

Table 1. Containers for Pleural Fluid Collection

|  |  |
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| Container | Primary Study |
| Plain red-top tube | Determination of protein, LDH, amylase, and glucose levels (if needed, determine triglyceride cholesterol level) |
| Ethylenediaminetetraacetic acid–treated, lavender-top tube | Cell count and differential |
| Heparin-treated blood gas syringe | Determination of pH |
| Sterile container | Gram staining and culturing (for aerobic and anaerobic organisms, mycobacteria, fungi) |
| 50-mL heparin-treated container (eg, 5 green-top tubes) | Cytologic analysis |

The gross appearance of the pleural fluid, as well as results of certain laboratory studies, may provide useful diagnostic information. The color, turbidity, viscosity, and odor are essential characteristics of any fluid. Table 2 lists the clinical significance of the gross characteristics of pleural fluid.

Table 2. Clinical Significance of Pleural Fluid Characteristics

|  |  |
| --- | --- |
| Characteristic | Significance |
| Bloody | Most likely an indication of malignancy in the absence of trauma; can also indicate pulmonary embolism, infection, pancreatitis, tuberculosis, mesothelioma, or spontaneous pneumothorax |
| Turbid | Possible increased cellular content or lipid content |
| Yellow or whitish, turbid | Presence of chyle, cholesterol or empyema |
| Brown (similar to chocolate sauceor anchovy paste) | Rupture of amebic liver abscess into the pleural space (amebiasis with a hepatopleural fistula) |
| Black | Aspergillus involvement of pleura |
| Yellow-green with debris | Rheumatoid pleurisy |
| Highly viscous | Malignant mesothelioma (due to increased levels of hyaluronic acid)long-standing pyothorax |
| Putrid odor | Anaerobic infection of pleural space |
| Ammonia odor | Urinothorax |
| Purulent | Empyema |
| Yellow and thick, with metallic (stainlike) sheen | Effusions rich in cholesterol (longstanding chyliform effusion, eg,tuberculous or rheumatoid pleuritis) |

Laboratory results can aid in narrowing the differential diagnosis of exudative pleural effusions. Diagnosis requires an integrative approach involving laboratory and clinical findings. Common laboratory studies of the following may indicate the diagnosis:

RBC and total WBC counts: RBC counts or more than 100,000 per cubic millimeter suggest trauma, malignancy, pulmonary embolism, injury after cardiac surgery, asbestos pleurisy, esophageal rupture, pancreatitis, tuberculous pleurisy, and catamenial hemothorax (thoracic endometriosis). The total pleural fluid leukocyte count is virtually never diagnostic. Counts exceeding 10,000 per cubic millimeter are most common with parapneumonic effusions; however, other inflammatory diseases are another cause.

Neutrophil, eosinophil, and basophil counts: Neutrophilic predominance indicates an acute inflammatory process near the time of thoracentesis. Significant eosinophilia occurs when the ratio of pleural fluid and total pleural fluid counts is more than 10%; the most common cause is air or blood in the pleural space.

**Imaging Studies**

After the initial stabilization of the patient, the evaluation of pleural effusion in the ED begins with confirming the presence and then the location of the effusion. This step is the most important in the evaluation of a pleural effusion.

Common imaging studies used to confirm pleural effusion are

* chest radiography,
* ultrasonography,
* CT scan.

Chest radiography is the primary diagnostic tool because of its availability, accuracy, and low cost. Chest radiographs can be used to determine the cause of the effusion (eg, enlarged cardiac silhouette, underlying lung, parenchymal disease). The most common radiologic appearance is blunting of the costophrenic angle and/or sulci (sharp angle between the diaphragm and rib cage). As fluid accumulates, blunting becomes more pronounced, and an upwardly concave meniscus seems to ascend the lateral chest wall; this is called the meniscus sign. Clues indicating pleural effusion include generalized homogenous opacity and diffuse haziness as the fluid forms layers posteriorly (ground-glass appearance), visibility of pulmonary vessels through the haziness, and an absence of air bronchogram.

Ultrasonography can be used to detect as little as 5-50 mL of pleural fluid, with 100% sensitivity for effusions of 100 mL or more.

Chest CT scanning (including use of lung windows views) permits imaging of the entire pleural space, pulmonary parenchyma, and mediastinum simultaneously.

**Procedures**

After the presence of a pleural effusion is established, the cause should be identified. This step can be critical in evaluating pleural effusions because unnecessary invasive procedures cause morbidity and mortality. When a decision is made to investigate the cause of the pleural effusion, thoracentesis is the first-line invasive diagnostic procedure. Thoracentesis also can be used as a therapeutic modality. Chest tubes serve a solely therapeutic role. They are used for evacuating air or fluid from the pleural space and for administering fibrinolytic (eg, urokinase, streptokinase) or sclerosing agents (eg, doxycycline, bleomycin, talc, minocycline).

Other procedures used to diagnosis the cause of a pleural effusion include percutaneous pleural biopsy, thoracoscopy, and open pleural biopsy. However, of all these procedures, thoracentesis and chest tube placement usually suffice for evaluation or treatment of pleural effusions in the ED. Ancillary procedures (eg, bronchoscopy, perfusion lung scanning, pulmonary arteriography) can complement the other invasive procedures.

**TREATMENT**

**Prehospital Care**

Most commonly, a pleural effusion is an incidental finding in a stable patient. Emergency medical services are required more often by patients with a toxic condition, respiratory distress, or cardiovascular instability.

As with any other life-threatening condition, direct initial management toward stabilization of the airway to ensure adequate oxygenation and ventilation. Administer supplemental oxygen to all unstable patients.

After airway stabilization, address and support the patient's circulatory status.

For any unstable patient, time is a critical factor. Patients in unstable condition require prompt evaluation by an emergency physician because ultimate treatments required for stabilization are not available in the prehospital setting.

Upon arrival in the ED, disclosure of physical findings (eg, deviation of the trachea, distended neck veins, absence of breath sounds, muffled heart sounds, peripheral edema, ascites, subcutaneous emphysema) is important.

**Emergency Department Care**

On the basis of presentation in the ED, patients with pleural effusions may be stable, requiring hospital admission; stable, not requiring hospital admission; or unstable. Generally, any patient who requires thoracentesis in the ED is admitted to the hospital. When a patient is stable hemodynamically, time may be available to investigate the patient's past medical history. Previous hospitalization and outpatient records and radiographs can be invaluable.

Stable patients who do not require admission include those in whom the clinical circumstances clearly explain the effusion and/or prior investigations of the cause were performed, effusions are typical of the disease or asymptomatic, and diagnostic or therapeutic thoracentesis is not required.

Such patients include the following: patients with effusions due to viral pleurisy, with a free pleural fluid level thinner than 10 mm on a lateral decubitus radiograph; asymptomatic patients with pleural effusions associated with systemic diseases such as congestive heart failure, renal disease, and hepatic cirrhosis; patients with small (free pleural fluid level <10 mm on the lateral decubitus radiograph) pleural effusions after recent (<3 d) thoracic or abdominal surgery; and patients with asymptomatic effusions immediately postpartum.

In such patients, thoracentesis is not indicated and can be deferred. Therapy for the specific cause, if indicated, should be initiated, and no improvement occurs after a few days, diagnostic thoracentesis should be performed.

Stable patients requiring admission include most patients with pleural effusion thicker than 10 mm on the lateral decubitus radiograph. Such patients include the following: patients with no prior history of pleural effusions, patients with parapneumonic effusions who do not appear to have a toxic condition, and patients with a prior history of pleural effusions who have a change in their usual symptoms or effusion. Often, these patients do not require a monitored bed and can be admitted to a regular floor.

Unstable patients include those with a toxic appearance, respiratory distress, or cardiovascular compromise due to the effusion. The initial treatment focus should be stabilizing the airway and circulation. Patients with dyspnea or severe respiratory distress should sit, because the seated position increases tidal volume, decreases the work of breathing, and may improve symptoms of congestive heart failure and/or pulmonary edema. Life-threatening traumatic or medical conditions (eg, tension hydropneumothorax, massive effusion with contralateral mediastinal shift, pulmonary embolism, esophageal perforation, traumatic rupture of the thoracic duct, strangulated diaphragmatic hernia) must be ruled out. These patients require immediate diagnostic and therapeutic thoracentesis in the ED.

**MEDICATION**

Antibiotics and diuretics commonly are used in the initial management of pleural effusion in the ED.

Other less commonly used drugs include anticoagulants (eg, heparin, thrombolytics), anti-inflammatory agents (eg, aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], corticosteroids), cardiac glycosides (eg, digoxin), and afterload reducers (eg, ACE inhibitors). The selection of drugs in each class depends on the cause of the effusion and its clinical presentation. Particular attention must be given to potential drug interactions, adverse effects, and preexisting conditions.

Expeditiously initiate empiric systemic antibiotic coverage for infections or potentially septic conditions (eg, parapneumonic effusions, empyemas, esophageal perforation, hemothorax, intraabdominal abscesses) in the ED. Base initial antibiotic selection on the microorganisms presumed present and the overall clinical picture. Considerations include the patient's age, comorbid conditions, duration of the illness (acute versus subacute or chronic), setting (community versus nursing home), geographic location, and prevalence of resistance. When available, results of pleural fluid Gram staining should guide antibiotic selection.

Generally, initial antibiotics used in the ED should have a broad spectrum of coverage for both aerobic and anaerobic microorganisms. Most commonly, 2 antimicrobial agents are necessary to ensure adequate coverage. Various effective combinations exist. One combination is a third-generation cephalosporin, such as cefotaxime (Claforan) or ceftriaxone (Rocephin), and clindamycin (Cleocin). If the patient is a nursing home resident, a cephalosporin with enhanced antipseudomonal activity, such as ceftazidime (Fortaz) or cefoperazone (Cefobid) with clindamycin (Cleocin) is recommended.

**Further Inpatient Care**

The patient condition and the cause of effusion dictates whether admission to a regular floor or ICU is required. Consultations with pulmonary specialists or surgeons should begin in the ED.

For some patients, definitive treatment may include serial thoracenteses, instillation of fibrinolytic agents (eg, streptokinase, urokinase), chemical pleurodesis (eg, doxycycline, bleomycin, talc), pleuroperitoneal shunt placement, intrapleural administration of talc during thoracoscopy, systemic chemotherapy, or mediastinal radiation.

**Further Outpatient Care**

Arrange for follow-up with the patient's primary care physician or a pulmonary specialist within 2-3 days, especially if thoracentesis is deferred.

If early follow-up seems unlikely, give the patient clear instructions to return to the ED in 2-3 days for reevaluation.

**Complications**

Delaying diagnostic thoracentesis and antibiotic therapy for parapneumonic and other effusions, when antimicrobial therapy is indicated, increases the risk of empyema, pulmonary fibrosis, and sepsis.

**Prognosis**

Prognosis varies and depends on the cause and characteristics of the pleural effusion.

Patients who seek medical care earlier in the course of their disease and those with prompt diagnosis and treatment have a substantially lower rate of complications than those who do not.