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# Diagnosis and Treatment of Pleural Effusion

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## Introduction

The pleural space, between the parietal pleura covering the chest wall and the visceral pleura covering the lung, contains—in a healthy person—a few milliliters of fluid that acts as a lubricant between the 2 surfaces. Pathological accumulation of fluid in this space is called pleural effusion.[1]

## Etiology, Pathogenesis, and Epidemiology

Pleural fluid originates in the pleural capillaries (mainly those of the parietal pleura), lymphatics, intrathoracic blood vessels, the interstitial pulmonary space, and the peritoneal cavity. It is reabsorbed mainly through the lymphatics of the parietal pleura. The mechanisms that cause pleural effusion all result in an increase in the production or a decrease in the removal of pleural fluid and may be related to changes in hydrostatic capillary, intravascular or extravascular colloid osmotic, and negative intrathoracic pressures (Table 1).

TABLE 1
**Mechanisms of Production of Pleural Effusion**

| |
|---|
| Systemic increase in hydrostatic pressure |
| Decreased oncotic pressure in the microvascular circulation |
| Increased permeability of the pleural microvascular circulation |
| Increase in pulmonary interstitial fluid |
| Impaired lymphatic drainage |
| Movement of fluid from other cavities or sites such as the peritoneal, retroperitoneal, or subarachnoid spaces, or catheters |
| Decrease in negative pressure within the pleural space |
| Vascular rupture in the chest |
| Rupture of the thoracic duct |

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The prevalence of pleural effusion is slightly in excess of 400/100 000 population. Congestive heart failure is the most common cause of pleural effusions overall. However, the predominant etiologies among the exudates are pneumonia, malignancy, and pulmonary embolism. Table 2 shows the most common causes of pleural effusion.

## Methods Used to Investigate Pleural Disease

### *Medical History*

Patients with pleural effusions should be studied systematically. As a first step a complete medical history should be taken with special emphasis on the patient's history of exposure to asbestos, current and recent medications, and the prior or current presence of entities such as heart disease, tuberculosis, neoplastic disease, and connective tissue disease. Secondly, a complete physical examination should be performed. Based on the overall picture provided by the clinical variables, medical history, physical examination, results of basic laboratory tests, and of any additional tests ordered because of a suspected diagnosis, it is possible to establish a diagnosis before thoracentesis and order the pertinent tests.

### *Radiographic Techniques*

An effusion of more than 75 mL is often visible on chest radiographs. Pleural effusions can be either free flowing or loculated and either typically or atypically sited (subpulmonic, fissural, or mediastinal) sited. The amount of fluid varies. When there is a doubt in the case of small effusions the existence of pleural fluid should be confirmed by chest ultrasound or radiographically using a lateral decubitus projection on the affected side. Anomalies in the lung parenchyma can help to confirm the suspected diagnosis, and computed tomography can contribute useful additional information.

TABLE 2
**The Most Common Causes of Pleural Effusion**

| | |
|---|---|
| Physical agents<br>Chest injury<br>Electrical burn<br>Radiation therapy<br>Iatrogenic causes<br><br>Pharmacotherapy<br>Nitrofurantoin<br>Bromocriptine<br>Procarbazine<br>Dantrolene<br>Mitomycin<br>Metronidazole<br>Propylthiouracil<br>Practolol<br>Methysergide<br>Methotrexate<br>Amiodarone<br>Ergotamine<br>Bleomycin<br>Minoxidil<br><br>Decrease in oncotic pressure<br>Chronic hepatic disease<br>Nephrotic syndrome<br>Hypoalbuminemia from various processes<br><br>Cardiovascular diseases<br>Heart failure<br>Pulmonary embolism<br>Constrictive pericarditis<br>Obstruction of the superior vena cava<br>Fontan procedures<br>Splenic vein thrombosis<br>Rupture of a dissecting aortic aneurysm<br>Cholesterol embolism<br>Heart bypass surgery<br>Postinfarct-postpericardiotomy<br><br>Infections<br>Bacterial: pneumonia or systemic infection<br>Tuberculosis<br>Parasitosis<br>Mycosis<br>Viral: respiratory, hepatic, cardiotropic<br>Other pathogens | Neoplastic disease<br>Mesothelioma<br>Cancers<br>Lymphoproliferative syndromes<br>Sarcomas<br>Myeloma<br>Others<br><br>Diseases of the immune system<br>Rheumatoid arthritis<br>Disseminated lupus erythematosus<br>Drug-induced lupus<br>Mixed connective tissue disease<br>Ankylosing spondylitis<br>Sjögren's syndrome<br>Angioimmunoblastic lymphadenopathy<br>Churg-Strauss vasculitis<br>Wegener's granulomatosis<br>Familial Mediterranean fever<br>Sarcoidosis<br>Extrinsic allergic alveolitis<br>Allergic bronchopulmonary aspergillosis<br>Post lung transplant rejection<br><br>Infradiaphragmatic and digestive disease<br>Esophageal rupture<br>Sclerotherapy of esophageal varicose veins<br>Strangulated transdiaphragmatic hernia<br>Abdominal surgery<br>Peritonitis<br>Inflammatory intestinal disease<br>Spleen disease: rupture, infarction, angioma<br>Subphrenic, hepatic, or splenic abscess<br>Bile duct obstruction<br>Pancreatitis and pancreatic pseudocysts<br>Ovarian hyperstimulation syndrome<br>Meig's syndrome<br>Postpartum<br>Liver transplant<br>Ascites from other causes<br><br>Others<br>Benign asbestos-related effusion<br>Uremia<br>Yellow nail syndrome<br>Lymphangioleiomyomatosis<br>Histiocytosis X<br>Trapped lung<br>Myxedema<br>Fetal pleural effusion<br>Amyloidosis |

*Thoracentesis*

Pleural fluid should always be investigated using thoracentesis except when the suspected effusion is clearly secondary to a specific underlying disease (for example heart failure) (level C recommendation; see explanation at the end of this article). The morbidity associated with thoracentesis carried out by an experienced operator is low. In the case of small effusions, thoracentesis can be undertaken if the distance between the horizontal line of the pleural effusion and the chest wall is more than 1 cm on an ipsilateral decubitus view. Otherwise, ultrasound guidance is necessary. Since thoracentesis can cause bleeding in patients with a platelet count under 50 000/μL, these patients must receive prior coagulation therapy. The most common complications are vagal reaction (10%-14%) and pneumothorax (3%-8%). A chest radiograph is not essential after thoracentesis except when complications such as pneumothorax are suspected (level D recommendation).

The following properties of the fluid sample are analyzed: color, appearance (pus in the case of empyema, milky with lipid effusion, and bloody in hemothorax), and smell (putrid in infections caused by anaerobic microorganisms, and ammoniac in the case of urinothorax). Hemorrhagic fluid is more likely in

TABLE 3
**Study of Pleural Fluid and Biopsy Specimens***

| Specimens | Diagnostic Thoracentesis | Pleural Biopsy |
|---|---|---|
| Biochemical analysis | | |
| Biochemistry: glucose, proteins, LDH, cholesterol,† Triglycerides,† amylase† | Dry tube or with heparin | |
| pH | Syringe with heparin in anaerobiosis | |
| ADA,† IFN-γ,† ANA,† RF,† others† | Dry tube | |
| Cells: white blood cell count and differential, hematocrit† | Tube with EDTA (pink or mauve top) | |
| Microbiology | | |
| Gram stain† | Tube without heparin | |
| Culture of aerobic and anaerobic bacteria† | Blood culture bottles | |
| Fungal cultures† | Tube without heparin | Tissue in saline solution |
| Mycobacterium tuberculosis culture and smear test† | 100 mL flask without heparin | Tissue in saline solution |
| Pathology†† | | |
| PF for cytology and other cytologic studies | Heparinized or citrated tube | |
| Tissue for histology | | Tissue in formol or fresh tissue |

*LDH indicates lactate dehydrogenase; ADA, adenosine deaminase; IFN-γ, interferon-γ; ANA, antinuclear antibodies; RF, rheumatoid factor; EDTA, ethylenediaminetetraacetic acid; and PF, pleural fluid.
†Optional.
††Samples not processed for several hours should be stored at room temperature.

effusions caused by malignancy, trauma, or pulmonary embolism.[2] Table 3 lists the tests usually carried out on pleural fluid.

*Biochemical parameters*. Proteins, lactate dehydrogenase (LDH), and albumin are measured in pleural fluid to differentiate between transudate and exudate. This method is discussed in greater detail below. Glucose levels in pleural fluid and blood are compared. The pH value, which should be measured with a blood gas analyzer,[3] is generally between 7.45 and 7.55 for transudates and between 7.30 and 7.45 for exudates. In small effusions, the use of local anesthesia may give rise to an artificially low pH value.[4] The combination of a low pH (under 7.30) and low glucose values (under 60 mg/dL) occurs in complicated parapneumonic effusions, and effusions secondary to malignancy, tuberculosis, rheumatoid arthritis, esophageal rupture, and, less often, systemic lupus erythematosus. Low pH values are also occasionally associated with hemothorax, pulmonary embolism, and pancreatic pleural effusion. In parapneumonic effusions, low pH and glucose levels are associated with a higher probability that chest drainage will be necessary.[5] In malignant effusions this combination indicates more extensive involvement of the pleura, a situation in which the sensitivity of cytology increases and the likelihood of successful pleurodesis decreases; this combination is associated with shorter survival.[6]

Cholesterol, as well as being a useful marker for differentiating between transudative and exudative effusions, also helps to distinguish between chylothorax and pseudochylothorax when analyzed in conjunction with the triglycerides. This topic is discussed in the relevant section below. Pleural amylase levels can be much higher than the upper limit of normal in serum, particularly in effusions caused by pancreatitis, malignancy, or esophageal rupture. Similar high levels occur, although less often, in effusions secondary to ruptured ectopic pregnancy, tuberculosis, hydronephrosis, parapneumonic effusion, hepatic cirrhosis, and heart failure. The source of the amylase is salivary in esophageal rupture and tumors.

Optionally, other biochemical parameters can be measured, including adenosine deaminase (ADA), interferon γ, antinuclear antibodies, rheumatoid factor, and tumor markers whose diagnostic value is analyzed with respect to the diseases for which they may have clinical application.

*Total white blood cell and differential counts. Red blood cell count.* The white blood cell count has no diagnostic value, and can rise to over 10 000 µL in effusions caused by pneumonia, pancreatic disease, pulmonary embolism, pericardiotomy, and systemic lupus erythematosus. Polymorphonuclear cells tend to predominate in recent effusions and lymphocytes in long-standing ones. The neutrophilic pleural effusions include the following: effusions caused by pneumonia, pancreatitis, subphrenic abscess, pulmonary embolism, and the early stages of pleural tuberculosis. The principal cause of pleural eosinophilia (over 10% eosinophils) is the presence of air or blood in the pleural space. Eosinophilia is also found, albeit more rarely, in benign asbestos-related effusions, and in those caused by drug treatment, pulmonary embolism, fungi, parasites, eosinophilic pulmonary infiltration syndromes (such as Churg-Strauss syndrome), and acute or chronic eosinophilic pneumonia. If basophils exceed 10% of the differential count, the spread of leukemia to the pleura should be suspected.

Although only a few milliliters of blood will color large quantities of pleural fluid, the red blood cell count in hemorrhagic effusions usually exceeds 100 000 µL, and pleural hematocrit levels should be determined in such cases. Hemothorax is defined as a hematocrit level

in pleural fluid 50% higher than that of peripheral blood. When the red blood cell count is low, errors are common when automated cell counters are used.

*Cultures.* Pleural fluid cultures for fungi and for bacteria in aerobic and anaerobic media should be ordered whenever such infections are suspected. The value of polymerase chain reaction in the diagnosis of tuberculosis is discussed in the relevant section below.

*Cytology.* Pleural fluid cytology is among the tools offering the highest yield for diagnosing malignancy. The sensitivity of this test ranges from 40% to 87% depending mainly on the cytologist's training, the extent of pleural involvement, and tumor type (yield is higher in adenocarcinoma). Cytology of sequential specimens increased yield up to 30% in some studies (C). Immunocytochemical techniques use various antibodies to differentiate between epithelial and mesothelial cells. Since no single technique is totally specific, a panel comprising at least 4 tests is recommended. The use of cytology to diagnose rheumatoid arthritis is discussed below.

### *Pleural Biopsy*

Pleural tissue specimens for use in diagnostic studies should be obtained in patients with exudative effusions of unknown cause. Various methods are used to obtain such specimens. These are described below from least to greatest complexity.

*Pleural needle biopsy.* This is the simplest way of obtaining pleural biopsies. Abrams and Cope needles are the tools most often used, and the diagnostic yield is similar in both cases. At least 4 samples of the parietal pleura must be obtained for pathology plus 1 for *Mycobacterium tuberculosis* culture (D).[7] The procedure requires only local anesthesia, and hospitalization is not necessary in most cases. Needle biopsy can establish a firm diagnosis of tuberculous pleuritis (with a sensitivity of more than 85%), malignancy (a sensitivity of 45% to 60% that can be complemented by pleural cytology), and pleural amyloidosis. Diagnostic yield is increased in patients with cancer by the use of ultrasound or computed tomography guidance during the procedure. Needle biopsy is contraindicated in patients with a platelet count under 50 000 μL, skin infection in the incision area, respiratory insufficiency (because of the danger of pneumothorax), and when the effusion is very small (because of the risk of injury to the abdominal viscera). When performed by an operator with skill and experience, this procedure is associated with few complications. Possible complications include pneumothorax, which occurs in under 10% of cases in most series, infection of the pleural cavity, hemothorax, and laceration of the liver or spleen. A chest radiograph should be obtained after pleural biopsy to rule out pneumothorax.

*Thoracoscopy.* A thoracoscope facilitates examination of the pleural cavity and biopsy of the parietal and visceral pleura under visual guidance. Thoracoscopy can be performed with local anesthesia and sedation. The diagnostic yield for cancer is over 90%, and this procedure is particularly recommended in patients with a history of asbestos exposure (because of the possibility of mesothelioma). If clearly malignant lesions are observed, pleurodesis can be carried out immediately during the procedure.

*Thoracotomy.* Thoracotomy is only indicated in very specific situations and only when other diagnostic methods have failed.

### *Other Diagnostic Methods*

Occasionally, the diagnosis of patients with pleural effusion requires extrapleural study.

*Fiberoptic bronchoscopy.* Fiberoptic bronchoscopy is indicated if there are pulmonary symptoms (hemoptysis, stridor, or asymmetric chest sounds) or lesions in the lung parenchyma such as nodules or atelectasis.

*Chest ultrasound.* Ultrasonography is most useful for locating small or encapsulated effusions, identifying the existence of pockets, detecting pleural masses, and as a guide for pleural biopsies, and punctures.

Although some authors have proposed the use of ultrasound imaging for differentiating between transudates and exudates, the specificity of the technique for this purpose is low.

*Computed tomography.* Computed tomography is used to investigate the mediastinum and the lung parenchyma, to detect pleural masses, and as a guide for biopsies. When used appropriately, this technique can also help to establish a diagnosis of pleural effusion secondary to pulmonary embolism. If the clinical findings or results of laboratory tests point to an abdominal disease as the cause of the patient's condition, abdominal imaging with computed tomography or ultrasound can be used to rule out such disease.

*Positron emission tomography.* This imaging technique can be useful in the identification of malignant effusions, although experience in the study of pleural disease is still scant.

*Other studies.* Depending on the suspected diagnosis, other studies can be ordered, including serum autoantibodies, Doppler ultrasound of the lower limbs, etc.

**Key Points**

– Thoracentesis is indicated in all patients with pleural effusion of unknown cause when the effusion is large enough, that is, when the distance between the line of the effusion and the chest wall on an ipsilateral decubitus radiographic view exceeds 1 cm (D).

– Ultrasound guidance of thoracentesis is useful in small or loculated effusions (C).
– A chest radiograph is not requisite after thoracentesis unless pneumothorax is suspected (D).
– The appearance and smell of pleural fluid should be evaluated (D).
– The following tests are indicated in nonpurulent effusions: white blood cell and differential counts, pH, proteins, and LDH.
– Other biochemical parameters in pleural fluid that are useful in the assessment of these patients are glucose, cholesterol, triglycerides, albumin, ADA and interferon γ (D). Pleural fluid/serum ratios are also relevant.
– Pleural fluid cytology is indicated in all cases of pleural effusion, and repetition of such studies increases sensitivity (C).
– At least 4 pleural biopsy specimens should be sent for histology and 1 for *M tuberculosis* culture (D).
– If diagnosis is not confirmed by the less invasive tests, thoracoscopy should be considered (C).
– Fiberoptic bronchoscopy is indicated when there are pulmonary symptoms or radiographic abnormalities in the lung parenchyma (C).

## Diagnostic Algorithm

Figure 1 shows the general diagnostic algorithm recommended for the evaluation of these patients. Progress from one step to the next is determined by the lack of an etiologic diagnosis and the absence of any contraindications to each succeeding diagnostic test. Firstly, a full medical history should be obtained and a complete physical examination undertaken. Radiographic findings may help to guide the initial suspected diagnosis. A malignant etiology is more likely when a mass or atelectasis is found, or when the effusion is massive.[8] Thoracentesis is indicated when the cause is not obvious and there is sufficient volume. This technique provides an etiologic diagnosis in 25% of patients, and it has been shown to be useful in guiding the diagnosis of patients in up to 90% of cases.[1]

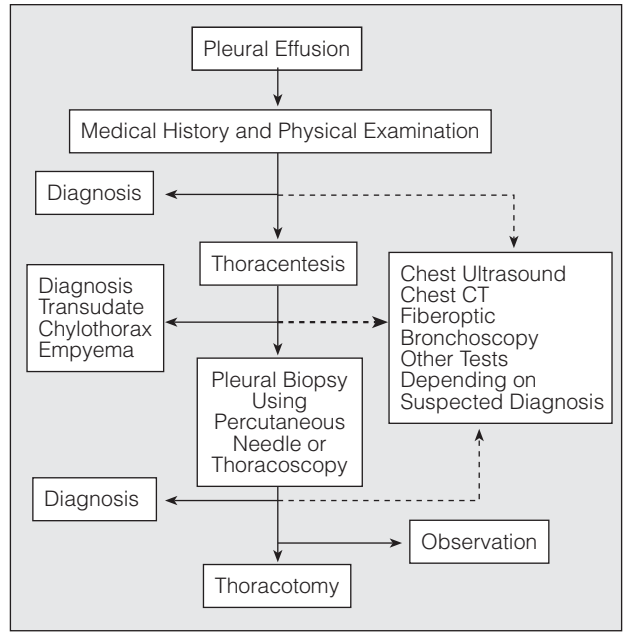


**Figure 1. General diagnostic algorithm for patients with pleural effusion. CT indicates computed tomography.**

TABLE 4
**Pathophysiologic Classification of Transudates by Mechanism***

| |
|---|
| Increased hydrostatic pressure |
| Pulmonary venous hypertension: heart failure, volume overload, nephrotic syndrome, glomerulonephritis |
| Systemic venous hypertension: pulmonary embolism,* atrial or cavopulmonary anastomosis (Fontan procedure) |
| Decreased oncotic pressure |
| Hypoalbuminemia |
| Lymphatic obstruction |
| Obstruction of the superior vena cava |
| Thrombosis of the brachiocephalic trunk |
| Metastatic cancer. Malignancy |
| Decreased pleural pressure |
| Pulmonary atelectasis |
| Connection with other cavities containing transudates |
| Peritoneal cavity. Ascites: cirrhosis (portal hypertension), peritoneal dialysis, Meig's syndrome |
| Retroperitoneal cavity. Urinoma: urinothorax |
| Subarachnoid space. Spinal fluid: thecal-pleural or ventricular fistulas |
| Infusion recipients |
| Perforation or erosion caused by central venous catheters |
| Excessive production |
| Fibrous tumors |
| Meig's syndrome |

*Mechanisms not yet fully demonstrated

Pleural biopsy is indicated in the case of exudates of unknown cause. Two procedures are used to obtain such specimens: percutaneous needle biopsy of the parietal pleura with or without guidance (ultrasound or computed tomography) and thoracoscopy. The choice of technique will depend on the initial suspected etiology (the sensitivity of each method for the suspected etiology should be considered), the patient's clinical condition, the availability of means, and the operator's experience in each technique.

Tuberculosis and malignancy are unlikely in clinically stable patients with no history of exposure to asbestos who do not present with weight loss or fever and have under 95% lymphocytes in pleural fluid and an effusion that occupies less than one third of the hemithorax. Conversely, the likelihood of a malignant etiology is very high in afebrile patients with bloody effusions who have had symptoms for more than 1 month and present with pleural masses, atelectasis, or enlarged nodes on chest radiography or computed tomography.[9] The justification for using thoracoscopy or occasionally thoracotomy should be evaluated on a case-by-case basis taking into account the likely pretest diagnosis, the benefits of confirming the diagnosis, and the risks inherent in the procedure.

Despite the diagnostic tests available, in most case series the etiology of pleural effusions remains

unknown after study in 5% to 10% of patients diagnosed with this condition.[10]

## Characteristics According to Etiology

*Transudates. Distinguishing Transudates From Exudates*

Transudate is the term used to denote an accumulation of fluid in the pleural space when the surface of the membranes enclosing this space is not directly affected by the pathological process. Transudates are the result of alterations in the pressures that regulate the passage of liquid though the pleural space. Increased pressure in the left cardiac chambers (especially the left atrium) is the most common etiology for the production of pleural transudate. Table 4 shows other, less common, etiologic and pathological mechanisms, although the influence of some of these has not been definitively demonstrated.

It is generally accepted that differentiating between transudates and exudates is a useful first step in the study of any pleural effusion of unknown cause. Excluding rare exceptions, once an effusion has been classified as a transudate, further diagnostic procedures or studies of the pleural zone are unnecessary.

The clinical picture obtained from an interpretation of the medical history and the findings of physical examination and noninvasive tests appears to be the best initial approach to differentiating between transudates and exudates.

The etiology of a pleural effusion is, however, often difficult to establish, and thoracentesis is a useful tool for confirming diagnosis and/or ruling out other associated diseases.

The gross appearance of pleural fluid can help differentiate between transudates and exudates.

However, effusions caused by heart failure or hepatic hydrothorax can be bloody, and chylothorax (milky effusions) secondary to hepatic cirrhosis are often transudates. In fact, assessment of the appearance of pleural fluid does not appear to facilitate a more precise differentiation than that obtained solely on the basis of the clinical picture prior to thoracentesis.

However, the biochemical criteria have been shown to have a higher specificity and sensitivity than the clinical picture for distinguishing transudative from exudative pleural fluid. Several biochemical parameters are used to differentiate between the 2 types of fluid, and various cutoff points have been proposed (Table 5).[11] The most commonly used and most precise criteria are those defined by Light and colleagues.[1] According to Light's method, an effusion is considered to be an exudate if it fulfills any of the following criteria:

– A pleural fluid/serum protein ratio greater than 0.5.
– A pleural fluid/serum LDH ratio greater than 0.6.
– A pleural fluid LDH level more than two thirds of the upper limit of normal for serum LDH levels.

Light's criteria have a sensitivity for exudates of nearly 100%, and the main drawback is their lower specificity, which results in between 15% and 30% of transudates being classified as exudates.

This error may lead to patients with transudative effusions undergoing inappropriate invasive procedures associated with morbidity and not receiving appropriate treatment for the underlying causative disease. The use of other distinguishing criteria, such as the serum/effusion gradient of albumin or total protein (the latter being equally precise but more economical than the former, with a cutoff point of 3.1) reduces the number of false positives for exudates in patients receiving effective diuretic treatment.[12]

TABLE 5
**Biochemical Parameters Proposed in the Literature for the Identification of Pleural Transudates[1,11]***

| Parameter in PF | Cutoff Points |
|---|---|
| Proteins | <3 g/dL |
| LDH | <2/3 the upper limit for serum LDH |
| Cholesterol | <45 mg/dL |
| | <50 mg/dL |
| | <55 mg/dL |
| | <60 mg/dL |
| Cholinesterase | <1390 U/L |
| | <1/10 the upper limit for serum cholinesterase |
| | <1600 U/L |
| | <1700 U/L |
| sL-selectin | <240 ng/mL |
| **PF/serum ratios** | **Cutoff points** |
| Proteins | <0.5 |
| | <0.6 |
| LDH | <0.6 |
| | <0.9 |
| Cholesterol | <0.3 |
| Cholinesterase | <0.23 |
| | <0.27 |
| | <0.29 |
| Bilirubin | <0.6 |
| **Serum-PF gradient** | **Cutoff points** |
| Albumin | >1.2 |
| Proteins | >3.1 |

*LDH indicates lactate dehydrogenase; PF, pleural fluid; and sL-Selectin, soluble selectin.

*Empyema and Parapneumonic Effusion*

Parapneumonic pleural effusion is defined as an effusion associated with bacterial pneumonia, abscess, or bronchiectasis.

*Pathogenesis.* Parapneumonic effusions pass through 3 phases: the exudative stage, the fibropurulent stage, and the organizing stage. The exudative stage is characterized by the accumulation of sterile pleural fluid secondary to an increase in capillary permeability caused by the release of various cytokines: interleukin (IL) 6, IL-8, tumor necrosis factor-α, and vascular endothelial growth factor. In these patients, pleural fluid has a glucose level above 60 mg/dL, a pH of more than 7.20, and the effusion can be resolved with antibiotics. In the fibropurulent stage, bacterial invasion of the pleural space leads to endothelial injury, which gives rise to a decrease in fibrinolytic response, consequent deposition of fibrin on both pleural surfaces, and the possible

TABLE 6
**Parapneumonic Pleural Effusion and Empyema: Light's Classification and Corresponding Treatment[1]***

| Category | Type | Characteristics | Treatment |
|---|---|---|---|
| 1 | Nonsignificant | <1 cm thick on an ipsilateral decubitus view. Thoracocentesis not required | Antibiotic |
| 2 | Typical parapneumonic | >1 cm thick, glucose >40 mg/dL, pH >7.20, negative Gram stain and culture | Antibiotic + consider therapeutic thoracentesis |
| 3 | Borderline complicated | pH, 7-7.20 or LDH >1000 Negative Gram stain and culture | Antibiotic + pleural drainage tube + consider fibrinolytics |
| 4 | Simple complicated | pH <7.0. Positive Gram stain or culture. Not loculated, no pus | Antibiotic + pleural drainage tube + fibrinolytics |
| 5 | Complex complicated | pH <7.0. Positive Gram stain or culture. Multiloculated | Antibiotics + pleural drainage tube + fibrinolytics + consider VAT |
| 6 | Simple empyema | Frank pus. Single loculation or free flowing fluid | Antibiotics + pleural drainage tube + fibrinolytics + consider VAT |
| 7 | Complex empyema | Frank pus. Multiple loculations. Often requires decortication | Antibiotics + pleural drainage tube + fibrinolytics + VAT, + other surgical procedures if VAT fails |

*LDH indicates lactate dehydrogenase; and VAT, video-assisted thoracoscopy.

formulation of loculations. At this stage, pleural fluid contains a large number of polymorphonuclear cells, bacteria, and cell detritus. The increase in local metabolic activity can justify the fall in pH and glucose and the increase in LDH levels. During the organizing stage, various growth factors appear, including basic fibroblast growth factor, platelet-derived growth factor, transforming growth factor-β, establishing the final phase characterized by the deposition of fibrin and eventually fibrous collagen tissue. These 3 stages are usually sequential and progressive, as shown in the classification defined by Light and Lee (Table 6).[1] Although these patients must be treated promptly, in 50% disease does not progress to the fibroproliferative phase even 3 weeks after the start of the process, so that a chest drainage tube, fibrinolytic agents, and video-assisted thoracoscopy (VAT) can sometimes be effective in the later stages.

*Microbiology.* Parapneumonic effusions occur during the clinical course of more than 57% of bacterial pneumonias, and 5% to 10% of these patients develop empyema.[13] The presence of parapneumonic pleural effusion should be considered in all patients with bacterial pneumonia. It can affect patients at any age, but is more common in aging adults and children and especially in patients with chronic conditions such as diabetes, alcoholism, and aspiration risk factors.[14,15] When pleural effusion is associated with nosocomial pneumonia the prognosis is poor, patients recover more slowly, length of hospital stay is longer, and the microbiology is different.

The microorganisms most often isolated in community-acquired pneumonias are gram positive aerobic and anaerobic bacteria, while those associated with nosocomial pneumonia are staphylococci and gram-negative aerobes (A). Empyemas caused by gram-negative bacteria are more common in patients with comorbidity, especially diabetes or alcoholism.[14]

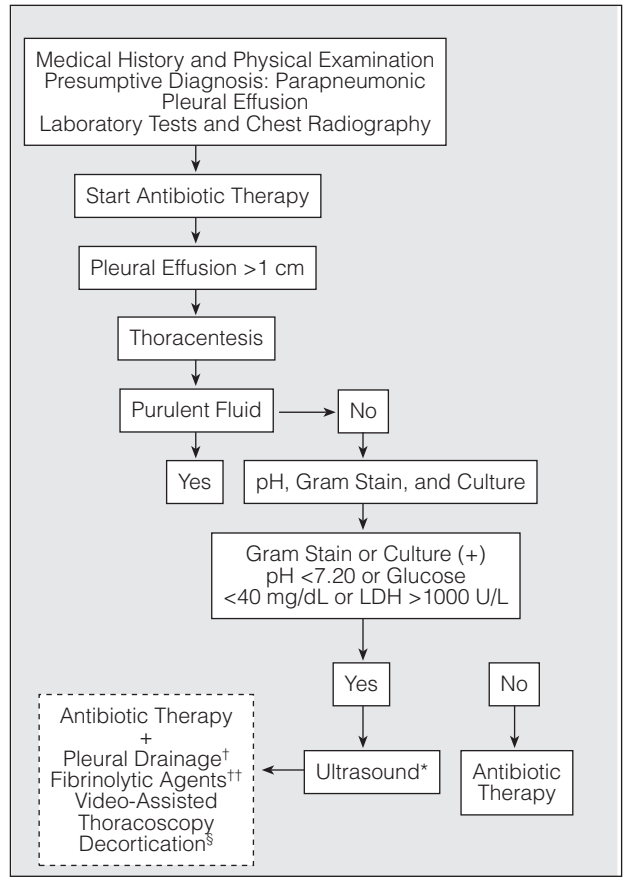


**Figure 2. Therapeutic algorithm for parapneumonic pleural effusion. LDH indicates lactate dehydrogenase.**
***Evaluate the presence of pleural pockets.**
**†Consider placement of a small-bore catheter and treatment with fibrinolytics.**
**††Streptokinase 250 000 U/d for 3 days or urokinase 100 000 U/d for 3 days are equally safe and effective.**
**§Rescue thoracotomy, after failure of video-assisted thoracoscopy in organizing empyemas.**

The proportion of cases in which the causative microorganism is isolated varies greatly, and increases depending on whether the parapneumonic effusion is simple, complicated, or empyema.

*Diagnosis.* The presence of microorganisms or purulent content in pleural fluid confirms the diagnosis of parapneumonic effusion, while pus indicates empyema. In the absence of these signs, the diagnosis of parapneumonic effusion is presumptive.

Parapneumonic pleural fluid is a predominantly polymorphonuclear exudate, and the effusion evolves in parallel with the resolution of the pneumonia in response to antibiotic treatment.[13]

Pleural fluid must be tested for infection in all patients.[13] However, cultures are negative in most patients and in such cases pH and biochemical markers are a valuable diagnostic and prognostic aid. The pH value is the parameter that best identifies infected parapneumonic effusions (level A recommendation).[5] However, a pH under 7.20 does not have 100% sensitivity.[16] In such cases, a glucose level below 40 mg/dL and an LDH level in excess of 1000 U/L can be useful alternatives for identifying infected parapneumonic effusions. In loculated pleural effusions, the pH can vary between one pocket and another.[17]

*Treatment.* Antibiotic therapy forms the basis of the treatment of all parapneumonic effusions, but there is still debate about the indication and timing of other pleural treatments.[18]

Figure 2 shows the treatment algorithm for these patients. The American College of Chest Physicians developed a consensus statement on the medical and surgical treatment of parapneumonic effusions using evidence-based methods.[19] This document defines 4 risk categories: *a)* category 1 (very low risk): effusion of less than 1 cm on ipsilateral decubitus film, with negative Gram stain and culture and unknown pH; *b)* category 2 (low risk): effusion greater than 1 cm, with negative Gram stain and culture and a pH value above 7.20; *c)* category 3 (moderate risk): free-flowing effusion occupying more than half the hemithorax, loculated, or with thickened parietal pleura, positive Gram stain or culture, or pH less than 7.20; and *d)* category 4 (high risk): purulent pleural fluid. The consensus statement makes the following recommendations, which should be interpreted with caution because of the methodological problems affecting the articles analyzed:

*1.* Patients with category 1 and 2 parapneumonic effusion may not require pleural drainage (D).

*2.* Pleural drainage is recommended in category 3 and 4 effusions (C).

*3.* Therapeutic thoracentesis alone or drainage tube alone appear to be inadequate for the treatment of many patients with category 3 and 4 effusions (C). Nevertheless, in some cases these measures may be effective and result in complete resolution. Careful monitoring is recommended during the initial stage of the disease, and further measures are unnecessary when the effusion resolves completely (D).

*4.* Fibrinolytics, VAT, and surgery are acceptable additional treatments for patients with category 3 and 4 parapneumonic infusions (C).

ANTIBIOTICS. In all cases, empiric antibiotic treatment must be started as early as possible and subsequently adjusted in light of the results of cultures (D). The antibiotic regimen should be chosen taking into account whether the pneumonia is community-acquired or nosocomial, the characteristics of the patient, the microbiological peculiarities of the local geographical area, and the activity of the chosen antibiotic in pleural fluid (taking into consideration, for example, that the pH of pleural fluid is acid and the penetrative capacity of the antibiotic may be decreased in the presence of a thickened pleura, particularly in empyema).

The penetration of cephalosporins into the pleural space is slow, but concentrations are stable and persistent. The penetration of quinolones is better than that of the penicillins, and the pleural penetration of aminoglycosides is reduced in empyema.

Guidelines on the diagnosis and treatment of pneumonia have recently been published in Spain.[20,21] The treatment regimen for cases of complicated parapneumonic effusions or empyema must include coverage for anaerobic bacteria. Duration of treatment depends on the bacteriology, the effectiveness of drainage, and the resolution of symptoms.[22] Resolution usually takes over 2 weeks, and monitoring with serum inflammatory markers, such as C-reactive protein, can be useful, particularly in the case of indolent disease.

PLEURAL DRAINAGE. The optimum size of the catheter is still a cause of debate. In a review of hundreds of cases, it was concluded that excellent results can be obtained with a small-bore catheter used in conjunction with fibrinolytic agents. However, no randomized trials have been carried out (C).

INTRAPLEURAL FIBRINOLYTICS. The conclusion of a recent Cochrane review[23] was that intrapleural fibrinolytic treatment provided significant benefits, reducing the length of hospital stay and the number of cases requiring surgery as well as the duration of fever and/or pleural drainage. However, owing to the paucity of randomized controlled trials undertaken to date and the fact that only a small number of patients have been studied, the available evidence is insufficient to support routine use of this treatment. In a recent double-blind randomized trial enrolling a considerable number of patients undertaken by the MIST1 group,[15] streptokinase failed to produce better results than placebo with respect to mortality, need for surgery, radiographic evolution, and length of hospital stay. The routine use of this drug is not, therefore, recommended (B). It is, however, likely that this treatment will prove beneficial in certain groups of patients and under certain circumstances, but additional studies are required to identify these groups and conditions. Streptokinase and urokinase (250 000 U/d and 100 000 U/d, respectively, for 3 days) are equally effective, but the former is

associated with a higher incidence of nonlethal complications.[19]

SURGICAL PROCEDURES. The options for surgical treatment are thoracotomy with decortication, minithoracotomy, VAT, and rib resection with open drainage. Of these, VAT is the option most widely used in the last decade. This procedure is, in general, associated with more favorable outcomes, reducing the length of hospital stay, the number of postoperative complications, and the duration of surgery, although randomized trials are needed in this area (C).[19] In organizing empyema, however, rescue thoracotomy is required in between 10% and 29% of cases due to failure of VAT.

*Prognosis.* It is difficult to clearly define prognostic factors because such a wide range of treatment approaches are used. In the opinion of many authors, purulent pleural fluid, delay in starting pleural drainage, diabetic comorbidity, and loculation are all associated with a poor prognosis. Yet in a prospective study of 85 patients managed on a similar protocol (antibiotics, pleural drainage, and fibrinolytics), purulent pleural fluid was the only variable found to have predictive value, and even in this variable the predictive value was not high enough to be clinically useful.[16]

**Key Points**

– The presence of parapneumonic pleural effusion should be considered in all patients with bacterial pneumonia (C).

– Whereas the causative pathogen is isolated in only a low percentage of cases in parapneumonic effusions overall, in complicated parapneumonic effusion and empyemas the etiologic agent is established in over 50% of cases (A).

– While, gram-positive aerobes are the microorganisms most commonly isolated in community-acquired pneumonia, staphylococci and gram-negative aerobes are associated with nosocomial pneumonia.

– The pH value is the parameter that best distinguishes and identifies infected parapneumonic effusions (A).

– It is often necessary to establish a differential diagnosis because of overlapping clinical signs, biochemistry, and/or appearance of pleural fluid (B).

– Patients with category 1 and 2 parapneumonic pleural effusion with a pH greater than 7.20 and negative bacteriology may not require pleural drainage (D).

– Pleural drainage is recommended for the management of patients with class 3 and 4 effusions in the presence of ∫< pH lower than 7.20 and/or positive Gram stain or culture with or without purulent fluid (C).

– Therapeutic thoracentesis alone or drainage tube alone appear to be insufficient in the treatment of many patients with category 3 and 4 parapneumonic effusions (C), although in individual cases these measures may be effective and lead to complete resolution. Patients must be monitored carefully in the first stage of the disease, and no further measures are necessary if resolution is complete (D).

– Fibrinolytics, video thoracoscopic interventions and surgery are acceptable additional treatments for patients with category 3 and 4 parapneumonic effusions (C).

– All these patients must receive antibiotics. Early empiric treatment is recommended in all these patients, with adjustment of the treatment regimens, if necessary, when the results of cultures are available.

– While there is no consensus on the ideal tube size for pleural drainage, a small-bore catheter used in conjunction with fibrinolytics is probably useful (C).

– Although intrapleural fibrinolytic therapy can provide benefits and shorten the length of in-hospital stay (B), the routine use of these agents is not recommended (B).

– Streptokinase 250 000 U/d or 3 days and urokinase 100 000 U/d for 3 days, are equally effective and safe regimens (C).

– Surgical treatment should be considered in cases in which chest drainage has failed (B).

– VAT is the most widely used surgical treatment, and it produces favorable outcomes. Randomized trials are, however, needed (C).

– No definitive prognostic factors have been identified, but purulent fluid is the most consistent indicator. Early diagnosis and treatment is essential in all cases (C).

### *Pleural Tuberculosis*

The frequency of tuberculous pleural effusion is highly variable and depends on the incidence of tuberculosis in each country. In Spain, this entity represents a considerable problem because it is estimated that the pleura is affected in 23.3% of all patients with tuberculosis.[24]

*Pathogenesis.* In tuberculosis, pleural effusion is caused by the rupture of a subpleural caseous focus into the pleural space, generally 6 to 12 weeks after primary infection. Several studies have indicated that tuberculous pleurisy appears to be due to a delayed hypersensitivity reaction rather than to the direct action of the bacillus, and that infection with *M tuberculosis* triggers a series of poorly understood immunological reactions.[25]

In a minority of cases, tuberculous pleural effusion can take the form of pseudochylothorax or empyema. Pseudochylothorax develops in long-standing effusions. Tuberculous empyema is a pleural infection by *M tuberculosis* that produces an accumulation of purulent pleural fluid. It generally occurs in patients who have had pulmonary or pleural tuberculosis, and often some 10 years may elapse before the empyema is detected.

TABLE 7
**Sensitivity of Each of the Criteria Used to Diagnose Tuberculous Pleural Effusion[25]**

| Criteria | n | Percentage |
|---|---|---|
| Ziehl-Neelsen staining of pleural fluid | 14/254 | (5.5) |
| Culture of *Mycobacterium tuberculosis* in pleural fluid | 93/254 | (36.6) |
| Ziehl-Neelsen staining of pleural tissue | 64/248 | (25.8) |
| *M tuberculosis* culture in pleural tissue | 140/248 | (56.4) |
| Caseating granulomas | 198/248 | (79.8) |

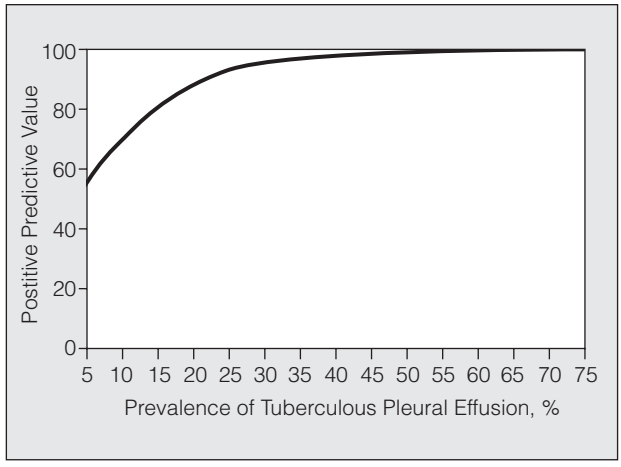


**Figure 3. Impact of the prevalence of tuberculous pleural effusions on the positive predictive value of a high concentration of adenosine deaminase for the diagnosis of such effusions (sensitivity 100%, specificity 95%).**

*Diagnosis.* The diagnosis of pleural tuberculosis is confirmed by the identification of the bacillus in pleural fluid or pleural biopsy, or visualization of granulomas in the pleura. Most cases of tuberculous effusion are not characterized by any specific clinical signs or symptoms that distinguish them from other types of effusions. Furthermore, neither chest radiographs nor the tuberculin skin test provide sufficient information to establish a diagnosis.

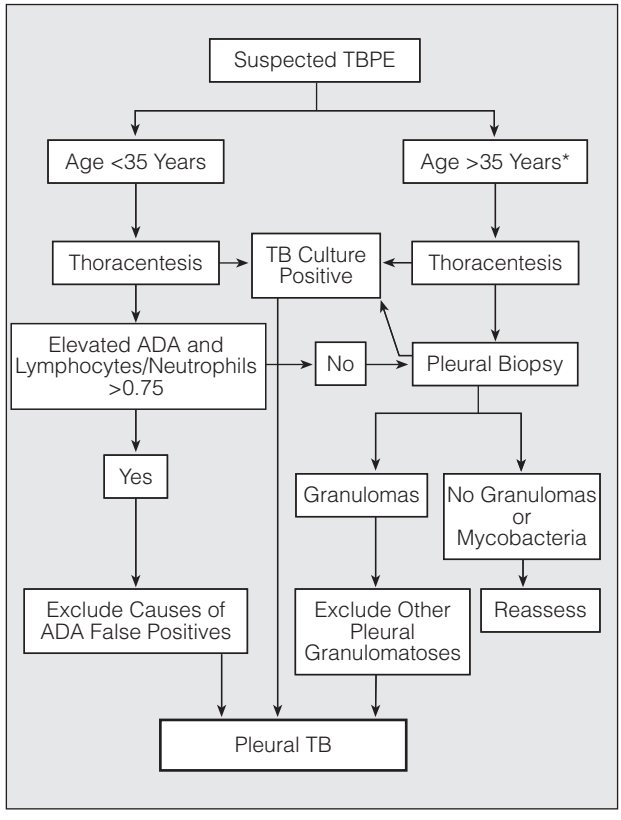


**Figure 4. Algorithm for the diagnosis of pleural tuberculosis. TBPE indicates tuberculous pleural effusion; TB, tuberculosis; and ADA, adenosine deaminase.**
***Patients aged under 35 years should also be included in this group if ADA analysis is not available or if there is no experience locally with this technique.**

Pleural fluid analysis is very useful for investigating the possibility of tuberculosis, since the effusion is almost always an exudate and is predominantly lymphocytic in 93% of cases[25]; although polymorphonuclear cells may predominate in patients whose symptoms have only started within the preceding 2 weeks.[1] If the effusion is eosinophilic, it is unlikely to be tuberculous.

A definitive diagnosis of tuberculous pleural effusion is established by the isolation of *M tuberculosis* in pleural fluid or biopsy (A). The yield of Ziehl-Neelsen stain and pleural fluid culture is low, but can be increased by concurrent culture of a pleural tissue specimen (Table 7).[25] Sputum culture is useful if the lungs are involved, but the yield of this technique is scant when no parenchymal lesions are visible on a chest radiograph except in patients with human immunodeficiency virus infection. Demonstration of granulomas in a biopsy specimen is diagnostic of tuberculous pleural effusion if the following entities are ruled out: sarcoidosis, rheumatoid arthritis, tularemia, and fungal disease (A).[1] The yield is approximately 80%,[25] but can rise to 86% if a specimen is sent for culture, and to 98% if thoracoscopy is performed.

In recent years, the usefulness of a series of biochemical markers in the diagnosis of tuberculous pleural effusion has been investigated. These include, among others, ADA, IFN-γ, lysozyme, IL-2, soluble IL-2 receptors, IL-1, tuberculostearic acid, and activated T lymphocytes. In our opinion, the clinical utility of only 2 of these markers—ADA and IFN-γ—has been demonstrated. Since there is no universally accepted cutoff point for either of these parameters, each hospital must establish its own level depending on cases managed by the facility and the test methods used.

In a meta-analysis, a maximum combined sensitivity and specificity of 93% was found for ADA.[26] The specificity of this parameter may be higher when it is used in conjunction with a lymphocyte/neutrophil ratio in pleural fluid of 0.75 or greater.[27]

While a single low ADA does not rule out the diagnosis of tuberculous effusion, persistently low ADA levels do appear to exclude it. High ADA values can also be found in some nontuberculous exudates,[26,28] including certain malignant effusions (mainly those caused by lymphomas, adenocarcinomas, and mesothelioma), rheumatoid arthritis, intracellular infections, parapneumonic effusions, and most empyemas.

In tuberculous pleural effusions, the ADA isoenzyme that rises is ADA-2,[29] and in nontuberculous effusions accompanied by a raised ADA level, the isoenzyme with high activity is ADA-1. However, even the combined use of ADA, ADA-2, and the 2'-deoxyadenosine deaminase/ADA ratio does not fully distinguish between tuberculous and nontuberculous effusions. ADA analysis is more important in the study of pleural effusions in patients aged under 35 years, a cohort that has a considerably higher prevalence of tuberculosis in Spain. Consequently the positive predictive value of ADA is

higher in these patients (Figure 3). Given that the prevalence of malignant pleural effusion in these patients is low, in hospitals with experience in ADA analysis the presence of high ADA activity and a lymphocyte/neutrophil ratio in pleural fluid above 0.75, a high probability diagnosis of tuberculous effusion could be established and treatment started after ruling out the other etiologies mentioned above that give rise to false positives in ADA (Figure 4).

IFN-γ is a lymphokine released by CD4+ sensitized lymphocytes that increases the mycobactericidal activity of macrophages. Several study have demonstrated its usefulness in the diagnosis of pleural effusions caused by tuberculosis.[26,28,30] In a recent meta-analysis, the maximum joint sensitivity and specificity of this marker was 96%.[26] In clinical practice, the decision concerning the best parameters to use should take into account the high yield of ADA, the higher cost of IFN-γ, and the experience of the laboratory carrying out the analysis.[31]

Polymerase chain reaction is based on the amplification of the deoxyribonucleic acid of the mycobacteria. The sensitivity of this technique in the diagnosis of tuberculous pleural disease varies between 20% and 80%. Results, which depend on the technique used[32] on the number of bacilli in the fluid sample analyzed, are positive in 100% of tuberculous effusions with positive culture and 30% to 60% of fluids with negative culture. As the specificity of this technique ranges between 78% and 100%, its use in clinical practice is not recommended.

*Treatment.* The currently recommended treatment for tuberculous pleural effusion is an initial regimen of rifampicin, isoniazid, and pyrazinamide for 2 months followed by rifampicin and isoniazid for 4 months (A).[33] Ethambutol should be added to this regimen in areas with a high incidence of primary resistance to antituberculous drugs (over 4%) or when the patient has received prior treatment with such drugs.

A paradoxical increase in the effusion occurs in up to 16% of patients after start of treatment. Approximately 50% of patients present pleural thickening a year after starting treatment, but there is no agreement about the characteristics of the associated pleural fluid. Neither repeated thoracentesis[34] (A) nor corticosteroid therapy[35] (B) help to prevent this development. The functional repercussions of this thickening are slight in most cases.

Patients with tuberculous empyema should receive treatment with the 4 drugs mentioned above at maximum doses.

An antibiogram should be obtained to determine the sensitivity of the causative pathogen. It is advisable to measure concentrations of each drug in pleural fluid since penetration can be reduced as a result of pleural thickening and this may result in subtherapeutic levels and acquired resistance.

Placement of a chest tube is necessary in these patients. Fibrinolytics are sometimes useful, and thoracoscopy, decortication, and even thoracostomy may be necessary.

**Key Points**

– When tuberculosis is the suspected etiology, both pleural fluid and a biopsy specimen should be cultured because the identification of *M tuberculosis* will confirm the diagnosis (A).

– Visualization of granulomas in the biopsy specimen confirms the diagnosis provided the following etiologies are ruled out: sarcoidosis, rheumatoid arthritis, tularemia, and fungal diseases (A).

– In patients aged under 35 years, the presence of elevated ADA levels and a lymphocyte/neutrophil ratio above 0.75 indicates a high probability that the effusion is tuberculous if the causes of possible false positives are ruled out. When only one of these 2 criteria is fulfilled, a biopsy is essential (B).

– Pleural tuberculosis should be treated with rifampicin, isoniazid, and pyrazinamide for 2 months at the usual doses. This should be followed by a regimen of rifampicin and isoniazid for a further 4 months (A). Corticosteroid therapy does not prevent pleural thickening in tuberculous effusions (B).

### *Malignant Pleural Effusion*

The tumors that most often produce malignant pleural effusion are lung and breast carcinomas and lymphomas, but almost any tumor can cause this condition.

*Diagnosis.* A diagnosis of malignancy can only be confirmed by the detection of neoplastic cells in pleural fluid or tissue specimens. The yield of cytology reported in the literature varies considerably between studies depending on the extent of pleural involvement and the type of primary tumor involved (for example, the yield in squamous cell carcinoma—a growth characterized by cells closely linked by intercellular bridges—is lower than that obtained in other, less dense, neoplasms such as small cell tumors). The yield of cytology is better in malignant effusions associated with a low pH because of the close relationship between low pH and extensive neoplastic involvement of the pleura.[1,36]

Although clearly positive tumor markers in pleural fluid are not definitively diagnostic, they may help to identify appropriate candidates for more invasive techniques such as thoracoscopy. The principal drawback of such markers is their low sensitivity and specificity, and for this reason the use of a panel of markers is recommended because it can increase the yield of cytology in approximately one third of cases.

Flow cytometry can complement cytology in some cases,[37] especially in lymphocyte-predominant effusions when lymphoma is suspected.[1]

PLEURAL NEEDLE BIOPSY. Most guidelines recommend the addition of a biopsy procedure when initial cytology is negative and etiology is still unknown after 2 weeks of evolution.[38,39] Percutaneous pleural biopsy is recommended in such cases,[40,41] but in light of the advances in imaging techniques some authors prefer computed tomography or ultrasound guided needle

biopsy. This technique could replace blind biopsy in over two thirds of cases.[42]

Pleural needle biopsy has a lower yield than cytology in malignant pleural effusions, even when both procedures are repeated, but sensitivity increases when the results of both tests are combined.

When pleural needle biopsy is compared to thoracoscopy, the superiority of the latter is clear,[43,44] but the choice between blind needle biopsy and thoracoscopy should be made taking into account the experience of the operator in both techniques, the availability of means, and the clinical aggressivity of the effusion. While a needle biopsy can be performed without hospitalization, thoracoscopy is more complex and the patient must always be admitted.

Thoracoscopy does, however, facilitate both diagnosis and therapeutic application of talc to control a recurrent effusion).

*Treatment.* When a diagnosis of malignant effusion has been confirmed in most cases it will be necessary to consider palliative treatment aimed mainly at alleviating the dyspnea caused by the tendency of the effusion to recur.

THERAPEUTIC THORACENTESIS. This procedure must be considered in almost all dyspneic patients with malignant pleural effusions to ascertain its effect on the dyspnea and to measure the rate of recurrence of the effusion. In the case of a massive effusion occupying a hemithorax and contralateral mediastinal shift, this therapeutic procedure is urgent and it may also be necessary to proceed directly to chest tube drainage followed by pleurodesis.

If pleural fluid pressure is not being monitored, aspiration of more than 1500 mL is not advised.[45]

If dyspnea is not noticeably alleviated by thoracentesis, the possibility that the lung parenchyma has been significantly impaired by lymphangitic carcinomatosis, atelectasis, thromboembolism, or tumor embolism should be considered.

A centrally located mediastinum, particularly when it is retracted ipsilaterally to the effusion, suggests the presence of a proximal bronchial obstruction or a lung trapped by tumor or fibrin. In such cases particular caution should be exercised when therapeutic thoracentesis is considered because the lung will not reexpand Monitoring pleural pressure during removal of fluid is highly recommended in such cases, and fluid removal should be stopped if a pleural pressure of -20 cm $H_2O$ is reached.[45]

PLEURODESIS. Pleurodesis is recommended in patients who have a malignant pleural effusion and are expected to survive more than a few weeks, especially in the case of tumors that are refractory to chemotherapy. Chemotherapy should be tried prior to pleurodesis in small cell lung cancer, lymphoma, metastatic breast carcinoma, and other neoplasms that are clearly sensitive to such therapy. However, the decision to use pleurodesis should not be delayed if the response of the effusion to chemotherapy is not satisfactory. Before a sclerosing agent is injected, the ability of the lung to reexpand should be confirmed. A trapped lung should be suspected if fluid removal generates highly negative pleural pressures, the pH of pleural fluid is less than 7.20, or computed tomography reveals marked thickening of the visceral pleural, a condition that will make pleurodesis impossible or very complicated.

*CHOICE OF SCLEROSING AGENT.* Over 30 sclerosing agents are discussed in the literature. Uneven results have been reported, but the most important agents are talc and tetracyclines and their derivatives.[46]

– Talc can be administered in a saline solution (slurry) or instilled in powder form using thoracoscopy (poudrage).

Although in one recent multicenter trial no clear differences were found between these 2 methods of application except in pleural metastases secondary to lung and breast cancer,[47] a Cochrane meta-analysis shows that better results were obtained with thoracoscopic talc poudrage than with slurry (B).[48] This is probably because the talc, which is not water-soluble, tends to accumulate in the lower region of the pleural cavity in slurry applications, thereby producing irregular adhesions and multiloculations. Talc with a large particle size is recommended because it causes less extrapleural dissemination.[49] The dose recommended is approximately 5 g.[38]

– Tetracycline derivatives. Repeated applications of doxycycline are required to achieve a success rate of around 70%. This agent usually causes very intense pain and is also potentially hepatotoxic. Minocycline can cause serious, although rare, complications, including hypersensitivity reactions, vestibular symptoms, and even hemothorax.

– Other sclerosing agents. Bleomycin, which is expensive and potentially toxic, is no more effective than other candidate agents. Silver nitrate was first used by Spengler in 1906, and is now once again in the news because of some experimental studies. However this substance appears to cause more alveolar inflammation than talc and such complication could, in turn, lead to a higher risk of further deterioration of respiratory function in elderly patients or patients whose clinical situation is delicate.

ALTERNATIVES TO PLEURODESIS IN MALIGNANT EFFUSIONS. *INSERTION OF A PLEUROPERITONEAL SHUNT.* The insertion of a pleuroperitoneal shunt may be indicated in patients with recurrent effusion when re-expansion is impossible because the lung is trapped by tumor or fibrin.

*PARIETAL PLEURECTOMY.* This procedure should be restricted to patients in good general health, and there are currently very few indications for this intervention (certain cases of mesothelioma).

*INTRAPLEURAL CATHETER CONNECTED TO A DRAINAGE BAG OR VACUUM FLASK.* Continuous drainage can be a good procedure for use in patients with a short life expectancy,[50] as an alternative to performing repeated drainage procedures.

TABLE 8
**Pleural Effusion in Less Common Systemic Diseases***

| Connective tissue disease | Clinical | Frequency of PE | Characteristics of PF | Type of PE |
|---|---|---|---|---|
| Polymyositis/dermatomyositis | Muscle weakness, facial exanthema | Very rare | Not described | Small |
| Sjögren's syndrome | Mucosal dryness | 1% | Lymphocytic exudate | Small, unilateral |
| Mixed connective tissue disease | Mixture of SLE, scleroderma and PM/DM. snRNP Titers (+) | <10% | Exudate | Small |
| Churg-Strauss syndrome | Asthma, eosinophilia, sinusitis, mononeuritis multiplex | Rare | Eosinophilic exudate | Bilateral |
| Wegener's granulomatosis | Necrotizing granulomatous vasculitis, glomerulonephritis, involvement of the upper and lower airways. | 5%-55% | PMN exudate | Small, unilateral |
| Angioimmunoblastic lymphadenopathy | Generalized lymphadenopathy, hepatosplenomegaly, anemia | 12% | Lymphocytic exudate | Unilateral or bilateral |
| Ankylosing spondylitis | Back pain and spinal rigidity | <1% | PMN exudate | Small, unilateral |
| Familial Mediterranean fever | Acute, recurrent polyserositis | 40% | PMN exudate | Small |
| Eosinophilia-myalgia syndrome | Ingestion of contaminated L-tryptophan | 12% | Eosinophilic exudate | Bilateral |
| Temporal arteritis | Headache, mandibular claudication, increased GSR | Rare | PMN exudate | Small, unilateral |

*PE indicates pleural effusion; PF, pleural fluid; SLE, systemic lupus erythematosus; PMN, polymorphonuclear; PM/DM, polymyositis/dermatomyositis; snRNP, small nuclear ribonucleoprotein; and GSR, global sedimentation rate.

*Pleural mesothelioma.* Pleural mesothelioma is a malignant neoplasm originating in the pleura. It develops mainly as a result of asbestos exposure at some time during the previous 20 to 40 years, and in Spain it is usually associated with occupations related to the construction, shipbuilding, and transport industries.[51]

The 3 principal histologic subtypes are epithelial, sarcomatous, and mixed. Pleural biopsy specimens are required for diagnosis, and using thoracoscopy or thoracotomy will improve the yield. Pleural mesothelioma must be distinguished from benign mesothelial hyperplasia and metastatic pleural adenocarcinoma. Today, the use of a panel of immunohistochemical markers is almost indispensable (D). A positive reaction to calretinin, HBME-1, and cytokeratin 5/6 suggests mesothelioma, while a positive result for the carcinoembryonic antigen, B72.3, the human epithelia antigen (Ber-EP4), MOC 31, or BG8 is indicative of adenocarcinoma metastatic to the pleura.

The most commonly used of the many staging classifications that exist is the system proposed by the International Mesothelioma Interest Group.[52] Survival is very variable, with a mean of 9 to 12 months, and several prognostic factors have been described, mainly general patient characteristics or cytohistologic parameters. In recent years, a trimodal treatment has been proposed—extrapleural pneumonectomy, radiation therapy, and chemotherapy—and it is possible that this approach may improve survival in patients with completely resectable epithelial tumors (resection margins free of tumor) and no extrapleural lymph node involvement (D).[53] Before this treatment is undertaken, the patient's ability to undergo a surgical intervention should be evaluated, and tumor extension should be studied with computed tomography, echocardiogram, magnetic resonance imaging, positron emission tomography, and mediastinoscopy. In patients who are not eligible for surgery the only treatment that has been shown to increase survival is a combination of cisplatin and pemetrexed (A).[54] When necessary, palliative treatments for pain and dyspnea, such as pleurodesis, should be undertaken along with prophylactic radiotherapy of the chest wall to prevent tumor spread to puncture sites.

## Key Points

– In most cases of malignant pleural effusions therapeutic thoracentesis should be considered to relieve dyspnea (D).

– Pleurodesis is recommended if the effusion is recurrent and the patient is expected to live more than a few weeks (D).

– Trapped lung should be suspected if fluid removal generates highly negative pleural pressures, the pH of pleural fluid is under 7.20, or computed tomography reveals marked thickening of the visceral pleura; this condition will make pleurodesis impossible or very difficult (D).

– Talc is the most effective sclerosing agent for pleurodesis (B).

– An intrapleural catheter connected to a bag can be a good solution for patients with a short life expectancy (D).

– Pleuroperitoneal shunt may be indicated in patients with recurrent effusion and trapped lung (D).

– A panel of immunohistochemical markers is essential for the diagnosis of pleural mesothelioma (D).

– In the management of patients with pleural mesothelioma, improved survival is achieved with a combination of cisplatin and pemetrexed in patients who are not candidates for surgery (A) and possibly with a trimodal treatment approach (extrapleural pneumonectomy, radiotherapy, and chemotherapy) in patients with completely resectable epithelial tumors and no extrapleural nodal involvement (D).

### *Pleural Effusion in Connective Tissue Disease*

Connective tissue diseases are a heterogeneous group of immunologically–mediated inflammatory diseases that share clinical characteristics, such as articular involvement of the serous membranes and blood vessels. They are characterized pathologically by connective tissue lesions, fibrinoid degeneration, and the formation of granulomas and fibrosis.[55]

The lungs and the pleura are target organs because they are highly vascularized and their connective tissue content is high.[56] However, there are discrepancies between the high degree of pleural involvement described in postmortem studies and the few published works describing the characteristics of pleural effusion in this setting. The grade of current scientific evidence is based on publications describing isolated cases or case series.

We will deal in greater detail with the 2 most common and best known connective tissue disorders. The others are summarized in Table 8.

*Systemic Lupus Erythematosus.* The lungs and pleura are affected by the autoantibodies and immune complexes that characterize this disease, which mainly affects women of childbearing age. Up to 50% of patients will have pleural effusion (75%-93% in post-mortem series).

Patients usually present with symptoms such as fever, cough, and pleuritic chest pain.[57] The effusion is usually small and bilateral (50%) and associated with cardiomegaly and alveolar infiltrates or basal atelectasis. Patients with systemic lupus erythematosus can also develop pleural effusion secondary to other processes (pulmonary embolism, pneumonia, nephrotic syndrome, etc). The first step should be to rule out the possibility of a lupus-like syndrome caused by pharmacotherapy (chlorpromazine, hydralazine, isoniazid, methyldopa, minocycline, procainamide, or quinidine) because in these cases the effusion will resolve spontaneously when drug treatment is stopped.[1]

The pleural fluid is a serous or serohemorrhagic exudate, which usually has normal glucose and pH values and an LDH under 500 U/L. An antinuclear antibody titer in pleural fluid of greater than 1/320, a pleural fluid/serum antinuclear antibody ratio of greater than 1, a homogeneous immunofluorescence pattern, or the presence of lupus erythematosus cells are consistent with a diagnosis of pleural effusion caused by systemic lupus erythematosus. However, since the results are similar to those obtained from serum, these tests are not recommended in the initial pleural fluid specimen. Pleural biopsy can be useful if immunofluorescence studies are performed as these reveal the mottled and diffuse stain pattern of the nuclei.[58] Response to treatment with corticosteroids is usually good.

*Rheumatoid Arthritis.* The most common pulmonary manifestation of rheumatoid arthritis is pleuritis, with or without pleural effusion (50% of all patients present pleural adhesions or effusion on autopsy). However, in the largest clinical series, the frequency of associated pleural effusion is estimated at less than 4% of patients with rheumatoid arthitis.[59] Although rheumatoid arthritis is 3 times more common among women, the frequency of associated pleural effusion is 4 times more common among men. Although often asymptomatic; these effusions can be associated with chest pain and fever. In most cases they are unilateral and occupy less than half the hemithorax.

Comorbid cardiomegaly caused by pericarditis and pulmonary nodules can occur; up to 80% of patients present subcutaneous nodules. The level of clinical activity in the pleural and articular regions may vary.[1]

The gross appearance of pleural fluid in rheumatoid arthritis varies from clear to purulent (pseudochylothorax) and the biochemical characteristics are similar to those of synovial fluid: exudates with low glucose (under 40 g/L) and pH levels (under 7.20), elevated LDH (over 700 U/L) and low complementary values.[60] High cholesterol levels and cholesterol crystals are sometimes found in chronic pleural effusions.

Although low specificity has been reported for both rheumatoid factor titers in pleural fluid (above 1/320) and the pleural fluid/serum ratio greater than 1 using latex agglutination, a large recent study using nephelometry obtained better results in pleural fluid with cutoff points of 20 U/mL (sensitivity 87%, specificity 95%,) and 60 U/mL (sensitivity 52%, specificity 99%).[61]

The cytologic characteristics of pleural fluid may suggest a diagnosis of rheumatoid arthritis: 2 types of multinucleated macrophages (the first thin and elongated and, the second large and round) together with necrotic background material and a noticeable paucity of mesothelial cells.[62] The existence of rheumatoid arthritis cells or ragocytes is nonspecific. Although blind pleural biopsy can sometimes demonstrate these rheumatoid nodules, in most cases it will reveal only nonspecific inflammatory changes. The characteristic thoracoscopic picture that has been described is a granular, inflamed and thickened parietal pleura with numerous vesicles some 0.5 mm in diameter. This is similar to the histologic picture associated with rheumatoid nodules and synovitis secondary to rheumatoid arthritis.[63]

Effusions caused by rheumatoid arthritis can be transient, persistent, or recurrent.

They can improve after drainage, which is recommended when clinically indicated. No controlled trials have been carried out to evaluate the effectiveness of nonsteroidal antiinflammatory drugs or corticosteroids (either systemic or intrapleural) in the management of persistent or recurrent pleural effusion. These effusions can spontaneously develop into empyemas.

### *Pleural Effusion and Cardiac or Vascular Disease*

*Pleural effusion secondary to congestive heart failure.* Congestive heart failure is the most common cause of transudate and probably of all pleural effusions in adults. The effusion is the result of an increase in hydrostatic pressure (pulmonary venous hypertension) that results in the movement of fluid into the interstitial pulmonary space and from there to the pleural space. Most pleural effusions caused by congestive heart failure are bilateral (75%) and usually larger on the right. Unilateral confusions occur predominantly on the right side (2 to 1 ratio) and are occasionally intrafissural ("pseudotumor" or "evanescent tumor"). Thoracentesis is only indicated in the presence of fever, pleuritic chest pain, or other signs that might indicate another intercurrent disease.[1] The pleural fluid is predominantly lymphocytic and clear yellow in color. It fulfills the criteria of a transudate,

TABLE 9
**Mechanisms Responsible for Postsurgical Pleural Effusion**

| Transudate | Exudate |
|---|---|
| Pulmonary atelectasis | Diaphragmatic inflammation |
| Heart failure | Mediastinal inflammation |
| Transfusions during surgery | Mediastinal or abdominal bleeding |
| Preoperative ascites | Interruption of lymphatic drainage |
| Ice cooling of mediastinal area | Pericarditis |
| Pleurotomy | |

although diuretics may increase the concentration of certain components to the exudative range.[64]

*Pleural effusion after aortocoronary bypass.* In the week after the coronary bypass, most patients (89%) present a small pleural effusion, which is usually bilateral (67%) and resolves spontaneously and progressively.[1] They are associated with pericardial effusions.

Many patients are asymptomatic or only report shortness of breath. These effusions have been related to surgical wounds and intrapleural bleeding. The early pleural effusions are usually hemorrhagic exudates, predominantly eosinophilic with elevated LDH levels.[65]

One month after the intervention, a small effusion persists in two thirds of the patients, usually on the left side.

Only 10% of patients have effusion occupying more than 25% of the hemithorax. Predisposing factors mentioned in the literature include the use of an internal mammary artery graft, topical hypothermia with iced slush, and cardiopulmonary bypass.[66] The pleural fluid is serous and predominantly lymphocytic. Thoracoscopic pleural biopsies reveal an intense lymphocytic pleuritis that may progress to pleural fibrosis and occasionally lead to trapped lung if the visceral pleura is affected.

Diagnosis is reached by exclusion, and can be established in asymptomatic patients with postoperative small pleural effusion on the left side. Since many pleural effusions resolve spontaneously, therapeutic thoracentesis is only recommended in patients with large infusions. A few patients require thoracoscopy and pleurodesis because of multiple recurrence.[67]

*Pleural effusion and pericardial disease.* More than 25% of patients with pericardial disease develop pleural effusion, usually bilateral or predominantly left-sided. These are mainly transudates related to increased pulmonary and systemic pressures or secondary to the disease causing the pericarditis.[68]

However, few cases have been reported and more detailed studies are required.[69] Echocardiography and magnetic resonance imaging are used to obtain a definitive diagnosis. Therapy should be directed towards treating the pericardial disease.

*Pleural effusion after cardiac injury (Dressler's syndrome).* Dressler's syndrome is characterized by the onset of fever, pleural pericarditis, and pulmonary infiltrates 3 weeks (range 2-86 days) after a myocardial or pericardial injury. It has been described after acute myocardial infarction, heart surgery (18%-30%), chest injury, pacemaker implantation, angioplasty, and transthoracic puncture of the left ventricle.

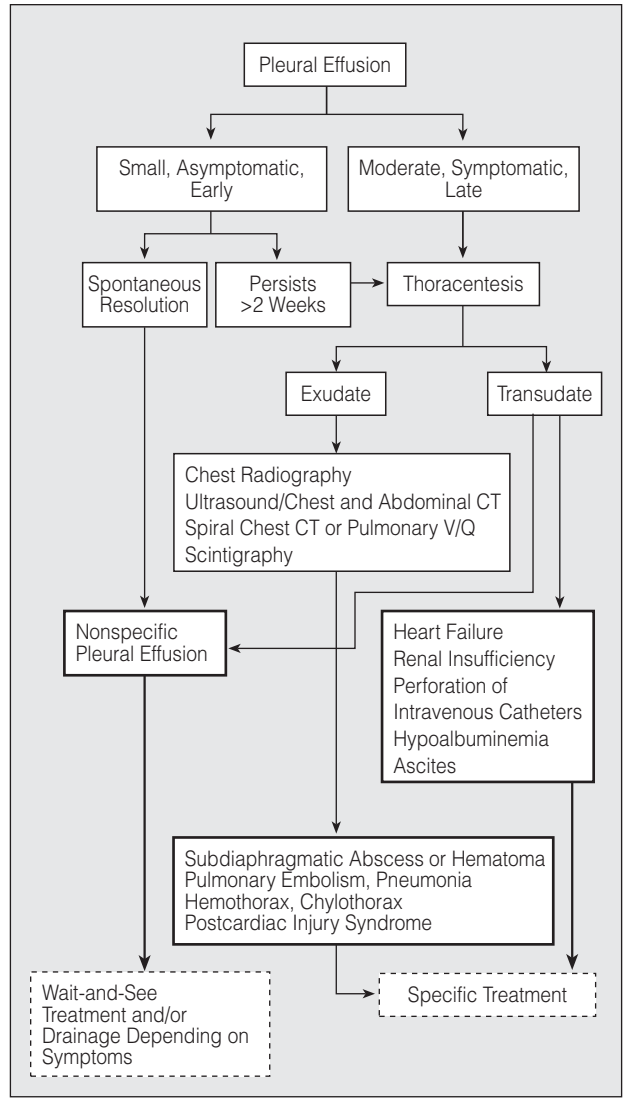


**Figure 5. Algorithm for the management of pleural effusion after cardiac or abdominal surgery. CT indicates computed tomography; and V/Q, ventilation/ perfusion.**

There appears to be a close relationship between the presence of effusion and antimyocardial antibodies.[70] Although Dressler estimated the incidence to be between 3% and 4% after acute infarction, the current figure is less than 1% owing to early thrombolytic treatment and angioplasty, as well as new drugs (angiotensin converting enzyme inhibitors, beta-blockers, and statins) that have immunomodulatory effects. The pleural effusion is usually a small serous or serohemorrhagic exudate composed mainly of polymorphonuclear cells in the acute phase and mononuclear cells in later stages. Confirmation of the existence of pericardial effusion by

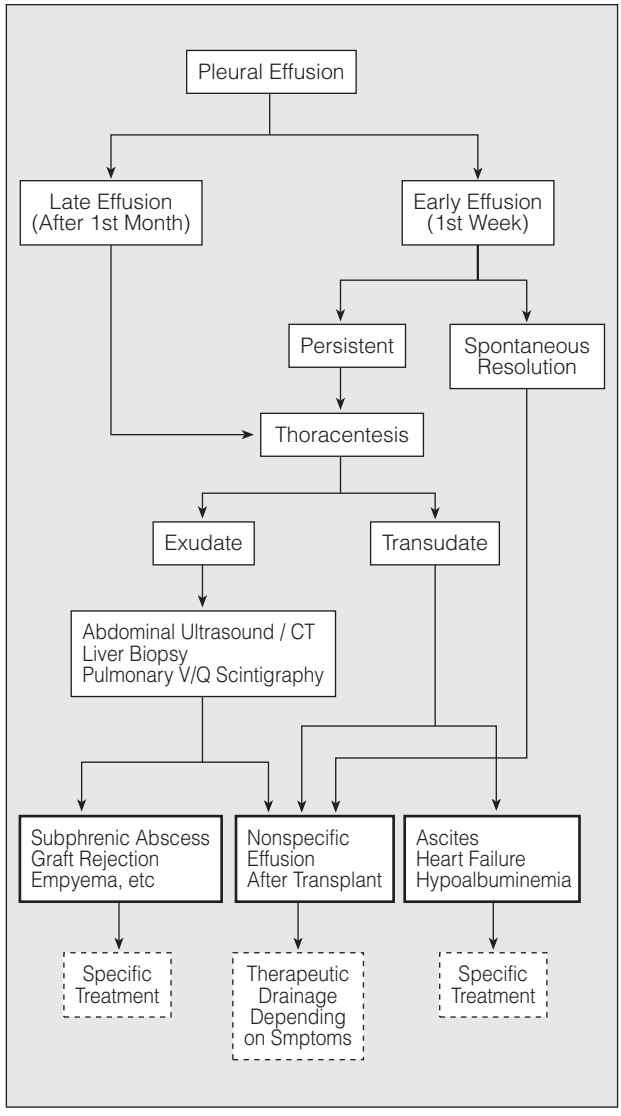


**Figure 6. Algorithm for the management of pleural effusion after liver transplantation CT indicates computed tomography; V/Q ventilation/ perfusion.**

TABLE 10
**Pathophysiologic Mechanisms of Pleural Effusion in Digestive Diseases**

| |
|---|
| Common to all the diseases |
| Diaphragmatic irritation |
| Interruption of lymphatic drainage from the peritoneal cavity to the pleura |
| Pleural metastasis |
| Esophageal disease |
| Movement of gastric content to the mediastinum |
| Extravasation of sclerosing material |
| Hepatic disease |
| Movement of ascitic fluid through the diaphragm |
| Rupture of abscesses in the pleural cavity |
| Pancreatic disease |
| Diaphragmatic necrosis |
| Pancreatic pleural fistula |
| Spleen disease |
| Fistula between the spleen and the pleura |

means of echocardiography is a useful aid to diagnosis.

Diagnosis is reached by exclusion.[71] The clinical presentation can be mild and self-limiting, and in more severe cases the response to nonsteroidal anti-inflammatory agents and corticosteroids is good. Anticoagulant therapy should be avoided because of the risk of hemopericardium.[1]

*Pleural effusion caused by pulmonary thromboembolism.* Although pleural effusion is detected on chest radiograph in 30% to 50% of patients with pulmonary embolism, these patients represent less than 5% of etiologies in many studies on pleural effusions. An increase in vascular permeability appears to be involved in the pathogenesis of this effusion. The most common clinical symptoms are dyspnea and/or pleuritic chest pain, which occur in over 70% of patients. The effusions usually occupy less than one third of the hemithorax and are generally seen as blunting of the costophrenic angle. They are sometimes associated with pulmonary infiltrates secondary to pulmonary infarcts. The pleural fluid is often bloody, fulfills the biochemical criteria of an exudate, usually presents marked mesothelial hyperplasia, and can be associated with pleural eosinophilia. In the absence of prior trauma or malignancy, this picture should raise the suspicion of pulmonary embolism.[72] The bloody appearance of the pleural fluid is not associated with prior anticoagulation therapy. Nor is it a contraindication for such treatment because hemothorax is a rare complication of heparin treatment and is usually associated with an excessive dose of the anticoagulant agent.

Even more rare is pleural effusion caused by systemic cholesterol embolization as a complication of medical interventions (aortic catheterization, thrombolytic therapy) or vascular surgery in patients with arteriosclerosis; this entity can also be associated with pleural eosinophilia.[73]

### *Postsurgical Pleural Effusion*

The majority of the patients who undergo abdominal or cardiac surgery present pleural effusion in the immediate postoperative period.

The incidence of such effusions ranges between 60% and 80% depending on the diagnostic technique used, and it is somewhat lower (35%) when the intervention is in the lower abdomen. These small asymptomatic effusions, defined as nonspecific, appear on the first or second day after surgery and disappear spontaneously within 2 to 4 weeks, although they may occasionally last longer.[66] They are generally transudates, and various factors are involved in their pathogenesis (Table 9).[74] After heart surgery, 18% to 30% of patients present associated pleural effusion or Dressler's syndrome as discussed above.

Since many other complications of surgery can cause pleural effusion,[71,75] diagnostic thoracentesis is necessary if an effusion occurring after abdominal or heart surgery has a late onset, fails to resolve, or is highly symptomatic. Establishing whether the effusion is an exudate or transudate will determine what additional diagnostic tests are required to confirm or rule out other possible etiologies presented in the diagnostic algorithm

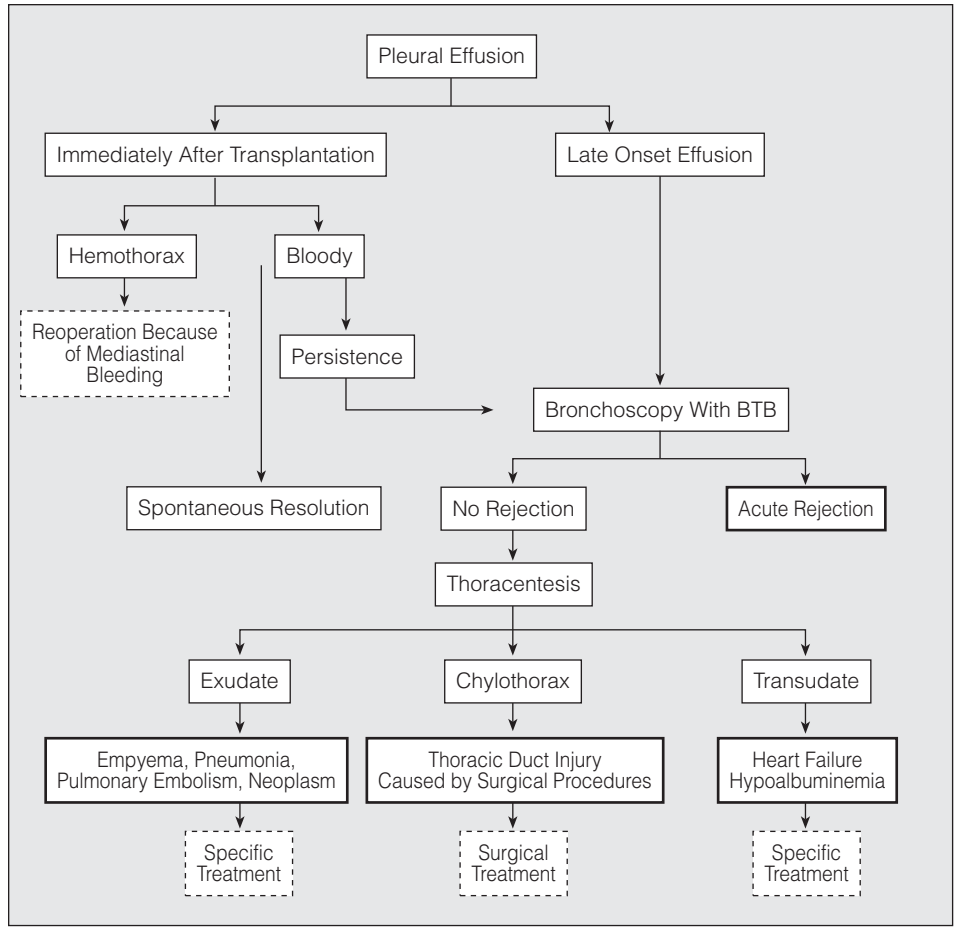


**Figure. 7. Algorithm for the management of pleural effusion after lung transplantation. TBB indicates transbronchial biopsy.**

(Figure 5). Nonspecific postsurgical effusion is, therefore, a diagnosis of exclusion.

Effusions caused by abdominal or cardiac surgery are managed by treating the etiologic cause, and drainage using a range of techniques is indicated in nonspecific postoperative effusions when required by the patient's clinical status.

*Pleural effusion after liver transplantation.* Over 50% of patients who undergo a liver transplant subsequently develop a nonspecific unilateral or bilateral pleural effusion.[76] The effusion starts in the first 7 days after the intervention, is asymptomatic, and usually resolves spontaneously within a month, although it can sometimes persist for more than 6 months. The pleural fluid is usually a transudate of multifactorial origin (pretransplant ascites, hypoalbuminemia, administration of intravenous fluids and transfusions) but may be an exudate, when the cause is diaphragmatic irritation related to the surgery. In persistent transudative effusions, all other possible etiologies must be excluded. If the nonresolving effusion is an exudate, the following must be ruled out: subphrenic abscess or hematoma, hemothorax secondary to anticoagulation therapy, graft rejection, pulmonary embolism, pneumonia, and anastomosis obstruction in suprahepatic veins. A diagnosis of nonspecific postsurgical effusion can only be established when all other possible etiologies have been excluded.

The diagnostic algorithm is shown in Figure 6.

*Pleural effusion after lung transplantation.* After lung transplantation, the 2 pleural cavities are connected until the development of new adhesions separates them. Consequently, any pleural effusion, whatever the cause, may be bilateral, and any intervention undertaken on one cavity will also affect the other. Pleural effusion occurs during the early postoperative period after lung transplantation in all patients and is multifactorial in origin (increased permeability caused by ischemia-reperfusion injury, interruption of lymphatic drainage, acute early temporary rejection, mediastinal bleeding).[77] The effusion is a predominantly neutrophilic bloody exudate that resolves within a few days. No tests are required unless it persists for more than 3 weeks, the patient presents symptoms such as fever or pleuritic chest pain, or new fluid accumulates.

The first step in such cases is to perform transbronchial biopsies in order to rule out acute graft rejection because this is the most common etiology for pleural effusion at any time after lung transplantation.[78]

Once acute rejection has been ruled out, pleural fluid

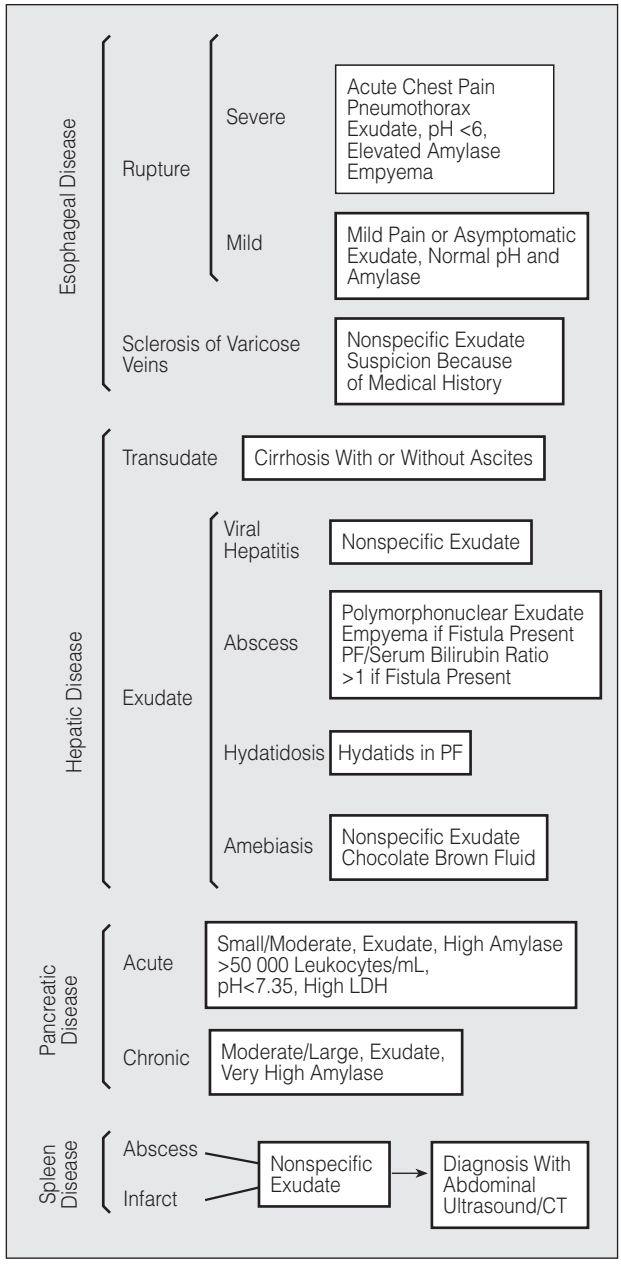


**Figure 8. Digestive diseases that cause pleural effusion. PF indicates pleural fluid; LDH, lactate dehydrogenase; and CT, computed tomography.**

obtained by thoracentesis should be tested (Figure 7). Hemothorax is associated with increased postoperative mortality.[77]

### *Pleural Effusion and Benign Digestive Disease*

Many digestive diseases cause pleural effusion, and the mechanisms are diverse (Table 10).[79,80] Figure 8 shows the benign digestive diseases associated with pleural effusions. These may evolve with or without abdominal symptoms.[81,82]

These effusions are managed by treating the causative disease. In patients who are experiencing severe symptoms (mainly dyspnea) pleural fluid can be evacuated. It should not be forgotten, however, that in the case of effusions accompanied by severe ascites, the removal of ascitic fluid will reduce the volume of the pleural effusion.

Since there is no evidence that any one drainage technique is better than another, the decision concerning which technique should be used must be taken on a case-by-case basis taking into account symptoms, risk factors, and comorbidity.

### *Drug-Induced Pleural Effusion*

Drugs have been shown to cause pleural effusion, albeit very rarely. The mechanisms involved are poorly understood, although several hypothesis have been postulated including hypersensitivity reaction and direct toxicity through inflammatory or oxidative processes. The list of drugs that cause pleural effusion grows daily and currently includes a broad range including cardiovascular, antiinflammatory, chemotherapeutic, and antibiotic agents. The best known are amiodarone, nitrofurantoin, methysergide, bromocriptine, and the ergoline derivatives. If a drug-related etiology is suspected, the treating physician should consult a comprehensive list of causative agents such as can be found in the literature.[1,83] Another source of information is the web site www.pneumotox.com. Any clinician carrying out a differential diagnosis of a pleural effusion must consider the possibility that it may be drug induced, and this makes a medical history indispensable. In order to establish a causal relationship, the physician must know what medications the patient has been taking, whether the timing of presentation is consistent with a diagnosis of drug-related effusion and, if possible, must demonstrate resolution of the effusion on withdrawal of the medication. This is necessary because there are no specific findings that confirm this diagnosis. The pleural effusion can be unilateral or bilateral and is often associated with pneumonitis. The pleural fluid is occasionally eosinophilic, although this finding has no diagnostic value. Pleural biopsy in such cases usually only reveals nonspecific inflammation. As a general rule, other plausible causes for pleural effusion should be ruled out before attributing the effusion to a drug. Treatment obviously consists in withdrawal of the causative medication, and in most cases the effusion will then resolve.

### *Asbestos-Related Benign Pleural Disease*

Asbestos is associated with a number of pleural manifestations.[84,85]

Benign pleural disease is the most common respiratory condition caused by asbestos exposure.

It occurs in around 50% of people who have been continuously exposed to asbestos in the workplace.

The latency period tends to be more than 20 years, and the incidence is directly proportional to the intensity of exposure and the time lapsed since initial

TABLE 11
**Etiology of Chylothorax**

| |
|---|
| Congenital malformations of the lymphatic system |
| Atrophied thoracic duct |
| Lymphatic aplasia and dysplasia |
| Lymphangioma |
| Intestinal lymphangiectasis; protein-losing enteropathy |
| Neoplasms |
| Lymphomas |
| Metastatic cancer |
| Kaposi sarcoma (acquired immunodeficiency syndrome) |
| Mediastinal tumors |
| Teratoma |
| Retrosternal goitre |
| Thymoma |
| Aortic aneurysm |
| Infections |
| Tuberculosis |
| Filariasis |
| Pneumonia |
| Empyema |
| Diseases that affect the lymph vessels |
| Lymphangioleiomyomatosis |
| Pulmonary tuberose sclerosis |
| Gorham's syndrome |
| Lymph duct cyst |
| Yellow nail syndrome |
| Castleman's disease |
| Idiopathic causes |
| Miscellaneous |
| Sarcoidosis |
| Behçet's syndrome |
| Amyloidosis |
| Hypothyroidism |
| Systemic lupus erythematosus |
| Transudates |
| Hepatic cirrhosis |
| Nephrotic syndrome |
| Heart failure |
| Traumatic causes |
| Iatrogenic |
| Postsurgical |
| Superior vena caval and left subclavian thrombosis |

exposure. A history of asbestos exposure should take the form of a complete occupational history including, in date order, all the patients' jobs, the specific activities involved, and the materials handled throughout their whole working lives. The recommended method for screening patients for asbestos-related benign pleural disease is plain chest radiograph using oblique projections if possible. However, if better definition of the lesions is needed, high resolution computed tomography using 2 cm collimation is the best tool.

Pleural plaques are the most common complication associated with asbestos exposure, although this condition has also been reported after tuberculosis, hemothorax, and chest injuries. These plaques are hyalinized collagen formations that are nearly always found on the parietal pleura and are usually circumscribed. The prevalence of plaques appears to correlate directly with the intensity of exposure and the latency period. They are usually bilateral, and the best tool for their detection is chest computed tomography, although oblique chest radiography may suffice in some cases. In 30% of cases plaques are found in conjunction with pulmonary asbestosis. The possible effect of pleural plaques on respiratory function has been the object of many studies. To date, no conclusive evidence has been found of any effect. This means that any lung function abnormalities observed may be due to concomitant smoking or undetected pulmonary fibrosis. Although the pleural plaque formations are associated with a higher risk of developing asbestosis or neoplastic disease because they indicate a greater level of exposure to asbestos, it is not thought that they themselves become malignant.

Diffuse pleural fibrosis leads to a thickened visceral pleura that tends to limit respiratory movements. Its frequency correlates directly with the duration and intensity of exposure.

Consequently, the patients present a restrictive ventilatory defect, and this may progress to respiratory failure in the advanced stages of the disease. In such cases an improvement has been reported with noninvasive mechanical ventilation.

Asbestos-related pleural effusion occurs in patients with a history of exposure to asbestos who present with an exudative effusion but no signs of malignancy when monitored over a period of at least 3 years. The effusion is usually unilateral, predominantly left-sided, and serosanguineous.

Except for suggestive pleural calcification, there are no specific diagnostic findings in the examination of either pleural fluid or tissue. Diagnosis must, therefore, be based on the criteria discussed below and on ongoing monitoring.

Thoracoscopy is recommended in patients with persistent pleural effusion in order to rule out mesothelioma before establishing a diagnosis of benign pleural disease. In the long term, the effusion recurs in 30% of patients, and diffuse pleural fibrosis, rounded atelectasis, and mesothelioma develop in 20%, 20%, and 5% of cases, respectively.

Rounded atelectasis is a benign lesion usually caused by exposure to asbestos. The peripheral lung is trapped by the underlying pleural layer when the thickening pleura compresses the lung and gives rise to atelectasis. In plain chest radiography an increase in basal density can be observed together with thickening of the adjacent pleura. These characteristics are more clearly defined in chest computed tomography, which may reveal the following pathognomonic findings: a pulmonary mass contiguous to a thickened pleura and the curved swirl of the vessels and bronchi converging on the pulmonary hilum. These findings make possible a probable diagnosis that makes biopsy unnecessary in most cases.

Nevertheless, although it has not been demonstrated that rounded atelectasis can become malignant, the need to order histologic studies to rule out cancer should be considered on a case-by-case basis.

### *Pleural Effusion Caused by Benign Gynecological Diseases*

Pleural effusion is sometimes a sign of benign gynecological diseases, such as Meig's syndrome, endometriosis, or ovarian hyperstimulation syndrome. These entities should be included in the differential diagnosis of a pleural effusion of unknown cause.

Benign ovarian tumors are associated with ascites and pleural effusion (Meig's syndrome); the tumor releases substances that alter vascular permeability.[86] Although the pleural fluid is usually a nonspecific exudate, it can also occasionally be a transudate. Diagnosis is based on the demonstration of the existence of an ovarian tumor. Pleural fluid disappears when the tumor is excised. Very rarely, stage IV endometriosis is associated with the presence of pleural exudate. Diagnosis is established when the existence of endometriosis is confirmed by laparoscopy. These effusions do not require specific treatment because they disappear when the gynecological disease is treated.

Finally, ovarian hyperstimulation syndrome is increasingly common because of hormonal fertilization treatments.[87] Up to 32% of patients with severe forms of this condition present with pleural effusion, generally associated with severe respiratory distress and respiratory failure. The fluid accumulates because of alterations in vascular permeability as a result of hemoconcentration and the movement of ascitic fluid into the pleural space. This type of effusion is a nonspecific exudate and it is the patient's medical history (hormonal therapy or multiple births) that will suggest the diagnosis. In all cases, pulmonary embolism should be ruled out as this is very common in the advanced stages of ovarian hyperstimulation syndrome. Treatment is based on ensuring the patient's hemodynamic status by way of therapeutic fluid management including diuretics. Prevention of thrombosis is important, and paracentesis should be performed in patients with ascites. In the most severe cases involving pleural effusion and respiratory insufficiency, evacuation of pleural fluid and oxygen therapy are necessary.

### *Chylothorax and Pseudochylothorax*

*Chylothorax.* Chylothorax is defined as the presence of lymph or chyle in the pleural cavity. The chyle may originate in the thorax (owing to rupture of the thoracic duct or affluent vessels) or in the abdomen.

In chylothorax, unlike pseudochylothorax, the pleural surfaces are normal. If fetal and neonatal chylothorax is excluded, this entity is rare, affecting 3% of patients with pleural effusion studied consecutively in one hospital.[88] The causes of chylous effusions are shown in Table 11. The most common chylothoraces are tumor related (75% lymphomas), and the next most common are traumatic, iatrogenic, and idiopathic chylous effusions.

The etiology of most idiopathic cases, when the effusion persists after appropriate follow-up, is considered to be trauma. The increasingly widespread use of large veins for parenteral feeding and hemodynamic monitoring has made iatrogenic thrombosis of the superior vena cava or the left subclavian artery one of the most common causes of chylothorax, especially in children.

Chylothorax secondary to hepatic cirrhosis, nephrotic syndrome, or heart failure has the biochemical characteristics of a transudate.

TABLE 12
**Chylothorax: Therapeutic Modalities**

| |
|---|
| Conservative treatment |
| Treatment of the causative disease |
| Repeated thoracentesis |
| Continuous drainage |
| Dietary modifications |
| Medium chain triglycerides |
| Exclusively parenteral nutrition* |
| Pleurodesis using endothoracic tube* |
| Surgical treatment |
| Thoracoscopic pleurodesis |
| Pleuroperitoneal pump |
| Fibrin glue to seal the thoracic or intestinal duct |
| Thoracic duct ligation via thoracoscopy or thoracotomy |
| Anastomosis between the thoracic duct and the azygos vein |
| Lung transplant (in lymphangioleiomyomatosis) |
| In patients with concurrent ascites |
| Peritoneal venous shunts |
| Closure the diaphragmatic aperture with fibrin or suture using thoracoscopy |
| In the fetus |
| Intrauterine thoracentesis |
| Prenatal pleuroamniotic shunt |

*In high-volume chylothorax.

DIAGNOSIS. *CLINICAL COURSE.* The most common symptoms of nontraumatic chylothorax in adults are dyspnea on exertion and a sensation of heaviness of recent onset in the affected hemithorax. Fever and chest pain are rare because chyle (lymph) is not an irritant. This diagnosis is generally suspected after thoracentesis because of the appearance of the pleural fluid.

*APPEARANCE AND BIOCHEMISTRY OF PLEURAL FLUID.* While the pleural fluid in chylothorax is typically milky, both pseudochylothorax and empyema can also produce milky fluid. Furthermore, the fluid may be bloody, serous, or turbid in 50% of cases.[89,90] Empyema can be ruled out if the milky appearance disappears after centrifugation.

Measurement of triglyceride values in pleural fluid is considered to be the best (most practical and accessible) way of diagnosing chylothorax.[91] The sensitivity of a triglyceride value greater than 110 mg/dL is high, but since triglyceride values are also observed in association with pseudochylothorax, a pleural fluid/serum cholesterol ratio of less than 1 is also required. A third criterion has been proposed in order to exclude hypertriglyceridemia: a pleural fluid/serum triglyceride ratio of less than 1. Since the triglyceride content in pleural effusions can be due to several factors and not only diffusion from plasma, some authors consider this third criterion to be superfluous.

Irrespective of the final result of this debate, the diagnostic specificity of the combined use of the 3 criteria proposed is high.

TABLE 13
**Causes of Hemothorax**

| |
|---|
| Traumatic |
| Closed chest injury |
| Penetrating chest injury, including iatrogenic injuries |
| Spontaneous |
| Pleural |
| Malignancy (primary or metastatic) |
| Associated with rupture of adhesions in spontaneous pneumothorax |
| Pleural endometriosis |
| Pulmonary |
| Malignancy (primary or metastatic) |
| Necrotizing infection |
| Tuberculosis |
| Pulmonary embolism with infarction |
| Arteriovenous malformations |
| Hereditary hemorrhagic telangiectasis |
| Bullous emphysema |
| Pulmonary sequestration |
| Blood dyscrasias and complications of anticoagulation |
| Abdominal disease |
| Pancreatitis |
| Hemoperitoneum |
| Vascular disease |
| Rupture of an aortic aneurysm |
| Rupture of an aneurysm in the splenic artery |

Given that chylomicrons are the only components of chyle present in the blood exclusively during the postprandial period, demonstrating their presence in pleural fluid by electrophoresis or ultracentrifugation is considered diagnostic (gold standard). However, the accuracy of this measurement depends on the method used.

Lymphography has been the method most widely used to pinpoint the source of chylothorax (of lymph extravasation). Identification is, however, difficult in nontraumatic patients. Lymphatic scintigraphy has been proposed as an alternative method because it is a faster and less invasive procedure.

TREATMENT OF NONTRAUMATIC CHYLOTHORAX. An initial approach includes decompression of the pleural space and the thoracic lymphatics. Although decompression can sometimes be achieved by one or more thoracenteses, continuous drainage through an endothoracic tube is generally a more effective method and also facilitates measurement of the chyle flow rate in the many cases characterized by reaccumulation.

Table 12 shows the range of later treatment options. In patients with chylothorax caused by lymphoma refractory to chemotherapy and radiotherapy, talc pleurodesis using medical thoracoscopy has been shown to be an effective technique. Pleuroperitoneal shunt is considered to be a safe and effective treatment for persistent chylothorax in children in the absence of chylous ascites.

PROGNOSIS. The prognosis depends to a large degree on the etiology of the chylothorax.

Prolonged pleural drainage in these patients has a very negative impact on the patient's nutritional and immunological status. In one study of patients with nontraumatic chylothorax, survival at 22 months was 24%.

*Pseudochylothorax.* The terms pseudochylothorax and chyliform pleural effusion are synonyms, and this is a rare entity, much less common than chylothorax. Although the pleural fluid is turbid in appearance because of its high lipid content, it does not come from the lymphatic system as a result of a ruptured thoracic duct. Pseudochylothorax occurs in patients who have long-standing (mean, 5 years) pleural effusions. The 2 most common causes are tuberculosis and rheumatoid arthritis. Pleural effusions in patients with atelectasis and trapped lung (secondary to therapeutic pneumothorax) can also become pseudochylothoraces.

In many patients, the cause of the original effusion is never determined.

DIAGNOSIS. Analysis of pleural fluid is a useful diagnostic tool and can sometimes identify the etiology (if it is tuberculous, for example). Although the absence of cholesterol crystals in the pleural fluid sediment does not rule out pseudochylothorax, their presence is diagnostic. Cholesterol levels over 200 mg/dL are very suggestive of pseudochylothorax, and a pleural fluid/serum cholesterol ratio of 1 or higher confirms this suspicion.

TREATMENT. If the patient has a history of tuberculosis and has either not been treated or has received inadequate treatment, appropriate treatment must be implemented. When pseudochylothorax is caused by rheumatoid arthritis, treatment should be directed at achieving adequate control of the underlying disease. In patients with functional impairment, one or more therapeutic thoracenteses may alleviate symptoms, and if lung function is preserved, pleural decortication is indicated.

### *Hemothorax*

*Definition and etiology.* Hemothorax is the presence of blood in the pleural space. A pleural effusion is considered to be a hemothorax when the pleural fluid hematocrit level is 50% greater than that of peripheral blood.[1] Table 13 shows the causes of hemothorax. The most common are traumatic and iatrogenic (following surgery, vascular catheterization, or diagnostic or therapeutic transpleural punctures).

*Diagnosis.* The signs and symptoms of hemothorax vary depending on the cause, the volume, and the rate of accumulation. Acute traumatic hemothorax is usually associated with hemodynamic instability and pain, while the predominant manifestations in nontraumatic cases are dyspnea and other signs characteristic of fluid accumulation in the pleura.

A chest radiograph reveals the presence of either a free-flowing or a loculated effusion, and occasionally there are images consistent with a diagnosis of coagulates. Radiographs may also reveal associated lesions that will guide the etiologic diagnosis. Further imaging techniques (ultrasound and computed tomography) are necessary in

some cases to quantify and evaluate the hemothorax, identify the cause, and provide guidance for therapeutic procedures. A definitive diagnosis is obtained by way of thoracentesis and pleural fluid analysis.

*Treatment*

ACUTE HEMOTHORAX. In hemodynamically stable patients who have a small hemothorax (only blunting of the costophrenic angle or a volume calculated to be less than 300 mL) clinical radiographic monitoring is one option (C).

In hemodynamically unstable patients or when the volume is calculated to be greater than 300 mL, a large-bore pleural drainage tube—28F or 32F—must be placed in the midaxillary line at the sixth intercostal space and directed posteriorly (B); prior prophylactic antibiotic therapy is recommended (C).[92,93] Thoracotomy is indicated when over 1500 mL of fluid is removed in the initial drainage or when over 200 mL of fluid is removed per hour for more than 3 consecutive hours (B). In hemodynamically stable patients VAT is another alternative; this technique can sometimes be used to perform procedures aimed at achieving hemostasis.[94]

When the suspected cause of the hemothorax is rupture of an aortic aneurysm, contrast-enhanced computed tomography should be performed. Drainage is contraindicated in such cases as it may favor exsanguination (D).

RESIDUAL OR COAGULATED HEMOTHORAX. Small residual hemothorax (only blunting of the costophrenic angle) can be treated conservatively with respiratory physiotherapy and monitoring (C).

In patients with a persistent hemothorax estimated to be greater than 500 mL or persistent residual loculations occupying less than one third of the hemithorax, treatment is required to prevent the development of subacute (atelectasis, empyema, pneumonia) or chronic (fibrothorax) complications (C). During the first week drainage can be attempted using new chest tubes placed under ultrasound or computed tomographic guidance (D). If this approach is not effective, the condition can be treated by the instillation of fibrinolytic agents (streptokinase or urokinase) into the pleural space (B).[95] Another alternative to drainage, or if the fibrinolytics are not effective, is early thoracoscopic removal of the coagulates (C).[96]

Decortication is indicated if thoracoscopy is not effective or the hemothorax is chronic and gives rise to trapped lung (fibrothorax) (D).

### Key Points

– Clinical radiographic monitoring is an option in hemodynamically stable patients who have a small hemothorax (C).

– In hemodynamically unstable patients or when the volume is calculated to be greater than 300 mL, a large-bore pleural drainage tube—28F or 32F—must be placed in the midaxillary line at the sixth intercostal space and directed posteriorly (B); prior prophylactic antibiotic therapy is recommended (C).

– Thoracotomy is indicated when over 1500 mL of fluid is removed in the initial drainage or when over 200 mL of fluid is removed per hour for more than 3 consecutive hours (B).

– When the suspected cause of the hemothorax is rupture of an aortic aneurysm, contrast-enhanced computed tomography should be performed. Drainage is contraindicated in such cases as it may favor exsanguination (D).

Small residual hemothorax can be treated conservatively with respiratory physiotherapy and monitoring (C).

In patients with a persistent hemothorax estimated to be greater than 500 mL or persistent residual loculations occupying less than one third of the hemithorax, treatment is required to prevent the development of subacute or chronic complications (C). During the first week drainage can be attempted using new chest tubes placed under ultrasound or computed tomographic guidance (D). If this approach is not effective, the condition can be treated by the instillation of fibrinolytic agents into the pleural space (B). Another alternative, or if the fibrinolytics are not effective, is early removal of the coagulates via thoracoscopy (C).

– Decortication is indicated if thoracoscopy is not effective or the hemothorax is chronic and gives rise to trapped lung (fibrothorax) (D).

### List of Abbreviations

ADA: adenosine deaminase.
IFN: interferon.
IL: interleukin.
VAT: video-assisted thoracoscopy.

### Levels of evidence[97]

1++: high quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.

1+: well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.

1–: meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias.

2++: high quality systematic reviews of case–control or cohort studies or high quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.

2+: well conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal

2-: case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal

3: non–analytic studies, eg case reports, case series

4: expert opinion

### Grades of Recommendations[97]

A. At least one meta–analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or

A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results

B. A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or

Extrapolated evidence from studies rated as 1++ or 1+

C. A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or

Extrapolated evidence from studies rated as 2++

D. Evidence level 3 or 4, or extrapolated evidence from studies rated as 2 +

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