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Pleural effusions

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Epidemiology of pleural effusions

Approximately 1.5 million people develop pleural effusions in the United States each year.[1] Many different diseases may cause them. In an unpublished series of 2900 consecutive patients submitted to a diagnostic thoracentesis in a University Hospital (Lleida, Spain) during the last 17 years, the leading etiologies of pleural effusions were: cancer (27%), heart failure (20%), pneumonia (18%), tuberculosis (9%), pericardial diseases (3.5%), and cirrhosis (3%). It should be noted that figures for effusions which are not usually tapped, such as when the diagnosis is evident on clinical grounds (e.g., heart failure) or their size is too small (e.g., pulmonary embolism), are underrepresented. In some geographical areas, tuberculosis is the main cause of pleural effusion.[2] In contrast to adults, three-fourths of all pleural effusions in the pediatric population are parapneumonics.[3]

Pathogenesis of pleural effusions

Normally, the pleural space contains a small amount of fluid (about 0.26 $\pm$ 0.1 mL/kg body weight) which allows the lungs to expand and deflate with minimal friction during respiratory movements.[4] Pleural fluid normally originates in the capillaries of the parietal pleura, filtrates into the pleural space, and is then absorbed by the parietal pleural lymphatics. Effusions accumulate whenever the rate of pleural fluid formation exceeds that of its reabsorption, usually the result of simultaneous malfunction of both processes rather than just one alone (Table 1).

For the purpose of differential diagnosis, pleural effusions have classically been divided into transudates and exudates.[1] Transudates are caused by increased hydrostatic pressures (e.g., heart failure), decreased oncotic forces (e.g., hypoproteinemia), increased negative intrapleural pressure (e.g., atelectasis), or movement of ascitic fluid through the diaphragm (e.g., hepatic hydrothorax). In contrast, exudates are due to increased capillary permeability and/or impaired lymphatic drainage resulting from proliferative (e.g., malignancy) or inflammatory (e.g., parapneumonic effusions) processes.

Approach to patients with pleural effusions

Key elements to uncover the etiology of pleural effusions are clinical evaluation, imaging, pleural fluid analysis, and when applicable pleural biopsy.

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Table 1
Pathogenesis of pleural effusions.

Mechanisms	Examples
Increased pleural fluid formation	
Increased interstitial fluid in the lung	Heart failure, pneumonia, pulmonary emboli
Increased permeability of the pleural capillaries	Cancer, tuberculosis
Increased intravascular pressure in pleura	Heart failure, pulmonary hypertension, SVCS
Decreased pleural pressure	Atelectasis, trapped lung
Decreased serum oncotic pressure	Hypoalbuminemia
Increased fluid in peritoneal cavity	Cirrhosis, peritoneal dialysis, Meig's syndrome
Disruption of the thoracic duct	Chylothorax
Disruption of blood vessels in the thorax	Hemothorax
Decreased pleural fluid absorption	
Obstruction of draining lymphatics	Cancer, lymphoma
Elevation of systemic vascular pressures	Heart failure, SVCS

SVCS, superior vena caval syndrome.

Medical history and physical examination

The clinical history and physical examination may be very helpful in indicating potential causes of the pleural effusion or, at minimum, further appropriate investigations (Table 2).[5] While small effusions are usually asymptomatic, large ones almost always cause dyspnea and trepopnea, with or without chest pain or dry cough. Although the degree of breathlessness usually correlates with the effusion's size, this is not always the case. Patients with underlying lung diseases (COPD, carcinomatous lymphangitis, pulmonary emboli) may experience intense dyspnea with just small-to-moderate sized pleural effusions. Trepopnea is a form of positional dyspnea in which the patient has less dyspnea when lying on the side of the pleural effusion. Chest pain produced by parietal pleural involvement can be described as shooting (e.g., pulmonary embolism, pneumonia) or as dull aching (e.g., malignancy).[6] The former is often exacerbated during deep inspiration or coughing. At times, pleuritic chest pain is referred to the abdomen or, when the central diaphragmatic pleura is inflamed, to the ipsilateral shoulder.

Upon physical examination, dullness to percussion is the most reliable sign for ruling in pleural effusion (likelihood ratio positive = 8.7), while the absence of reduced tactile fremitus make this diagnosis less likely (likelihood ratio negative = 0.21).[7] Other physical exam findings that may be present are asymmetrical chest expansion, diminished or absent breath sounds, bronchial breathing, abnormal auscultatory percussion (method of Guarino) and friction rubs.[8]

Imaging

Chest radiographs

Once suspected, a pleural effusion is usually confirmed by chest radiograph. A small amount of pleural fluid causes the normally deep posterior and lateral costophrenic angles to appear shallow or blunted on upright posteroanterior and lateral chest radiographs. Additional fluid tracks up the pleural space, forming a meniscus, opacifying the lung and obscuring the diaphragmatic contour (silhouette sign). The lateral decubitus film with the affected side down is more sensitive than the posteroanterior film for the detection of small effusions, and indicates whether the fluid is free-flowing (Fig. 1).[9] On anteroposterior views, moderate to large effusions appear as a homogeneous increase in density spread over the lung fields with a still visible vascular tree (Fig. 2). At times, a substantial amount of pleural fluid accumulates in an infrapulmonary location without spilling into the costophrenic sulci. In such subpulmonic effusions the hemidiaphragm appears elevated, often with a lateral displacement of its dome and, if on the left side, the stomach gas bubble lies farther from the lung base.

Table 2
Medical history and physical examination in pleural effusions.

Findings	Potential causes of the pleural effusion
History	
Abdominal surgery	Postabdominal surgery, subphrenic abscess, pulmonary embolism
Asbestos exposure	Mesothelioma, benign asbestos pleural effusion
Cancer	Malignancy, paramalignant effusions (pulmonary embolism, atelectasis, postobstructive pneumonitis, postradiation therapy)
Cardiac procedures or myocardial infarction	Pleural effusion secondary to coronary artery bypass surgery, post-cardiac injury syndrome
Cirrhosis	Hepatic hydrothorax, spontaneous bacterial pleuritis
Collapse therapy for pulmonary TB	Tuberculous or pyogenic empyema, pyothorax-associated lymphoma, trapped lung
Dialysis	Heart failure, uremic pleuritis, pleural effusion secondary to peritoneal dialysis
Drug use	Drug-related effusions (eg., dasatinib, gonadotrophins, amiodarone)
Esophageal surgery, dilation or endoscopy	Chylothorax, esophageal perforation
Heart failure	Heart failure-related effusion
HIV	Pneumonia, TB, primary effusion lymphoma, Kaposi sarcoma
Neurosurgery	Intrathoracic migration of ventriculoperitoneal shunt, ventriculopleural shunt, duropleural fistula
Pancreatic disease	Pancreatic effusion (pancreatic-pleural fistula)
Radiofrequency ablation of lung or liver tumors	Pleuritis secondary to radiofrequency ablation
Recurrent episodes of pleuritic pain (plus fever, abdominal pain or arthritis)	Familial Mediterranean fever
Rheumatic autoimmune diseases	Rheumatoid pleurisy, lupus pleuritis, parapneumonic effusion, pulmonary arterial hypertension
Trauma	Hemothorax, chylothorax
Symptoms	
Fever	Parapneumonic effusion/empyema, TB, viral pleuritis, lupus pleuritis
Hemoptysis	Lung cancer, TB, pulmonary embolism, parapneumonic effusion
Weight loss	Cancer, empyema, TB
Signs	
Ascites	Hepatic hydrothorax, ovarian cancer, Meig's syndrome, constrictive pericarditis
Distended abdominal veins, encephalopathy, spider nevi	Cirrhosis
Pericardial rub	Acute pericarditis
S3 gallop, elevated neck veins, positive abdomino-jugular test, displaced apical impulse	Heart failure
Unilateral calf pain or swelling	Pulmonary embolism
Yellow dystrophic nails, lymphedema	Yellow nail syndrome

HIV, human immunodeficiency virus; TB, tuberculosis.

Three easily recognizable radiological patterns which aid differential diagnosis are bilateral, massive and loculated effusions (Table 3). The most common cause of bilateral pleural effusion is heart failure.[10] Other radiological findings in heart failure are cephalization or vascular redistribution, interstitial or alveolar edema, and enlarged cardiac silhouette. The last one is particularly telling because only a relatively small proportion (20%–30%) of patients with heart failure lacks this finding (Fig. 3). With bilateral pleural effusions and a normal heart size, the differential diagnosis should include malignancy and, less commonly, lupus pleuritis and constrictive pericarditis. Massive effusions opacify the entire hemithorax and displace mediastinal structures contralaterally, unless obstruction of the ipsilateral main stem bronchus by a neoplasm, or a fixed mediastinum by an invading tumor (e.g., mesothelioma) is present (Fig. 4). Around 60% of massive effusions are due to cancer, followed by parapneumonic effusions (20%) and, more infrequently, tuberculosis and hepatic hydrothoraces.[11] Loculated effusions, which occur in the presence of adhesions between contiguous pleural surfaces, are typically seen in conditions that cause intense pleural inflammation, such as parapneumonic effusions (Fig. 5), empyemas,

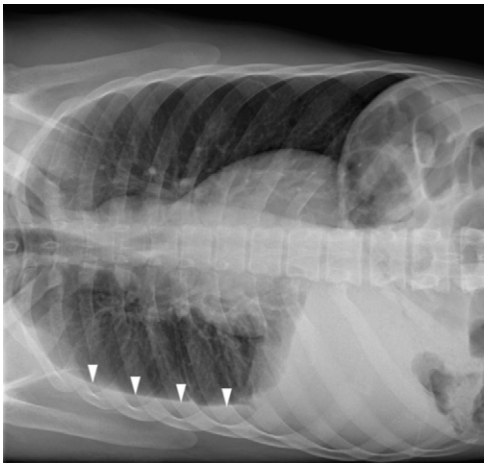

Fig. 1. Lateral decubitus radiograph showing a small amount of free-flowing pleural fluid (arrowheads).

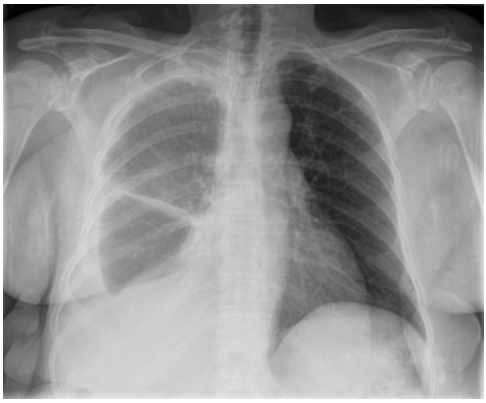

Fig. 2. Supine radiograph demonstrating blunting of the right costophrenic angle and a general increased haziness over the entire hemithorax in a patient with hepatic hydrothorax.

hemothoraces and tuberculosis. However, malignancy, pulmonary embolism and even heart failure may also produce loculations. In heart failure, loculated fluid within the lung fissure may give the appearance of an intraparenchymal mass that disappears with diuretic therapy. Hence the term "vanishing tumor".[10]

In a recent retrospective study, the sensitivity of identifying parapneumonic effusions was 86% for lateral, 82% for posteroanterior and 78% for anteroposterior chest radiographs, while the respective specificities were 87%, 81% and 76%.[12] The existence of a lower lobe parenchymal consolidation concealed the identification of some pleural effusions. Interestingly, chest radiographs missed 6% of effusions greater than 2 cm on computed tomography (CT), a size that may be significant enough to warrant a diagnostic thoracentesis. Therefore, consideration should be given to obtaining additional imaging, such as thoracic ultrasonography (TUS) in patients with lower lobe consolidation.

Ultrasonography

TUS is considered the standard of care in the safe localization, characterization, and aspiration of pleural fluid. The availability of a hand-held ultrasound machine allows the clinician to diagnose and

Table 3
Useful radiological signs in pleural effusions.

Radiological characteristics	Potential diagnoses
Chest radiograph	
Large o massive pleural effusion ($\geq 2/3$ of the hemithorax)	Malignancy, parapneumonic/empyema, tuberculosis, hepatic hydrothorax
Massive effusion without contralateral mediastinal deviation	Lung cancer (atelectasis), mesothelioma
Bilateral pleural effusion	Heart failure (cardiomegaly), malignancy, lupus pleuritis
Loculated effusion	Parapneumonic/empyema, tuberculosis, hemothorax, malignancy, pleurodesis, pulmonary embolism (if diagnostic delay >10 days), heart failure (vanishing tumor)
Air–fluid level in the pleural space	Bronchopleural fistula (pulmonary infection), gas-forming pleuropulmonary infection, spontaneous pneumothorax with pleural effusion, trauma, esophageal rupture
Focal consolidation	Pneumonia, lung contusion, alveolar cell carcinoma
Apical infiltrate	Tuberculosis
Interstitial infiltrates	Heart failure, viral pneumonia, lymphangitic carcinomatosis, benign asbestos pleural effusion, rheumatoid arthritis
Lung nodules or masses	Malignancy, multifocal infection, rheumatoid arthritis
Pleural calcification	Tuberculous empyema, asbestos exposure (pleural plaques), trauma (healed hemothorax)
Pericardial calcification	Constrictive pericarditis
Rib fissure or fracture	Trauma
Chest CT	
Pleural thickening	Malignancy (metastases or mesothelioma), organization of empyema or hemothorax, tuberculosis, pleurodesis, asbestos exposure, pleurodesis, coronary artery bypass surgery, uremia
Pleural nodules or masses	Malignancy (metastases, mesothelioma)
Bilateral mediastinal lymphadenopathy	Malignancy (metastases, lymphoma), sarcoidosis
Unilateral mediastinal lymphadenopathy	Lung cancer, parapneumonic/empyema, tuberculosis
Contrast-enhanced pleural surfaces	Empyema, complicated parapneumonic, tuberculosis, malignancy
Pericardial effusion	Pericardial diseases (metastatic or inflammatory)
Liver metastases	Malignancy

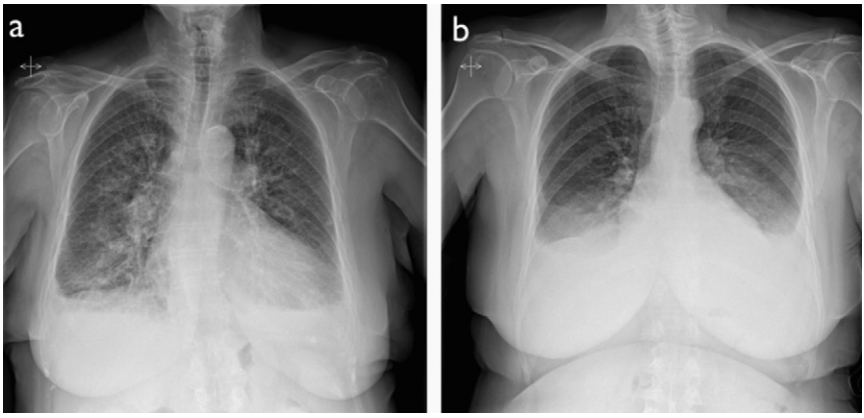

Fig. 3. Bilateral pleural effusions due to heart failure (a) and malignancy (b). Note the respective presence and absence of enlarged heart size.

manage pleural effusions at the point of care.[13] Not only is TUS more sensitive in detecting pleural fluid than chest radiographs,[14] but it can also distinguish between pleural fluid, pleural thickening and consolidation; suggest a malignant etiology (pleural nodules or thickening); support the need

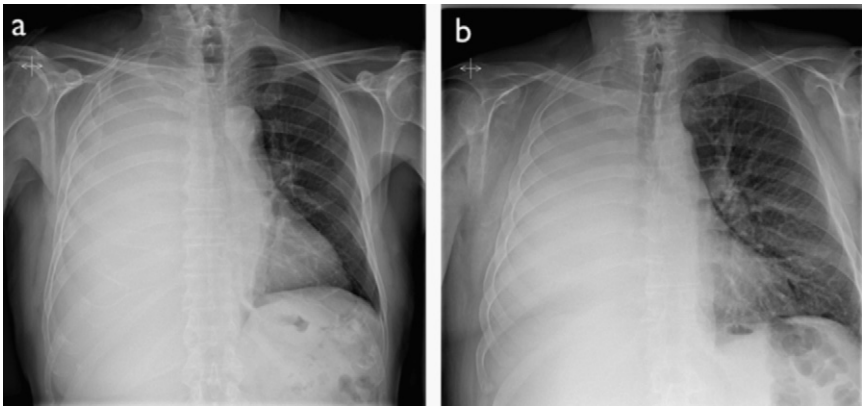

Fig. 4. Massive malignant pleural effusions with marked shift of the trachea and mediastinum away (a) and toward (b) the side of the effusion.

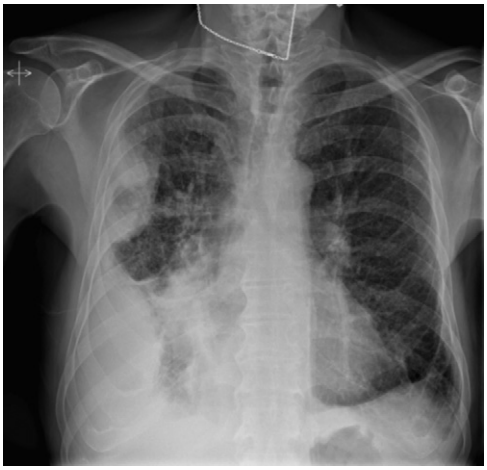

Fig. 5. Loculated parapneumonic effusion.

for chest drainage in parapneumonic effusions (pleural fibrinous septations); and guide pleural procedures (thoracentesis, chest tubes, and pleural biopsy), particularly if the effusion is small or loculated. For instance, a unilateral hemithorax opacification on chest radiograph, in which the distinction between pleural fluid, collapsed or consolidated lung or a combination may be difficult, is readily evaluated by TUS, which can also prevent a potentially dangerous needle or chest tube insertion into a vascularized tissue mass.

Sonographically, a pleural effusion appears as an anechoic (black area), homogenous space between parietal and visceral pleura surrounded by typical anatomic boundaries (chest wall, hemidiaphragm and lung surface). Sometimes the pleural fluid appears gray, because it is thick and echogenic. Loculated effusions may be located in a nondependent part of the thorax and have bands running across the dark areas of fluid, a common characteristic in inflammatory conditions (Fig. 6). TUS findings suggestive of malignancy include parietal pleural thickening of more than 1 cm, pleural nodularity and diaphragmatic thickness >7 mm (sensitivity 42% and specificity 95% for each criteria).[15]

Although most pleural effusions are readily identified, conditions such as obesity, heavy musculature, edema and the inability to properly position the patient may degrade image quality to

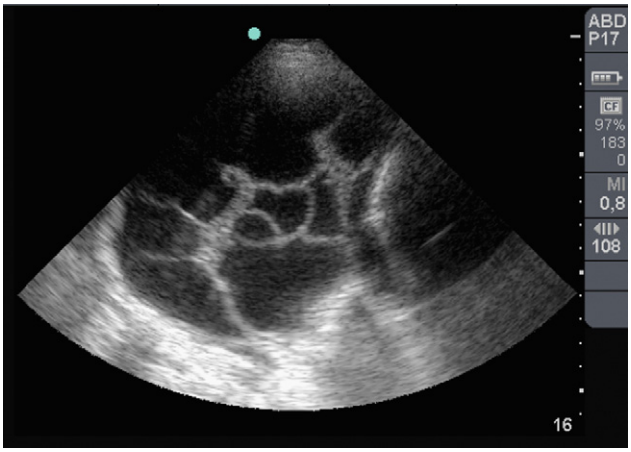

Fig. 6. Multiple septations on ultrasonography in a patient with a complicated parapneumonic effusion.

the point that typical TUS features are no longer discernible.[16] In addition, an extremely echogenic fluid (e.g., empyema, hemothorax) may require great expertise for a confident identification.

Computed tomography

CT enhancement of the pleura is optimal with an intravenous infusion of contrast and image acquisition after 60–90 s delay (late venous phase).[17] The same TUS features that aid in the differentiation of malignant from benign effusions are applicable to contrast-enhanced CT imaging. Thus, the presence of pleural nodules (Fig. 7) or thickening (Fig. 8), usually greater than 1 cm, strongly argues for malignancy.[18] However, these findings, while being very specific ($>$ 90%), are not sensitive enough (about 40%). In mesothelioma, mediastinal pleural thickening and rind-like pleural involvement have been reported in 95%[19] and 70%[20] of cases, respectively. Virtually all patients with empyema (Fig. 9) or tuberculosis show a parietal pleural enhancement on CT (Table 3). In infectious effusions, multiple pockets of gas within the fluid (from gas-forming organisms or following diagnostic thoracentesis or catheter insertion) suggest internal septations. Chest CT is also effective in demonstrating loculated fluid collections, lung parenchymal abnormalities hidden by the effusion, mediastinal lymphadenopathy, pericardial involvement, subdiaphragmatic disease (e.g., liver metastases, gastric tumors) and, with a CT angiography protocol, pulmonary emboli. Lastly, it is particularly useful in distinguishing empyema with air–fluid levels from lung abscess.

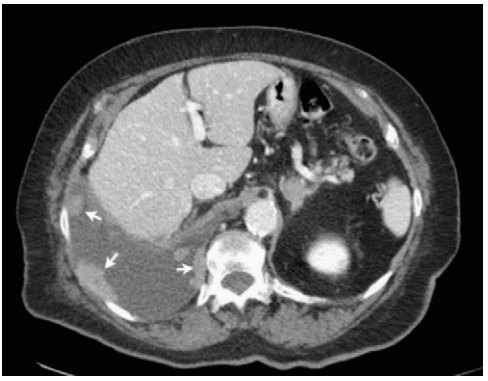

Fig. 7. Pleural nodularity (arrows) in a patient with mesothelioma.

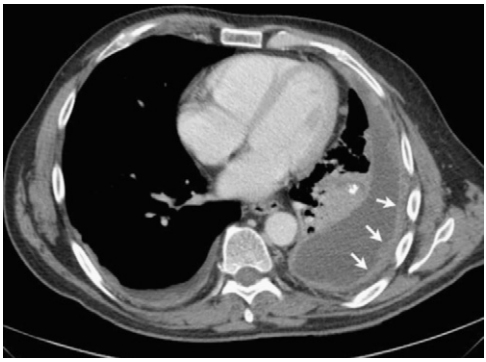

Fig. 8. Pleural thickening (arrows) in a malignant effusion.

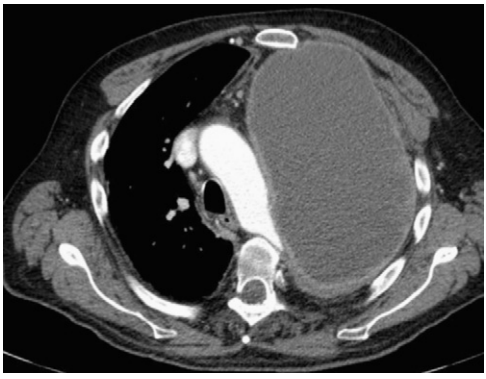

Fig. 9. Pleural enhancement on contrast CT in a patient with postpneumonectomy empyema.

Other imaging techniques

MRI has a limited benefit in pleural diseases. It is useful to characterize a hemothorax because of its ability to image blood and determine the age of the hemorrhage. The only advantage of MRI over CT lies in its superiority in determining whether a pleural tumor has invaded the chest wall and diaphragm.[21] Because of the lower availability and higher cost of MRI, this technique is reserved for difficult cases or those patients with an allergy to iodinated contrast.

The role of metabolic imaging, through 18-fluorodeoxyglucose positron emission tomography (FDG-PET), in the workup of pleural effusions has not been completely defined. Overall, it distinguishes malignant from benign pleural effusions with a sensitivity of 90% and a specificity of 75%–80%, using either visual or semi-quantitative analysis.[22,23] False positive scans may be due to infections (parapneumonics, empyema, tuberculosis) and talc pleurodesis. It should be noted that many studies have selected malignant effusions with associated morphological pleural abnormalities (i.e., thickening, nodules, masses), which tend to inflate test sensitivity. In mesothelioma, FDG-PET has also shown promise in guiding biopsies in the highest area of uptake within the thickened pleura, staging (i.e., nodal status, occult distant metastases), and assessing prognosis (high levels of FDG uptake generally indicating an unfavorable outcome) and response to chemotherapy.[24]

Pleural fluid analysis

Pleural fluid analyses, when combined with a complete patient history, physical examination and radiological studies, allow the clinician to make a definitive or confident diagnosis in almost all

Table 4
Some diagnoses that can be established definitively by pleural fluid analysis.

Condition	Pleural fluid test
Malignancy	Positive cytology
Empyema	Pus or positive culture
Tuberculosis	Positive acid-fast bacilli stain or culture
Hemothorax	Pleural fluid to blood hematocrit ≥ 0.5
Pancreatic diseases	Elevated amylase (pancreatic isoenzyme)
Chylothorax	Triglycerides > 110 mg/dL, chylomicrons present
Lupus pleuritis	High titer anti-dsDNA present
Cholethorax (biliopleural fistula)	Pleural fluid to serum bilirubin ≥ 1

patients.[5] In fact, many diagnoses can be definitely established by pleural fluid analysis in isolation (Table 4).

Appearance of pleural fluid

In some patients, the appearance of the pleural fluid as it is withdrawn from the pleural space yields useful diagnostic information. For example, if pus is aspirated, then the diagnosis of empyema is established. And if it has a putrid odor, anaerobic bacteria are frequently causative. When the pleural fluid is white or milky, the most likely diagnosis is either empyema or a high lipid effusion (chylothorax or pseudochylothorax). Rarely, a milky fluid is secondary to the extravascular migration of a central venous catheter in a patient receiving total parenteral nutrition containing lipids. Centrifugation of the fluid will separate a lipid effusion (supernatant remains white) from an empyema (supernatant is clear). A uniformly bloodstained fluid (i.e., red blood cell count greater than 10,000/μL) is suggestive of malignancy (the most common cause), trauma (including recent cardiac surgery), pulmonary embolism or pneumonia. About 60% and 40% of effusions in patients with pulmonary embolism and cancer, respectively, have a bloody appearance.[25] Finally, more than 85% of transudates do not have the "expected" watery appearance.[26]

Processing of pleural fluid

Aspirated fluid should be immediately placed into appropriate specimen tubes and, ideally, analyzed within 4 h of extraction. Only approximately 20–40 mL of pleural fluid are needed for a complete analysis, which should be divided between three sterile tubes, one each for biochemistry (5 mL), microbiology (5–10 mL) and cytology (10–25 mL). The tubes should contain an anticoagulant, either EDTA or heparin. For the determination of pleural fluid pH it is important to keep the fluid free from air contact or else CO_2 will escape and the pH will increase. Thus, the sample should be maintained anaerobically and the measurement should be accomplished with a blood gas machine.[1] For the aerobic and anaerobic bacterial cultures, it is best to inoculate 2–5 mL of pleural fluid directly into blood culture bottles at the bedside.[27]

Tests routinely performed on pleural fluid include cell count and differential, protein, lactate dehydrogenase (LDH), glucose, pH, cytology and, when infection is a concern, bacterial and mycobacterial cultures. In countries where it is available, adenosine deaminase (ADA) should also be part of the routine analysis.

Transudates versus exudates

The first step in determining the cause of an effusion is to differentiate transudates from exudates. The primary reason is that transudates have a very limited etiological spectrum, whereas exudates are associated with a multitude of diseases and warrant additional diagnostic testing to determine their precise underlying cause.[9] Most transudates are due to heart failure (80%) and liver cirrhosis (13%).[10] Infrequent or rare causes are atelectasis, trapped lung, nephrotic syndrome, peritoneal dialysis, hypoalbuminemia, superior vena cava obstruction, duropleural fistula, extravascular migration of a central venous catheter with saline or dextroxe infusion, and urinothorax.

Table 5
Light's criteria for identifying transudates and exudates.

An exudative pleural effusion meets one or more of the following criteria, while a transudate meets none
- Pleural fluid protein divided by serum protein >0.5
- Pleural fluid lactate dehydrogenase (LDH) divided by serum LDH >0.6
- Pleural fluid LDH $>2/3$ (67%) the upper normal limit for serum LDH

Exudate-transudate discrimination is most commonly done by using Light's criteria (Table 5).[28] For the calculation of protein and LDH ratios included in these criteria, it is not strictly necessary to use a serum sample obtained at the same time as the pleural fluid sample. Values from serum specimens being analyzed a few days before or after the thoracentesis do not significantly alter the fluid categorization.[29]

Light's criteria are stringent and highly sensitive (97.5%) in identifying exudates.[30] However, 30% and 18% of pleural fluid specimens from patients with heart failure and cirrhosis, respectively, fulfill at least one of Light's criteria for an exudate, generally by a small margin.[31] This situation is particularly likely if the patient has been receiving diuretics before the thoracentesis or the pleural fluid contains more than 10,000 erythrocytes/μL. Measuring the difference (gradient) between the serum and the pleural fluid albumin levels is useful in such patients since a difference greater than 1.2 g/dL is consistent with a transudative effusion, even though other criteria for an exudative effusion have been met.[31] More than 80% and 60% of heart failure- and cirrhosis-associated effusions misclassified as exudates by Light's criteria, respectively, are correctly categorized as transudates by the albumin gradient.[31] In the context of mislabeled hepatic hydrothoraces these figures can be improved (77%) if a pleural fluid to serum albumin ratio lower than 0.6, rather than the albumin gradient, is applied.[31] The discovery and implementation in clinical practice of specific biomarkers, such as natriuretic peptides for heart failure, may make exudate-transudate discrimination less crucial, although still valuable.[32]

Pleural fluid differential cell counts

A differential cell count revealing predominantly neutrophils ($>50\%$) indicates that the pleural process is acute, while one revealing predominantly lymphocytes ($>50\%$) indicates that the process is chronic. Parapneumonic effusions are the leading cause of neutrophil-predominant pleural effusions, although they may also be seen in patients with pulmonary embolism, pancreatitis, malignancy (20%) or tuberculosis (10%).[30] The latter two are responsible for almost all lymphocytic effusions. Eosinophilic pleural effusions have more than 10% eosinophils and more than half the cases are malignant or idiopathic, the greater the percentage of eosinophils the less the probability of malignancy is.[33]

Pleural fluid pH and glucose

Low pleural pH (<7.20) and glucose (<60 mg/dL) usually occur together, particularly in parapneumonic effusions. Pleural fluid pH may decrease as a result of increased acid production by pleural fluid cells and bacteria (e.g., complicated parapneumonic effusion and empyema, esophageal rupture) or by an abnormal pleural membrane that blocks hydrogen ion efflux from the pleural space into the circulatory system (e.g., malignancy, tuberculosis, and chronic rheumatoid pleurisy). Virtually all fluids from patients with empyema or esophageal rupture (an anaerobic empyema), 70% of rheumatoid pleuritis, 60% of non-purulent complicated parapneumonic effusions, and less than 10% of malignant and tuberculous effusions exhibit low pleural fluid pH and glucose levels.[25,34]

Pleural fluid acidosis can provide diagnostic and prognostic information in certain clinical scenarios. For instance, a low pleural fluid pH associated with a non-purulent parapneumonic effusion suggests that drainage of the pleural space is necessary to resolve the infectious process. Pus should not be submitted for pH determination because tube drainage should be instituted regardless of the value. Practically speaking, the thick, purulent fluid may clog the blood gas machine. A pH of less than 7.3 in malignant pleural effusions indicates a greatly advanced disease

and, consequently, a higher probability of positive cytological results, shorter life expectancy and poorer response to pleurodesis.[25,35]

Pleural fluid adenosine deaminase

Pleural fluid ADA levels more than 35 U/L in patients with lymphocytic exudates are nearly diagnostic of tuberculous pleurisy (sensitivity 93%, specificity 90%).[36] The main diseases that cause elevation of ADA in addition to tuberculosis are empyema, complicated parapneumonic effusions and lymphoma. The first two are easily distinguished from pleural tuberculosis by the fluid purulence and/or neutrophilia. Notably, when pleural fluid ADA activity is extremely high (>250 U/L), empyema or lymphoma, rather than tuberculosis, should be the first consideration.[36]

Pleural fluid cytology

Cytological examination of pleural fluid is a convenient and relatively efficient way to establish the diagnosis of pleural malignancy. Initial cytological studies are only positive in 50% of malignant effusions. If a second sample is analyzed, test sensitivity increases by 10% (60% total), but additional cytological examinations are not useful.[30] In addition to the number of submitted specimens, other factors may influence cytological yield, namely tumor type (e.g., lower positive results with sarcomas, lymphomas, squamous cell carcinomas and mesotheliomas), tumor burden in the pleural space and the expertise of the cytopathologist. Moreover, true negative findings of pleural fluid cytology in patients with proven malignant disease can be explained by factors unrelated to the metastatic involvement of the pleura (paramalignant effusions), including post-obstructive atelectasis and pneumonia, pulmonary embolism, pericardial involvement and radiation or drug-induced pleuritis.

Immunocytochemistry, as an adjunct to cell morphology, is very helpful in distinguishing benign from malignant mesothelial cells, and mesothelioma from adenocarcinoma. In addition, it may suggest the most likely primary site in patients with pleural metastases. A reasonable choice is a panel that combines EMA (epithelial membrane antigen), CEA (carcinoembryonic antigen), calretinin and thyroid transcription factor-1 (TTF-1) (Table 6).[32] The immunocytochemical analysis of malignant cells in pleural fluid for the expression of estrogen/progesterone receptors and c-erB-2 (breast cancer), as well as EGFR (non-small cell lung cancer)[37] may influence therapeutic decisions.

Pleural fluid flow cytometry is most useful in patients with lymphocyte-predominant exudates when lymphoma is a consideration. This is due to cytometry having the ability to define the clonality of a population of lymphocytes and determine whether cells are from a T or B lineage.

Pleural fluid cultures

Gram stain and pleural fluid cultures (both aerobic and anaerobic) should only be ordered when an infection is suspected. Cultures are expected to be positive in about 22% of patients with non-purulent complicated parapneumonic effusions and 70% with empyemas.[25,38] Negative results may be explained by the previous use of antibiotics or the inadequate processing of fluid samples. Non-groupable streptococci (*S. viridans, S. milleri*) and pneumococcus are the most commonly isolated pathogens in community-acquired empyema, whereas the staphylococcal species (particularly MRSA), *Enterococcus* and Enterobacteriaceae lead in causing hospital-acquired infections.

Table 6
Commonly used immunocytochemical markers on pleural fluid specimens.

Marker	Reactive mesothelial cells	Mesothelioma	Adenocarcinoma
EMA	Negative	Positive	Positive
CEA	Negative	Negative	Positive
Calretinin	Positive	Positive	Negative
TTF-1 (or alternatively napsin A)	Negative	Negative	Positive*

EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen; TTF-1, thyroid transcription factor 1.
* In lung adenocarcinoma.

Direct examination of pleural fluid by Ziehl–Neelsen staining detects acid-fast bacilli in less than 5% of tuberculous effusions. The yield of mycobacterial cultures of pleural fluid and sputum specimens in patients with tuberculous pleuritis is also low (15%–35% and 30%, respectively).[36,39] The use of liquid media (BACTEC or MODS) provides higher yields and faster results than conventional methods.[39]

Other pleural fluid tests

When the hematocrit of the pleural fluid exceeds half the simultaneous peripheral blood hematocrit, the patient has hemothorax. However, measuring the hematocrit in the pleural fluid is not absolutely necessary, since a confident approximation for it can be obtained by dividing the red cell count in the pleural effusion by 100,000. For example, a pleural fluid red cell count of 1,500,000/μL corresponds to a pleural fluid hematocrit of 15%.

An increase in the level of pleural fluid amylase, defined as a value greater than the upper limits of normal serum amylase (100–130 U/L), occurs in cases of malignancy (most common), esophageal rupture and pancreatic diseases.[34] Amylase is of the salivary type in the first two conditions, while the pancreatic isoenzyme predominates in acute or chronic pancreatitis. The highest amylase concentrations are seen in chronic pancreatic pleural effusions (pancreaticopleural fistula).

Triglycerides should be measured in the pleural fluid if a lymphatic leak is a consideration. Concentrations greater than 110 mg/dL strongly argue for chylothorax, whereas levels less than 50 mg/dL make chylothorax highly unlikely. For intermediate levels, between 50 and 110 mg/dL, the pleural fluid should be tested for the presence of chylomicrons, which would confirm the diagnosis of chylothorax.[25]

At cutoff values that achieve 100% specificity for the diagnosis of malignancy, classical tumor markers (CEA, CA 15-3, CYFRA 21-1, CA125) have low sensitivity individually ($<30\%$) and, when combined, a similar sensitivity to that of pleural fluid cytology (approximately 50%).[40] Pleural fluid mesothelin has a greater diagnostic accuracy than other tumor markers. At a cutoff of 20 nM it yields about 70% sensitivity and 90% specificity for identifying mesothelioma against other causes of pleural effusion.[41] Fibulin-3 has recently been reported to be a robust biomarker (sensitivity 84%, specificity 92% at a cutoff value of 346 ng/mL) for discriminating mesothelioma effusions from other malignant and benign effusions.[42] Further confirmatory studies are necessary. As a negative result does not reassure, and a positive one does not preclude the need for obtaining a definitive cytohistological diagnosis, the routine measurement of pleural tumor markers is not warranted.

A neutrophilic exudate with a pleural fluid C-reactive protein concentration >45 mg/L will most likely be parapneumonic (likelihood ratio positive about 8), and if greater than 100 mg/dL complicated parapneumonic (likelihood ratio positive $=5$).[38]

Finally, nuclear acid amplification tests to quickly detect *Mycobacterium tuberculosis* nucleotide sequences in pleural fluid specimens have attracted researchers' interest.[25] Commercially available tests, including the recently developed Xpert MTB/RIF which allows for the simultaneous detection of mutations conferring rifampin resistance,[43] are highly specific. However, they have demonstrated disappointingly low sensitivities (15%–60%) owing to different gene targets as well as different gold standards adopted by various laboratories.[25] For this reason, the use of these assays is still limited to investigational settings.

Undiagnosed pleural effusions

If pleural fluid analyses and CT (or angio-TC according to clinical probability and D-dimer testing) are not informative, there are three options available to the physician: observation, bronchoscopy and pleural biopsy.[5]

Observation

The best course of action if the patient is improving. Many self-limited pleural effusions are probably caused by viruses. Conversely, if the patient has malignancy, a spontaneous improvement

is unlikely to occur. The elapsed time to the re-accumulation of pleural fluid following a therapeutic thoracentesis and the resolution time of specific effusions, whether spontaneous or with treatment, help to narrow the differential diagnosis.[34] Pleural effusions that recur rapidly (24–72 h) after a large volume thoracentesis include hepatic hydrothorax, trapped lung, chylothorax, and peritoneal fluid from malignant ascites or Meig's syndrome. The resolution time for most benign pleural effusions ranges from 1 to 8 weeks. Even untreated tuberculous pleuritis usually resolves after 1–4 months, although the chance of developing active tuberculosis during subsequent years is high. Effusions that typically persist for 6 months or more are limited to unexpandable lung, post-coronary artery bypass graft (CABG) surgery, benign asbestos pleural effusion, rheumatoid pleurisy, lymphangioleiomyomatosis (chylothorax), cholesterol effusions, and yellow nail syndrome.

Bronchoscopy

This is indicated if the patient has one or more of the following: (1) hemoptysis, (2) atelectasis (e.g., mediastinum shifted toward the side of the effusion), (3) parenchymal lesion, (4) centrally located lung mass, or (5) massive pleural effusion.

Pleural biopsy

This is indicated when the less invasive diagnostic methods previously mentioned (e.g., pleural fluid analysis including two cytologies and ADA measurement, CT scan) have not yielded a diagnosis. Pleural biopsy may be blinded, image-guided or thoracoscopic. The latter two have largely replaced blind biopsy owing to their greater sensitivity and safety profile.

Currently, the need to perform a blind needle parietal pleural biopsy is restricted to the diagnosis of tuberculous pleuritis when pleural fluid ADA is unavailable or equivocal. Its yield for malignancy is around 45%, lower than that of pleural fluid cytology.[1] Moreover, in patients with cytology-negative malignant effusions, closed pleural biopsy is diagnostic in less than 20% of cases.[44] This low sensitivity is due to most of the malignant pleural deposits being scattered and occurring primarily along the diaphragmatic pleura and midline, locations that are inaccessible by needle. Conversely, tuberculous granulomata are much more homogeneously distributed over the pleura, resulting in the higher sensitivity ($>80\%$) of this biopsy modality for tuberculosis.[39]

CT-guided cutting needle biopsy is the method of choice whenever pleural thickening and/or nodules, particularly if >1 cm, exist and malignancy is suspected (sensitivity $>85\%$).[45] Specimens can be obtained through the same needle types designed for closed pleural biopsies (e.g., Abrams) or tru-cut needles (generally used to obtain core biopsies from solid tissue material). The procedure is performed by interventional radiologists and has the advantage of visualization and guidance in areas not discernable with TUS.

Thoracoscopy allows direct visualization of the pleural surface, biopsy of areas which appear abnormal, and therapeutic maneuvers such as complete fluid drainage and talc pleurodesis during the same procedure. A medical thoracoscopy (also referred to as pleuroscopy or local anesthetic thoracoscopy) is conducted by an interventional pulmonologist in an endoscopy suite, with the patient under conscious sedation, using a rigid or semirigid thoracoscope, and selecting one or two entry ports in the fifth to seventh intercostal space, mid-axillary line.[46] It is less invasive, safer, better tolerated and therefore preferable to video-assisted thoracoscopic surgery (VATS), which is usually done with multiple entry ports, and under general anesthesia in an operating theater. Pleuroscopy establishes the diagnosis of either tuberculosis or malignant effusions in almost 100% of cases.[46]

Despite invasive procedures, no diagnosis is ever established for approximately 15% of patients. The histological finding of nonspecific pleuritis (or fibrinous pleuritis) has been reported in nearly one-third of pleural biopsies taken by thoracoscopy.[47] In about 10% of patients with this apparently benign result, an underlying malignancy (particularly mesothelioma) is eventually proven during follow-up.[47] An algorithmic approach to the management of pleural effusions is shown in Fig. 10.

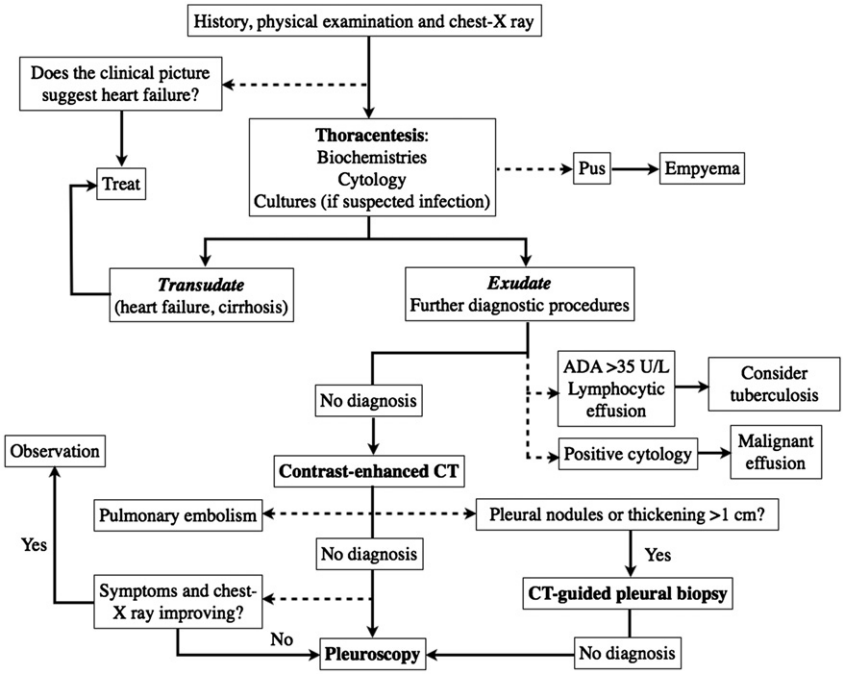

Fig. 10. Flow-chart for the diagnosis of pleural effusions ADA: adenosine deaminase; CT: computed tomography.

Management of selected diseases causing pleural effusions

In this section, salient features of several common causes of pleural effusions will be succinctly reviewed, but a more comprehensive discussion for readers can be found elsewhere.[9]

Heart failure

Heart failure is the leading cause of pleural effusions in octogenarian patients.[10] In most cases, fluid originates in the interstitial spaces of the lung as the result of increased wedge pressure. Contrary to traditional teaching, pleural effusions attributed to isolated right heart failure occur commonly in at least three subtypes of pulmonary arterial hypertension:[48] (1) idiopathic (14%), (2) secondary to systemic autoimmune diseases (33%) such as scleroderma, systemic lupus erythematosus and Sjögren syndrome, and (3) portopulmonary hypertension (30%).

The diagnosis of pleural effusions secondary to heart failure is generally straightforward on clinical grounds. On chest radiographs, these effusions are usually bilateral ($>60\%$), but if unilateral, they are more commonly on the right (only 10% are unilateral on the left).[10] More than 80% of cardiac effusions are small, occupying one-third or less of the hemithorax. Examination of pleural fluid reinforces the diagnosis of heart failure if Light's criteria for a transudate are met. However, in a typical clinical scenario (i.e., classical manifestations of heart failure and bilateral pleural effusions with cardiomegaly) a pleural tap is superfluous.[49]

The natriuretic peptides BNP, NT-proBNP, and MR-proANP are neurohormones synthesized by cardiomyocytes in response to parietal stress secondary to volume or pressure overload. Their elevation in serum or pleural fluid is considered an indicator of heart failure. Pleural fluid levels of NT-proBNP have a pooled sensitivity and specificity of 94%, a positive likelihood ratio of 15, and a negative likelihood ratio of 0.06 in identifying heart failure-related effusions.[50] The most widely used cut-off point is 1500 pg/mL. NT-proBNP is a more useful biomarker of heart failure than BNP

when measured in pleural fluid, but just as effective is MR-proANP.[51] However, because pleural fluid and serum natriuretic peptide levels are closely correlated and display similar discriminatory properties, a blood test alone may be sufficient.[50] Additional advantages of using pleural NT-proBNP are that it perfectly discriminates between transudates of hepatic or cardiac origin, and it also correctly identifies more than 80% of cardiac transudates mislabeled by Light's criteria.[50]

The vast majority of cardiac effusions resolve with diuretics in days to a few weeks. Removal of a moderate amount of fluid (0.5–1 L) should be considered in patients who are refractory to diuretics or have intense dyspnea because of large effusions. Rarely, a pleurodesis with doxycycline is necessary for persistently large symptomatic effusions. Some patients with persistent symptomatic pleural effusions due to heart failure have been managed with an indwelling pleural catheter (IPC).

Hepatic hydrothorax

Hepatic hydrothorax is a transudative pleural effusion that occurs in 6% of patients with portal hypertension and without any other underlying primary cardiopulmonary cause.[52] It develops from the passage of ascitic fluid from the peritoneal cavity to the pleural cavity via small diaphragmatic defects, which is facilitated by the negative intrathoracic pressure generated during inspiration. Approximately 15%–20% of patients with hepatic hydrothorax have no clinically detectable ascites, although it is almost always present in TUS or CT imaging.[53] These effusions are typically unilateral right-sided (80%), with 17% being left-sided and 3% bilateral.[52,53] One-third of hepatic hydrothoraces are large ($\geq 2/3$ of the hemithorax), causing significant dyspnea. Pleural fluid analysis is mandatory to confirm the diagnosis and exclude a spontaneous bacterial pleuritis (SBP). The latter should be considered in any patient with hepatic hydrothorax who develops fever, pleuritic chest pain, encephalopathy or unexplained deterioration of renal function. After excluding pneumonia, the diagnostic criteria for SBP are as follows: (1) positive pleural fluid culture and a pleural fluid neutrophil count > 250 cells/μL, or (2) pleural fluid neutrophil count > 500 cells/μL with a negative pleural fluid culture.[54]

Liver transplantation is the only life-prolonging intervention available for patients with hepatic hydrothorax. Immediate treatment of this condition involves dietary sodium restriction (≤ 2 g/d) and oral diuretics, along with a therapeutic thoracentesis if the pleural effusion is large enough. When there is resistance to medical therapy or side effects prevent maximizing oral diuretics (e.g., hepatic encephalopathy, renal failure), treatment options, while awaiting liver transplantation, include: transjugular intrahepatic portosystemic shunt, serial therapeutic thoracentesis, insertion of an indwelling pleural catheter, and VATS with diaphragm defects repair and pleurodesis (a strategy with significant morbidity and mortality).[52,53] Bedside pleurodesis has largely been unsuccessful due to the lack of pleural symphysis to the chest wall from rapidly ongoing pleural fluid accumulation. In cases of SBP, treatment with a third-generation cephalosporin should be empirically instituted, but chest tube drainage is never indicated unless pus is present.[54] In addition, life-long secondary prophylaxis with norfloxacin is recommended.

Malignant effusions

Pleural metastases

The majority of malignant pleural effusions are the result of metastases to the pleura from other sites. In our unpublished experience with 790 malignant effusions, the primary tumors were, in decreasing order of frequency: lung (37%), breast (17%), unknown site (10%), lymphoma (9%), gastrointestinal (8%), ovary (7%), and mesothelioma (3%). The frequency of primary pleural neoplasms (mesothelioma) varies widely according to the geographical area. Notably, pleural metastases may occur without the presence of effusion (''dry pleural dissemination'').

In about two-thirds of malignant effusions due to lung cancer, the diagnosis of both pleural metastasis and primary tumor is made simultaneously.[55] Conversely, 97% of patients who are evaluated for malignant effusions which eventually are ascribed to breast cancer had a previous personal history of this tumor type.[55] Malignant effusions are unilateral in 85% of cases and

two-thirds occupy half or more of the hemithorax on chest radiographs.[56] Chest CT should be done before the effusion is completely drained to ensure optimal diagnostic utility. More than half of CT scans in malignant pleural effusions do not show any pleural finding other than the pleural fluid, as described earlier. For the identification of the primary tumor site, initial studies should include chest CT, looking for lung cancer and mediastinal lymphadenopathy suggestive of lymphoma, and mammography to unravel a breast primary. If these studies are not contributory, an abdominal CT is indicated.

The prognosis of patients with metastatic malignant pleural effusions is dismal, with a median life expectancy of 4–6 months.[35] But survival is longer in breast cancer (13 months) and shorter in lung cancer (3 months).[35]

Mesothelioma

Malignant pleural mesothelioma is linked to occupational and environmental exposure to asbestos, and develops after a long latency period, often more than 30 years. Crocidolite (blue asbestos) is the most carcinogenic form. The disease mainly affects men aged 50–70. The most frequent symptoms at presentation are dyspnea, chest pain and weight loss. Radiographically, pleural effusions are mostly unilateral (90%), and more frequently involve the right hemithorax (60%).[9] Although metastases are not clinically evident at diagnosis, PET series reveal nodal

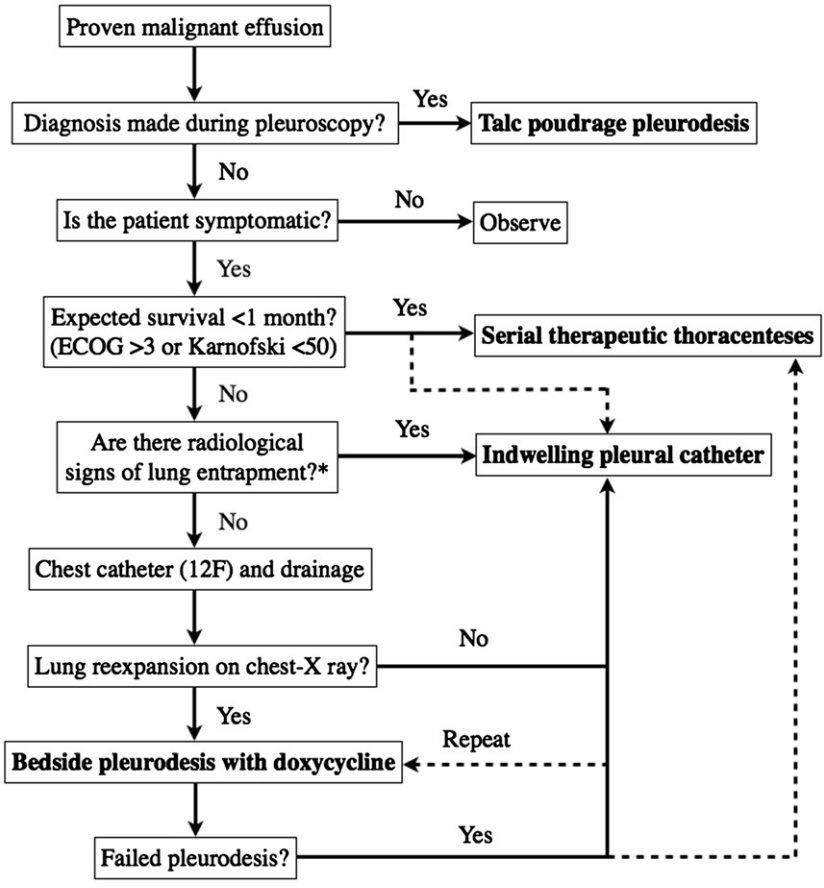

Fig. 11. An algorithmic approach to the treatment of malignant effusions *Lack of lung reexpansion after thoracentesis, or endobronchial obstruction with secondary atelectasis.

involvement and extrathoracic disease in about 25% of patients,[57] while necropsy series demonstrate distant metastases (e.g., liver, peritoneum) in 55%.[58] There are three main histological types of mesothelioma: epithelial ($>50\%$), sarcomatoid (10%), and biphasic or mixed. Median survival ranges, depending on the stage, from 7 to 17 months.[59]

Treatment of malignant effusions

Management of malignant effusions centers on palliation of dyspnea and prevention of the reaccumulation of pleural fluid to provide the highest possible quality of life, regardless of the need for other therapies. Treatment should be individualized based on the symptom's intensity, primary tumor origin, estimated survival, functional status, ability of the lung to reexpand after removal of pleural fluid, local expertise, resources available and, ultimately, patient's preferences (Fig. 11).[60] These factors determine whether the best management is one or a combination of the following: observation, therapeutic thoracentesis, systemic therapy (chemo- and/or radiotherapy), intrapleural injection of a sclerosing agent (pleurodesis), and implantation of an IPC.

For patients with an asymptomatic pleural effusion, no intervention is required and they can remain under observation. Serial large volume thoracenteses are usually reserved for patients with an anticipated life expectancy <1 month (ECOG performance status ≥ 3 or Karnofsky scale score ≤ 50).[61] Malignant pleural effusions related to small-cell lung cancer, lymphoma and breast adenocarcinoma may remit with chemotherapy, though early concurrent pleurodesis or, at least, a therapeutic thoracentesis before starting chemotherapy is favored.[62]

The two main treatments for the fluid accumulation with malignant effusions are pleurodesis and IPC. With pleurodesis, a chemical irritant is injected into the pleural space, creating an intense inflammation ultimately leading to the fusion of the visceral and parietal pleura.[63] Three prerequisites for a pleurodesis being attempted are[56]: (1) the patient has a symptomatic (dyspnea) malignant effusion, (2) the survival expectancy is >1 month, and (3) complete mainstem bronchial obstruction or lung entrapment (i.e., lung failure to reexpand after drainage of the effusion because of mechanical restriction of the visceral pleura) do not exist. Pleurodesis can be done through a chest tube or at the time of thoracoscopy. Many different sclerosing agents are available, but the most frequently used include talc, doxycycline, povidone and silver nitrate. The efficacy of pleurodesis is defined as complete success (absence of fluid reaccumulation until death), partial success (partial reaccumulation of fluid, but no further therapeutic thoracentesis required for the remainder of the patient's life) and lack of success (failure). Global response refers to the sum of the complete and partial responses. Talc pleurodesis via thoracoscopic insufflation (''poudrage'') has been the most commonly used method for pleural symphysis.[64] Talc can also be administered mixed with saline (talc ''slurry'') via a chest tube. When used, 4 g of a calibrated form in which the smaller particles (<10 μm in diameter) have been removed is the preferred choice.[56,65] Otherwise, the small talc

Table 7
How to perform doxycycline pleurodesis.

- Insert a small-bore chest catheter (12F)
- Drain pleural fluid in a controlled fashion*
- Confirm full lung reexpansion with a chest radiograph. If at least a partial pleural apposition is achieved, pleurodesis may still be attempted
- Premedication with a sedative agent (e.g., midazolam) may be used at the clinician's discretion
- Inject 500 mg of doxycycline in 100 mL of saline into the pleural space
- Clamp chest catheter for 1–2 h and then open it for drainage
- Remove chest tube within 12–24 h in the absence of excessive fluid drainage (>250 mL/d); or, a second dose of the sclerosing agent can be administered
- Pain during or after instillation of doxycycline should be controlled with opioid analgesics (e.g., morphine, hydromorphone, fentanyl)
- The entire pleurodesis procedure is normally accomplished in 12 h–72 h
- Assess chest radiograph at 30 days and then, according to the findings, at the physician's discretion

* A trial of intrapleural fibrinolytics may be a useful adjunct therapy for patients with multiloculated malignant effusions which fail to drain adequately, before attempting pleurodesis.

particles can be absorbed systemically through the pleural capillaries, precipitating an acute respiratory distress syndrome. We only recommend talc poudrage pleurodesis when pleural nodularity and/or thickening consistent with malignancy is visualized during an exploratory thoracoscopy.[66] Even so, if the diagnosis of malignant effusion has been already established by pleural fluid cytology or CT-guided pleural biopsy, an invasive intervention for palliation is hardly justified. Under these circumstances, instillation of doxycycline at bedside is the preferred technique (Table 7).[67] In a recent retrospective analysis, the reported overall success rates for 450 talc poudrage and 138 doxycycline pleurodesis procedures were 88% and 79% respectively.[68] Of note, patients with mesothelioma or lung cancer had poorer responses to pleurodesis.

More recently, IPC with subsequent patient-driven drainage over time is being increasingly recommended for the effective control of symptomatic malignant effusions. It consists of a 15.5F, 66 cm silicon rubber catheter with multiple fenestrations along the 24 cm proximal, which can be inserted on an outpatient basis or at bedside (Fig. 12). The catheter is tunneled and has a valve on the distal end that prevents fluid or air from passing in either direction unless the catheter is accessed with the matched drainage line. Pleural fluid is drained by the patient, caregiver or visiting nurse at home during regular intervals (e.g., every 2–3 days) or on an "as required" basis, by inserting the access tip of the drainage line into the valve of the catheter and then draining the fluid via an external tube into vacuum bottles (Fig. 13).[69] Certainly, IPCs should be considered the best option in patients with lung entrapment (see below) (Fig. 14) and also an attractive remedy following unsuccessful pleurodesis, yet some centers use them as primary management.[66,70] Symptomatic improvement is obtained in 95% of patients and spontaneous pleurodesis occur in 46% after an average of 52 days.[71] Resolution of malignant pleural effusions allows removal of the IPC

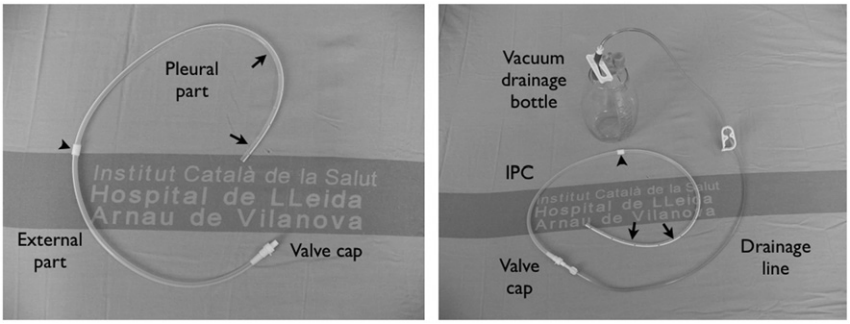

Fig. 12. Indwelling pleural catheter (IPC) including an intrapleural part having fenestrations for fluid drainage (arrows), a polyester cuff that resides in a subcutaneous tunnel to reduce infection risk and secure the catheter (arrowheads), and an external portion containing a one-way valve which can be connected to a vacuum drainage bottle.

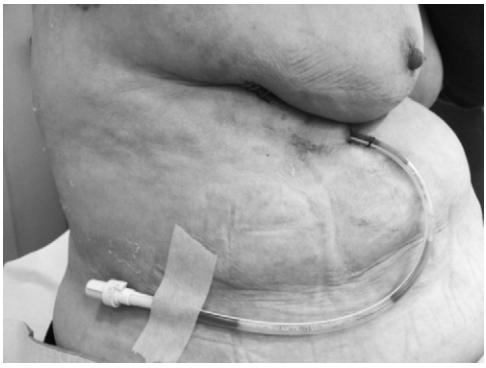

Fig. 13. Indwelling pleural catheter in place.

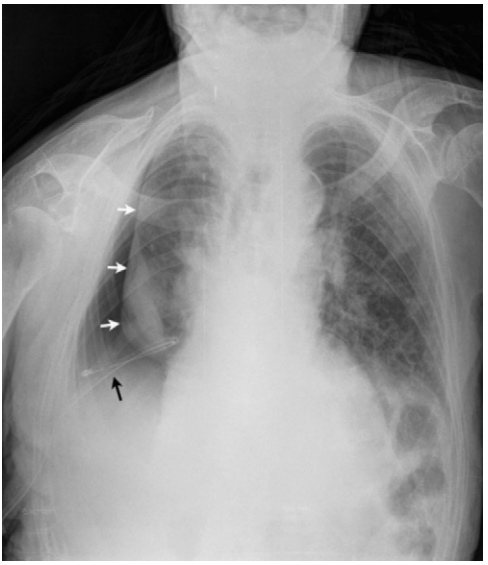

Fig. 14. Unexpandable lung (white arrows) after chest tube (black arrow) drainage in a patient with a malignant effusion.

before death in 60% of treated patients.[60] IPC-related complications are relatively rare and include catheter malfunction, symptomatic loculation of fluid, catheter blockage, pneumothorax, cellulitis and empyema. A recent randomized controlled trial demonstrated that there was no significant difference between IPCs and talc slurry pleurodesis in relieving patient-reported dyspnea.[72] In the future, delivering sclerosant agents via IPCs may lead to even greater patient benefits.[73]

Parapneumonic effusions

Approximately three-fourths of bacterial infections of the pleural space are parapneumonic in origin, the remaining resulting from complications of trauma, surgery, abdominal infections, esophageal perforation, and other conditions.[74] About 20% of patients with community-acquired pneumonia have evidence of pleural effusion in a standard chest radiograph, of whom 30% progress to complicated parapneumonic effusion or empyema.[75] Parapneumonic effusions that require chest tube drainage for resolution are designated as complicated parapneumonics. An empyema is defined as pus in the pleural space and virtually always requires drainage; the exception being small empyemas which may resolve with prolonged antibiotic therapy along with image-guided maximal needle aspiration, if technically feasible. The clinical challenge is to identify which non-purulent parapneumonic effusions also need intercostal tube drainage.[74] This is a critical decision because the delay of complicated effusions pleural drainage is associated with increased morbidity, duration of hospital stay, and mortality. The presence of any of the criteria listed in Table 8 strongly suggests that the parapneumonic effusion is unlikely to be cured with antibiotics alone and, therefore, tube thoracostomy is mandatory.[76] It should be emphasized that it is better to err on the side of caution by using chest tubes which might not be necessary rather than to leave a parapneumonic effusion undrained and at risk of empyema formation.

Although not formally tested in a randomized controlled trial, Dr Light has largely recommended that a therapeutic, rather than a diagnostic, thoracentesis should be performed at the first encounter of all patients with parapneumonic effusions.[1,9] Since a pleural tap to search for poor prognostic factors in pleural fluid (Table 8) is obligatory, once the needle is in the pleural space it seems prudent to take all the fluid out manually. If the fluid does not reaccumulate after the initial therapeutic thoracentesis, one need not worry about the pleural effusion. Exceptions to this strategy are large,

Table 8
Indications of pleural fluid drainage in parapneumonic effusions.

- Pleural effusion occupying $\geq 1/2$ of the hemithorax on a chest radiograph
- Loculated effusion on a chest radiograph, TUS or CT*
- Aspiration of pus (empyema)
- Pleural fluid pH < 7.20
- Pleural fluid glucose < 60 mg/dL
- Identification of microorganisms by Gram stain and/or cultures of pleural fluid
- No clinical improvement with antibiotics alone

* Particularly if there is parietal pleural enhancement with contrast-CT.

multiloculated effusions and empyemas, which are difficult to completely remove at one time; the direct insertion of a chest tube being the best approach.

Most complicated parapneumonic effusions and empyemas are loculated or septated due to fibrin bands that result from intense pleural inflammation, a circumstance which makes drainage of the pleural space difficult and causes lack of clinical response. Theoretically, intrapleural fibrinolytics disrupt the fibrinous pleural septations, facilitating drainage of infected fluids. The efficacy of fibrinolytics in complicated parapnemonic effusions is a matter of debate. A metaanalysis of seven randomized controlled trials, totaling 801 patients, revealed that fibrinolytic therapy was beneficial for the outcomes of treatment failure (i.e., surgical intervention or death) and surgical intervention.[77] The metaanalysis included the two largest trials ever performed: the Multicenter Intrapleural Sepsis Trial (MIST)1,[78] which did not substantiate any positive effect of intrapleural streptokinase, and the recently published MIST2.[79] The latter demonstrated a significant radiological improvement in the area of pleural opacity using a combination of intrapleural 10 mg tPA and 5 mg DNase, given twice daily for three days, compared with placebo.[79] Aside from that, treatment with tPA or DNase alone was shown to be ineffective.[79] DNase is an enzyme which cleaves free DNA and reduces pus viscosity.

Failure to improve clinically and radiographically after 7 days of antibiotics and chest tube drainage plus fibrinolytics (and DNase) in complicated parapneumonics is a common criterion for considering VATS with adhesiolysis, and possible minor decortication.[74] A summary flowchart for managing parapneumonic effusions is shown in Fig. 15.

Needless to say, all patients with parapneumonic effusions should receive antibiotics. For community-acquired pleural infections the suggested regimen is amoxicillin-clavulanate for a minimum of 3 weeks.[74,76] In penicillin allergic patients, moxofloxacin or the combination of levofloxacin and clindamycin can be used.

Other pleural effusions

Tuberculous effusions

Tuberculous pleural effusions are thought to result from the breakdown of a small subpleural caseous focus that releases its content into the pleural space, resulting in an immunological hypersensitivity reaction and formation of a paucibacillary effusion. Patients with pleural tuberculosis are typically young (median age of 35 years) and usually have a subacute illness characterized by fever (85%), chest pain ($> 70\%$), and cough ($> 60\%$).[80,81] About 10% of patients have human immunodeficiency virus coinfection, and tuberculin skin tests are negative in 25%.[81] Tuberculous effusions are nearly always unilateral and half of them occupy $\geq$ ½ of the hemithorax or are loculated.[81] Coexisting lung infiltrates may be seen in approximately 15% of chest radiographs and more than 60% of CT scans.[81] Sputum specimens stained with Ziehl–Neelsen dyes are microscopy positive in 15% of patients.[81]

Pleural fluid with tuberculous pleuritis is invariably an exudate, with lymphocytic predominance in 90% of cases.[39] Patients with fewer than 50% of lymphocytes in their pleural fluids are generally in an early stage of the disease, when mycobacterial cultures of sputum and pleural fluid are more likely to be positive.[81] ADA testing of pleural fluid is the easiest method for establishing the

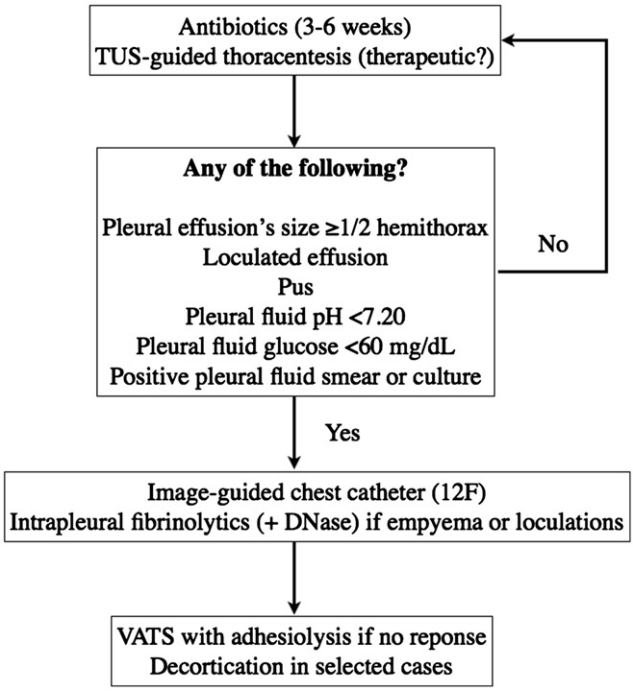

Fig. 15. Sequential management of parapneumonic effusions TUS: transthoracic ultrasound; VATS: video-assisted thoracoscopic surgery.

diagnosis of tuberculous pleurisy. Even in areas with low prevalence of tuberculosis, a low ADA test is valuable for ruling out the disease due to its high negative predictive value.[36] In clinical practice, a young patient with fever, a lymphocytic exudate with high ADA activity and a negative pleural fluid cytology should be considered to have tuberculosis until proven otherwise, and standard antituberculous therapy commenced.[39] A therapeutic thoracentesis is advisable in large effusions provoking breathlessness.

Pulmonary embolism

In any exudative effusion without diagnosis, pulmonary embolism should be ruled out. While the clinical probability of pulmonary embolism is unlikely after applying well-established clinical decision rules (Wells or Geneva scales), a normal D-dimer blood test nearly excludes the diagnosis and further testing is not needed. For the remaining situations (i.e., unlikely pretest probability with increased D-dimer, or patients in the pulmonary embolism "likely" category) an angio-CT should be ordered. Leg pain or swelling is present in less than 40% of the cases upon physical examination.[82]

Pleural effusions occur in 20%–50% of patients with pulmonary embolism, depending on whether chest radiograph or TUS/CT imaging is being evaluated.[83] They are unilateral in 85% of cases, and occupy a third or less of the hemithorax in 90%.[82–84] The effusions may become loculated in about 20% of patients, especially if the diagnosis is delayed for more than 10 days after symptoms develop.[83] The pleural fluid is an exudate with variable biochemical characteristics. The presence of a pleural effusion does not alter anticoagulation therapy.

Pericardial diseases

Post-cardiac injury syndrome is an immunological entity characterized by the onset of fever, pleuropericarditis and, occasionally, pulmonary infiltrates in the days, weeks or months following an acute myocardial infarction (Dressler's syndrome), cardiac surgery with pericardiotomy, blunt chest

trauma, or even minor precipitating events such as percutaneous coronary intervention, pacemaker implantation or catheter ablative therapy.[85] It affects less than 1% and 15% of patients after myocardial infarction and cardiac surgery, respectively.[86] Pleural effusions are small to moderate in size, unilateral, left-sided and exudative. Treatment consists of aspirin (Dressler's syndrome) or ibuprofen (remaining cases). Nonresponders require tapering doses of steroids (prednisone 0.5 mg/kg/d) over a span of 4–8 weeks. The use of oral colchicine in the postoperative period of a cardiac surgery (two 1 mg doses on the first day followed by a maintenance dose of 0.5 mg twice daily for 1 month) significantly reduces the risk of post-cardiac injury syndrome (odds ratio = 0.38).[85]

At least one-fourth of acute pericarditis and more than half of constrictive pericarditis cases have associated pleural effusions, which are small, but predominantly left-sided in the former and bilateral in the latter.[86] Although the characteristics of the pleural fluid have not been well reported, effusions are exudates in acute pericarditis and mostly exudative in constrictive pericarditis. Non-steroidal anti-inflammatory drugs or aspirin are the primary treatment for acute pleuropericarditis. Adjunctive colchicine (0.5 mg daily for 4–6 weeks) should be considered for preventing recurrences.[86]

Post-coronary artery bypass surgery

Almost all patients develop pleural effusions after CABG surgery.[1] The majority are unilateral, left-sided, small, and gradually disappear. However, the prevalence of pleural effusions occupying more than 25% of the hemithorax averages 10%.[87] Patients with these moderate to large postoperative effusions have shortness of breath. Chest pain and fever are unusual and their presence suggest pleural infection or postcardiac injury syndrome.[87] The differential diagnosis of post-CABG pleural effusions includes heart failure, pleural infection, pulmonary embolism, and chylothorax. Effusions that occur within the first month following surgery are thought to be due to the trauma of surgery itself, and therefore, are frequently bloody exudates which may contain more than 10% eosinophils.[1] Late effusions, which reach their maximum size more than 1 month post-CABG, are lymphocytic exudates probably representing a variant of the post-cardiac injury syndrome. Most patients with pleural effusions after CABG are cured with 1–3 therapeutic thoracenteses.[87] Though frequently prescribed, there is no evidence that the administration of anti-inflammatory agents is beneficial.

Autoimmune rheumatic diseases

Rheumatoid arthritis and systemic lupus erythematosus are the two autoimmune rheumatic diseases typically associated with pleural effusions.[88] Clinically apparent pleural effusions have been reported in 30% of patients with lupus during the course of the illness.[89] However, they are the initial manifestation of the disease in less than 5% of the cases.[89] The most common radiographical picture is a small to moderate unilateral or bilateral (40%–50%) effusion that could be associated with pericardial involvement.[9] The pleural fluid is an exudate with normal pH and glucose levels, and high antinuclear antibodies titers ($\geq$ 1:160).[9] Routine measurement of the pleural fluid antinuclear antibodies is unnecessary because it adds essentially nothing to the information obtained from the test on the serum. Nevertheless, testing can be helpful in lupus patients with pleural effusions of unknown significance in that negative or low pleural titers argue against lupus as the etiology of the effusion, and other causes should be pursued.[90] Treatment of lupus pleuritis should be individualized depending on the severity of symptoms: small asymptomatic effusions may not require treatment; non-steroidal anti-inflammatory drugs are useful for mild pleurisy, while corticosteroids therapy is indicated for more severe cases.

In rheumatoid arthritis, pleural effusions are identified in 4% of patients using chest CT.[91] Three-fourths of rheumatoid pleuritis cases occur in men with a long-standing history of rheumatic disease. When present, the effusion is small to moderate in size, and only occasionally symptomatic. The fluid is distinctive, with a low glucose level (80%) and pH, and the presence of tadpole-like macrophages (60%) on cytological smears.[91] Other than the usual control of the underlying arthritic process, symptomatic effusions may also require therapeutic thoracentesis and intrapleural instillation of corticosteroids.[91]

Chylothorax and cholesterol pleural effusions

Chylothorax and cholesterol effusions (also known as chyliform effusions or pseudochylothorax) are lipid-rich pleural effusions, which may give fluid a milky or opalescent appearance. The lipid content consists of chylomicrons/triglycerides in chylothorax, and cholesterol in cholesterol effusions. Chylothorax implies a chyle leak due to the disruption or blockade of the thoracic duct or its tributaries. Cholesterol effusions have no relationship with lymphatic vessels; rather, they are associated with long-standing pleural effusions (>5 years) with or without thickened pleural membranes.[92] The causes of chylothorax can be divided into four major categories[93]: (1) surgery (congenital heart and diaphragmatic-hernia repair surgeries, esophagectomy, lung resection), (2) tumors (lymphoma), (3) miscellaneous (cirrhosis, lymphangioleiomyomatosis, superior vena cava syndrome, use of dasatinib), and (4) idiopathic (10%). Cholesterol effusions are rare conditions secondary to tuberculosis or chronic rheumatoid pleuritis.

Notably, the absence of a milky appearance in chylothoraces occurs in half the patients, especially if they are fasting (e.g., in the postoperative period) or malnourished. The fluid is an exudate with high triglyceride concentrations in more than 85% of the cases.[93] The finding of a transudate should raise the suspicion of cirrhosis, where chylothorax appears to be produced by the transdiaphragmatic movement of chylous ascites to the pleural cavity. Pleural fluid in cholesterol effusions is an exudate characterized by cholesterol levels greater than 200 mg/dL, a cholesterol to triglyceride ratio >1, and cholesterol crystals on polarized microscopy (pathognomonic, but not a prerequisite).

Management of a chylothorax should proceed from conservative to more invasive treatments. There are three different strategies[92–94]: (1) treatment of the underlying condition (e.g., chemotherapy with or without radiation therapy for lymphomas); (2) conservative management, which consists of therapeutic thoracentesis or chest tube drainage for symptomatic relief, a period of total parenteral nutrition, and the use of octeotride to reduce intestinal chyle production; and (3) surgical and/or palliative options should be considered when conservative measures during a 2-week period have been unsuccessful, severe nutritional complications exist, or the average daily chyle loss exceeds 1–1.5 L for a 5–7 day period. Treatment modalities in high-output chylothoraces include embolization of the thoracic duct using interventional radiologic techniques, and VATS for the surgical repair of the lymphatic disruption or ligation of the thoracic duct. In low-output persistent chylothoraces or those caused by malignancy, controlling pleural effusion may require pleurodesis or an IPC.

Hemothorax

Hemothorax is the presence of a significant amount of blood in the pleural space. It is most commonly the result of penetrating or non-penetrating chest trauma, but there are also iatrogenic (e.g., pleural procedures, placement of a central venous catheter) and non-traumatic hemothoraces (e.g., malignant pleural disease, anticoagulant therapy, thoracic endometriosis, and spontaneous hemopneumothorax).

The treatment of choice is the immediate insertion of an intercostal chest drain, which allows for the complete evacuation of blood from the pleural space, the quantification of blood loss, and diminishing the incidence of subsequent fibrothorax and empyema. Immediate surgery, through VATS (hemodynamic stability) or thoracotomy (hemodynamic instability), is indicated in the situations listed in Table 9.[95]

Table 9
Indications of immediate surgical exploration in patients with hemothoraces.

- Blood loss through the chest tube greater than 1.5 L/24 h
- Blood loss less than 1.5 L, but hemodynamic instability and need for continuous blood transfusion
- Pleural bleeding of more than 250 mL/h for 4 consecutive hours

Pancreatic pleural effusions

Small bilateral pleural effusions are common in patients with acute pancreatitis and result primarily from the transdiaphragmatic transfer of fluid arising from inflammation of the pancreas and contiguous diaphragm. The effusion usually resolves as the inflammation subsides. However, when acute or chronic pancreatitis is complicated with a pancreatico-pleural fistula, chest symptoms (pain and dyspnea) dominate the clinical picture. In this setting, pleural effusions are large, sometimes occupying the entire hemithorax, and usually unilateral left-sided.[9] They reaccumulate rapidly after a therapeutic thoracentesis. The diagnosis is established by measuring the pleural fluid amylase, while the fistulous tract may be demonstrated by CT or magnetic resonance cholangiopancreatography. Three-fourths of patients who develop a pancreatico-pleural fistula have a pancreatic pseudocyst.[96] Initially, conservative measures with the aim of minimizing pancreatic secretions, while waiting for the spontaneous sinus tract closure, are recommended for a 2–4 week period. They consist of nasojejunal feeding, octreotide to reduce fistula output, and serial thoracentesis as needed. Refractory cases may require endoscopic retrograde cholangiopancreatography with bridging stent placement into the main pancreatic duct, and eventually surgery.[96]

Unexpandable lung

Unexpandable lung is the inability of the lung to fully expand to the chest wall. In clinical practice, the mechanisms for it are either a visceral pleural restriction or an endobronchial obstruction.[97] Pleural conditions that result in unexpandable lungs are lung entrapment (or entrapped lung) and trapped lung. Lung entrapment refers to visceral pleural restriction caused by an active inflammatory or malignant pleural process. For instance, lung entrapment complicates about 5%–20% of malignant effusions, particularly mesothelioma and lung cancer.[98] In these cases, pleurodesis is very unlikely to be successful. The diagnosis is suspected when the lung only partially reexpands on a chest radiograph after a therapeutic thoracentesis or chest tube drainage (pneumothorax *exvacuo*), and patient's symptomatic improvement is inadequate. The pleural effusion is typically exudative. An endobronchial obstruction by a tumor can have the same effect and may require bronchoscopic removal before considering pleurodesis.

On the other hand, trapped lung occurs when the visceral pleura become encased with a fibrous peel or rind, as a late consequence of an inflammatory condition (e.g., parapneumonic effusions, empyema, hemothorax, uremia, post-CABG surgery, and rheumatoid pleuritis). Current symptoms of acute pleural inflammation (fever and pleuritic pain) are generally absent, but may have been present in the past.[98] An effusion's size remains remarkably constant and pleural fluid analysis reveals either transudate or borderline exudate, mainly of lymphocyte predominance. Sometimes, trapped lung can be confirmed by the demonstration of a thick visceral pleural peel on chest CT. Patients with chronic asymptomatic pleural effusions only need reassurance, since any pleural drainage procedure will lead to fluid reaccumulation. If the fibrous rind is extensive, produces dyspnea and the patient is a good surgical candidate, decortication may be considered.[99]

Pleural effusions in renal disorders

Pleural effusions are reported in around 20% of patients with nephrotic syndrome.[9] They arise from an imbalance of the Starling forces, are usually bilateral and transudative. Finding an exudate should prompt an evaluation for pulmonary embolism.

Some patients with the uremic syndrome develop a fibrinous pleuritis, which may or may not be symptomatic (fever, chest pain, dyspnea). Effusions are mainly unilateral and may be large.[100] The pleural fluid is an exudate, and the diagnosis is one of exclusion in a patient with chronic kidney disease.[100] Pleuritis usually improves in weeks with an optimal program of dialysis and related therapy, yet one-fourth persist, progress or recur.[9] Occasionally, a marked pleural thickening results in restrictive ventilatory dysfunction that might lead to consideration for decortication. Patients who receive long-term hemodialysis often develop pleural effusions evolving from hypervolemia and heart failure.[101]

Pleural effusions take place in about 2% of patients undergoing continuous ambulatory peritoneal dialysis (CAPD).[102] They may be observed from the initiation of CAPD to several years later, with half

the cases during the first month. Nearly 90% of CAPD patients have a right-sided effusion resulting from the movement of dialysate fluid from the peritoneal cavity to the pleural space, as in hepatic hydrothorax.[102] A pleural fluid analysis reveals a transudate with a protein level consistently lower than 1 g/dL and glucose concentrations of several hundred to more than 1000 mg/dL. Therapy comprises transitory interruption of CAPD for 4–6 weeks, and therapeutic thoracentesis if the effusion is symptomatic. CAPD can then be resumed in half the patients without recurrence of the effusion.[102] If the effusion returns, pleurodesis or thoracoscopic repair of the diaphragmatic defects can be attempted. Ultimately, hemodialysis offers a temporary or permanent treatment modality for renal replacement if CAPD cannot be done due to pleural effusions.

Urinothorax is a collection of urine extravasated from the retroperitoneal to the pleural space. It generally develops in association with bilateral obstructive uropathy or trauma (usually iatrogenic).[92] Most, but not all effusions are unilateral, transudative, and have a pleural to serum creatinine ratio >1.[103] Management involves treating the underlying cause of the urine leak.

Bedside pleural techniques

General practitioners need to be familiar with the basic pleural techniques aimed at diagnosing (diagnostic thoracentesis) and treating (therapeutic thoracentesis and chest catheters) patients with pleural effusions.[104] These procedures should ideally be performed with bedside ultrasound guidance for patient safety. A wide variety of portable ultrasound machines can be used for pleural abnormalities visualization. A machine with a convex, microconvex (preferred) or sector probe of 3.5–5 MHz is suitable for examining the pleural space, while linear array transducers (7.5–10 MHz) are best for imaging the parietal pleura. Bedside TUS increases the rate of accurate puncture sites by 26% and prevents possible accidental organ puncture in 10%, when compared with puncture site localizations by clinical examination and chest radiograph.[105] The sensitivity and specificity of clinical examination for fluid detection using TUS as the gold standard are only 77% and 60%, respectively.[105]

Diagnostic thoracentesis

Diagnostic thoracentesis refers to the percutaneous aspiration of a small volume of pleural fluid to determine the etiology of a pleural effusion. Therefore, patients with undiagnosed pleural effusions should be submitted to this procedure, with two possible exceptions[104]: (1) small pleural effusions, defined as those thinner than 1 cm on decubitus chest films or 2–2.5 cm on CT/TUS; if aspiration is attempted anyway, it should be done with 25G ultrathin needles under TUS guidance; and (2) clinically evident heart failure without atypical features (i.e., unilateral left-sided effusion, bilateral effusions of disparate sizes, chest pain, fever, or no response to diuretics). Thoracentesis is urgent when hemothorax or empyema is being considered, because immediate tube thoracostomy is indicated in these situations.

There are no absolute contraindications to thoracentesis. Relative contraindications include uncontrolled coagulopathy, a very small volume of pleural fluid which creates a significant risk of iatrogenic pneumothorax or organ puncture, and cutaneous infection at the site of needle insertion.[104] Some guidelines recommend correcting an international normalized ratio to less than 2, transfusing platelets to more than 50,000/μL, or withholding certain medications (oral anticoagulants, heparin or clopidogrel) before performing minimally invasive procedures such as thoracentesis.[106] Although evidence supports no routine correction of these bleeding risks prior to thoracentesis,[107] in few situations is thoracentesis so urgent that it cannot wait for coagulopathy to be reversed.

Thoracentesis is considered a safe procedure with few complications. Pneumothorax occurs in 6% of the patients, but seldom requires the placement of a chest tube.[108] However, the pneumothorax rate is close to zero with TUS guidance. Hemothorax is a rare complication ($<1\%$) induced by the laceration of an intercostal vessel.[109] It is more prevalent in the elderly with chronic kidney disease, especially when the selected puncture site is close (6–9 cm) to the spine where the often tortuous

intercostal arteries run unprotected by the ribs.[109] Obtaining a chest radiograph after diagnostic thoracentesis is not required unless air is withdrawn, multiple attempts have been made or the patient develops symptoms such as dyspnea, cough or chest pain.[104]

Therapeutic thoracentesis

In therapeutic thoracentesis, large amounts of pleural fluid are removed to alleviate dyspnea caused by a large effusion. Occasionally, it can also be used as an alternative treatment modality in parapneumonic effusions, as mentioned earlier.[1] The fluid is generally aspirated manually via commercially available needle-catheter systems. Two precautions are important to bear in mind. First, removing as little as 300–500 mL is generally sufficient to relieve dyspnea in patients with undiagnosed effusions. This is particularly compelling in suspected but unconfirmed malignant effusions, in which a complete drainage of the pleural space may prevent or impede subsequent diagnostic (further pleural cytologies, pleural biopsy, thoracoscopy) and therapeutic procedures (pleurodesis, IPC) until fluid reaccumulates. Second, removal of more than 1–1.5 L at one time should generally be avoided to prevent reexpansion pulmonary edema ($< 0.5\%$).[104] The procedure must be stopped if the patient develops chest discomfort, persistent cough or dyspnea. Large volume thoracenteses are poorly tolerated in subjects with unexpandable lungs because they experience significant pleural fluid pressure drops with the evacuation of even moderate amounts of fluid. Empirical supplemental oxygen is frequently prescribed during the procedure.

When dyspnea does not improve after a large volume pleural aspiration in patients with malignant effusions, possible explanations such as pulmonary carcinomatous lymphangitis, atelectasis, pulmonary or tumor embolism, or COPD should be pursued.[56]

Chest tubes

Indications for the insertion of an intercostal chest drain are pneumothorax, hemothorax, empyema, complicated parapneumonic effusions, and malignant effusions requiring bedside pleurodesis. The chest tube's internal diameter is expressed in a range of French sizes (diameter in French/3 = diameter in millimeters). Currently, the use of small-bore chest tubes (≤ 14F) using the catheter over guide wire (Seldinger) technique is recommended as first-line management for all previous conditions (Fig. 16), with the possible exception of hemothorax.[110] The latter is better managed with large-bore catheters (> 20F) because of blood clots and the high volume of pleural fluid. In parapneumonics and empyemas, CT may guide pleural catheter insertion if anatomical location or configuration of the collection makes TUS-guided intervention technically difficult. The most common complications of small-bore chest tubes include drain blockage and dislodgment, while the most serious are laceration of an intercostal artery and organ puncture.[111] In malignant

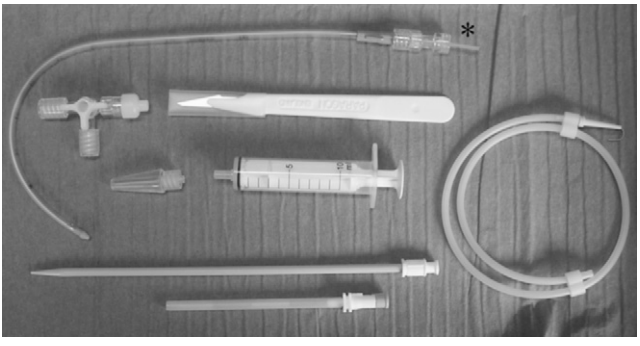

Fig. 16. Chest catheter 12F (*) and supplies for insertion using the Seldinger technique.

pleural effusions, the use of IPCs for the symptomatic relief and shortening of inpatient stays and hospital visits has been previously commented on.

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