# Diagnostic evaluation of a pleural effusion in adults: Initial testing

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## INTRODUCTION

Determining the cause of a pleural effusion is greatly facilitated by analysis of the pleural fluid. Thoracentesis is a simple bedside procedure with imaging guidance that permits fluid to be rapidly sampled, visualized, examined microscopically, and quantified for chemical and cellular content. A systematic approach to analysis of the fluid in conjunction with the clinical presentation allows clinicians to diagnose the cause of an effusion, narrow the differential diagnoses, and design a management plan in a majority of patients who undergo pleural fluid analysis.

An approach to pleural fluid analysis will be presented here. Pleural fluid microbiologic tests, pleural imaging, the technique of thoracentesis, and an approach to pleural effusions of uncertain etiology after the initial evaluation are discussed separately. (See "Imaging of pleural effusions in adults" and "Ultrasound-guided thoracentesis" and "Diagnostic evaluation of pleural effusion in adults: Additional tests for undetermined etiology".)

## INDICATIONS FOR THORACENTESIS

The indication for diagnostic thoracentesis is the new finding of a pleural effusion. Exceptions exist. For example, observation may be warranted in uncomplicated heart failure and viral pleurisy. In the former setting, the clinical diagnosis is usually secure; in the latter, there is typically a small amount of fluid. However, if the clinical situation is atypical or does not progress as anticipated, thoracentesis

should be performed. The indications and contraindications of thoracentesis are presented separately. (See "Ultrasound-guided thoracentesis".)

## CONDITIONS DIAGNOSED BY THORACENTESIS

Only a select number of diagnoses can be established definitively by thoracentesis. These include effusions as a result of malignancy, empyema, tuberculous pleurisy, fungal infection of the pleural space, chylothorax, cholesterol effusion, urinothorax, esophageal rupture, hemothorax, peritoneal dialysis, and extravascular migration of a central venous catheter ( table 1) [1]. Rarer conditions that can be diagnosed by thoracentesis include glycinothorax, cerebrospinal fluid leakage, and parasitic infection of the pleural space [1].

Positive pleural fluid lupus erythematosus (LE) cell preparation tests, pleural fluid antinuclear antibodies (ANA) titers ≥1:160, and a pleural fluid to serum ANA ratio ≥1 had previously been considered diagnostic of lupus pleuritis. However, none of these findings occurs solely in lupus pleuritis. Most clinical laboratories no longer perform lupus cell preparation tests, which are lengthy and complex [2-4]. Although LE cells may be incidentally detected by pleural fluid cytology, this finding has low diagnostic utility. This is because LE cells have been identified in routine pleural fluid cytologic examinations in non-lupus related effusions (eg, malignancy, rheumatoid arthritis) [2,5,6]. Similarly, small case series suggest that pleural fluid ANA titer ≥1:160 is not diagnostic of lupus pleuritis (specificity of 83 percent) [7] because such titers can also be found in exudative, parapneumonic, and malignancy-associated effusions [7-10]. Even an extremely high pleural fluid ANA >1:640 can occur in malignant effusions [10]. A pleural fluid ANA titer ≥1:160, however, remains a sensitive (86 to 100 percent) tool for detecting lupus pleuritis in patients with a known diagnosis of lupus [7-11] thereby differentiating between lupus pleuritis and other causes of pleural effusions in lupus patients. Using the ratio of pleural effusion to serum ANA of ≥1 [7,9,10] or ANA staining pattern in pleural fluid do not provide any additional diagnostic value for lupus pleuritis [8,10]. Thus, measuring pleural fluid ANA titers has better negative predictive value than positive predictive value and appears to be useful only for excluding the diagnosis of lupus pleuritis, particularly in patients who have a known diagnosis of SLE. (See "Pulmonary manifestations of systemic lupus erythematosus in adults".)

## PLEURAL FLUID ANALYSIS

Tests routinely performed on pleural fluid include the following:

- Cell count and cell differential

- pH
- Protein
- Lactate dehydrogenase (LDH)
- Glucose

Additional commonly performed tests in selected patients include amylase, cholesterol, triglycerides, N-terminal pro-brain natriuretic peptide (BNP), creatinine, adenosine deaminase, gram and acid-fast bacillus (AFB) stain, bacterial and AFB culture, and cytology.

**Gross appearance** — Initial diagnostic clues can be obtained by gross inspection of pleural fluid as it is being aspirated from the patient's chest [1]. Observations that are helpful for diagnosis are listed in the table ( table 2).

**Characterization** — The pleural fluid is next characterized as either a transudate or an exudate (calculator 1). (See 'Diagnostic criteria' below.)

**Transudates** — Transudates result from imbalances in hydrostatic and oncotic pressures in the chest, as occur with CHF and nephrosis, or conditions external to the pleural space. Examples of the latter include movement of fluid from the peritoneal, cerebrospinal, or retroperitoneal spaces, or from iatrogenic causes, such as crystalloid infusion through a central venous catheter that has migrated into the mediastinum or pleural space. Nevertheless, transudates have a limited number of diagnostic possibilities that can usually be discerned from the patient's clinical presentation ( table 3).

**Exudates** — In contrast, exudative effusions present more of a diagnostic challenge. Disease in virtually any organ can cause exudative pleural effusions by a variety of mechanisms, including infection, malignancy, immunologic responses, lymphatic abnormalities, noninfectious inflammation, iatrogenic causes, and movement of fluid from below the diaphragm ( table 4).

Exudates result primarily from pleural and lung inflammation (resulting in increased entry of fluid and protein due to elevated capillary permeability) or from impaired lymphatic drainage of the pleural space (resulting in a decreased removal of pleural fluid and protein). Exudates can also result from movement of fluid from the peritoneal space, as seen with acute or chronic pancreatitis, chylous ascites, and peritoneal carcinomatosis. (See "Mechanisms of pleural liquid accumulation in disease".)

**Diagnostic criteria** — The Light's Criteria Rule is a traditional method of differentiating transudates and exudates that measures serum and pleural fluid protein and LDH (calculator 1) [12]. Abbreviated versions of Light's Criteria Rule have similar diagnostic accuracy and have been recommended for clinical use [13,14].

According to the traditional Light's Criteria Rule, if at least one of the following three criteria (ie, component tests of the rule) is fulfilled, the fluid is defined as an exudate [12]:

- Pleural fluid protein/serum protein ratio greater than 0.5, or
- Pleural fluid LDH/serum LDH ratio greater than 0.6, or
- Pleural fluid LDH greater than two-thirds the upper limits of the laboratory's normal serum LDH

Combining results of two or more dichotomous tests into a diagnostic rule, as done by the Light's Criteria Rule, wherein only one component test result needs to be positive to make the rule result positive always increases sensitivity at the expense of decreasing specificity of the rule. As would be expected, therefore, the sensitivity of the Light's Criteria Rule is higher than the sensitivity of each of the three component tests of the rule but the specificity of the rule is lower than its individual components. This tradeoff of higher sensitivity for lower specificity in the design of Light's Criteria Rule is appropriate for evaluating pleural fluid because it is important that exudates not be missed, since they can have important prognostic implications. Some transudates, however, may be misclassified as an exudate because of the decreased specificity of the rule [15].

Light's criteria have been criticized for including both the pleural fluid LDH/serum LDH ratio and the pleural fluid LDH [13] because they are highly correlated [13,16].

Alternative diagnostic criteria also exist. A meta-analysis of eight studies (1448 patients) examined pleural fluid tests and found that several tests identified exudates with accuracy similar to those used in Light's criteria, but did not require concurrent measurement of serum protein or LDH [13]. Proposed two-criteria and three-criteria diagnostic rules, which require one criterion to be met to define an exudate, include:

- Two-test rule
    - Pleural fluid cholesterol greater than 45 mg/dL
    - Pleural fluid LDH greater than 0.45 times the upper limit of the laboratory's normal serum LDH
- Three-test rule
    - Pleural fluid protein greater than 2.9 g/dL (29 g/L)
    - Pleural fluid cholesterol greater than 45 mg/dL (1.165 mmol/L)
    - Pleural fluid LDH greater than 0.45 times the upper limit of the laboratory's normal serum LDH

The previous pleural fluid LDH cutoff point for differentiating between exudates and transudates in the traditional Light's criteria rule was 67 percent of (or 0.67 times) the upper limit of normal serum LDH. This has been changed to 45 percent, based on reanalysis of each criterion individually [13,16]. All available tests may misclassify pleural fluid as exudates or transudates when values are near the cutoff points [12,13,16]. Thus, clinical judgment is required when evaluating patients with borderline test results [17].

The need for clinical judgment is further underscored by recent observations that different LDH and protein laboratory assays perform differently when performed for pleural as opposed to serum samples [18]. Consequently, classification of pleural fluid into transudate or exudate using Light's criteria with different analytical platforms and assay methodologies may have up to 18 percent discordancy [18].

**Chemical and biochemical analysis** — The measurement of various chemical and biochemical constituents of pleural fluid can provide useful information. Pleural fluid protein, LDH, and glucose are routinely assayed while other chemical and biochemical tests are ordered in specific clinical situations.

**Protein** — Most transudates have absolute total protein concentrations below 3.0 g/dL (30 g/L), although acute diuresis in heart failure can elevate protein levels into the exudative range [19-21]. However, such patients have a serum to pleural fluid albumin gradient (the difference between the serum and pleural values) greater than 1.2 g/dL (12 g/L), or a protein gradient >3.1 g/dL, which correctly categorizes their effusions as transudates [21,22]. Elevated blood N-terminal pro-brain natriuretic peptide (NT-proBNP) also supports the diagnosis of heart failure when Light's criteria yield results in the exudative range [23]. (See 'N-terminal pro-BNP' below.)

- Tuberculous pleural effusions virtually always have total protein concentrations above 4.0 g/dL (40 g/L) [12]
- When pleural fluid protein concentrations are in the 7.0 to 8.0 g/dL (70 to 80 g/L) range, Waldenström's macroglobulinemia and multiple myeloma should be considered [24,25]

**LDH** — The level of pleural fluid LDH is one of the key criteria for differentiating transudates and exudates (see 'Diagnostic criteria' above). Several specific disease associations have been noted with pleural fluid protein and LDH levels:

- Pleural fluid LDH levels above 1000 IU/L (with upper limit of normal for serum of 200 IU/L) are characteristically found in empyema [26], rheumatoid pleurisy [27], and pleural paragonimiasis [28], and are sometimes observed with malignancy.

- Pleural fluid secondary to Pneumocystis jirovecii pneumonia has the characteristic finding of a pleural fluid/serum LDH ratio greater than 1.0 and a pleural fluid/serum protein ratio of less than 0.5 [29]. Such a pattern may also be suggestive of malignancy. Urinothorax is another cause of elevated pleural fluid LDH associated with low pleural fluid protein levels [30].

**Cholesterol** — Pleural cholesterol is thought to be derived from degenerating cells and vascular leakage from increased permeability. Measurement of pleural cholesterol has been used to improve the accuracy of differentiating transudative and exudative effusion. A pleural cholesterol level of greater than 45 mg/dL is not by itself a definitive criterion for an exudate, but does figure in the two and three-test rules as noted above [13].

An elevated cholesterol >250 mg/dL defines a cholesterol effusion (also known as pseudochylothorax or chyliform effusion), which can develop in patients with long-standing effusions. (See "Clinical presentation, diagnosis, and management of cholesterol pleural effusions", section on 'Diagnosis'.)

**Triglycerides** — Elevated pleural fluid triglyceride concentrations greater than 110 mg/dL supports the diagnosis of a chylothorax, a level less than 50 mg/dL excludes a chylothorax with reasonable likelihood, and an intermediate level between 50 and 110 mg/dL should be followed by lipoprotein analysis of the pleural fluid [31]. (See "Etiology, clinical presentation, and diagnosis of chylothorax", section on 'Pleural fluid analysis'.)

**Glucose** — A low pleural fluid glucose concentration (less than 60 mg/dL [3.33 mmol/liter], or a pleural fluid/serum glucose ratio less than 0.5) narrows the differential diagnosis of the exudate to the following possibilities [32]:

- Rheumatoid pleurisy
- Complicated parapneumonic effusion or empyema
- Malignant effusion
- Tuberculous pleurisy
- Lupus pleuritis
- Esophageal rupture

All other exudates have pleural fluid glucose concentration similar to that of blood glucose. All transudates have pleural fluid glucose concentrations similar to blood glucose except for pleural effusions with elevated pleural fluid glucose concentrations secondary to misplaced central venous catheters that infuse glucose-containing fluids into the pleural space [33] or migration of peritoneal dialysate fluid from the intraperitoneal space into the pleural space [34].

The mechanism responsible for a low pleural fluid glucose depends upon the underlying disease. Specific examples include:

- Decreased diffusion of glucose from blood to pleural fluid with rheumatoid pleurisy [35,36] or malignancy [37]

- Increased utilization of glucose by constituents of pleural fluid, such as neutrophils, bacteria (empyema), and malignant cells [38]

The lowest glucose concentrations are found in rheumatoid pleurisy and empyema, with glucose being undetectable in some cases. In comparison, when the glucose concentration is low in tuberculous pleurisy, lupus pleuritis, and malignancy, it usually falls into the range of 30 to 50 mg/dL (1.66 to 2.78 mmol/liter) [32].

**Creatinine** — Pleural fluid creatinine represents a confirmatory test for urinothorax when a transudate has a pleural fluid/serum creatinine ratio >1 [39,40].

**pH** — Pleural fluid pH should always be measured in a blood gas machine rather than with a pH meter or pH indicator paper, because the latter will result in inaccurate measurements [41,42]. A pleural fluid pH below 7.30 with a normal arterial blood pH is found with the same diagnoses associated with low pleural fluid glucose concentrations [43]. The pH of normal pleural fluid is approximately 7.60, due to a bicarbonate gradient between pleural fluid and blood [44]. Thus, a pH below 7.30 is abnormal. Transudates generally have a pleural fluid pH in the 7.40 to 7.55 range, while the majority of exudates range from 7.30 to 7.45 [43]. A urinothorax, however, is the only transudate that can have a pleural fluid pH <7.40 [39].

The mechanisms responsible for pleural fluid acidosis (pH <7.30) include;

- Increased acid production by pleural fluid cells and bacteria (empyema) [38,45].

- Decreased hydrogen ion efflux from the pleural space, due to pleuritis, tumor, or pleural fibrosis. Specific examples include malignancy [37], rheumatoid pleurisy [35,36], and tuberculous pleurisy.

A low pleural fluid pH has diagnostic, prognostic, and therapeutic implications for patients with parapneumonic and malignant effusions [46]. Patients with a low pleural fluid pH malignant effusion have a high initial positive yield on pleural fluid cytology. They also tend to have a shorter survival and poorer response to chemical pleurodesis than those with a pH >7.30, although the strength of these associations do not provide prognostic value for individual patients [47-49]. Clinicians should not use a low pleural fluid pH as the sole criterion for the decision to forego pleurodesis. (See "Management of malignant pleural effusions".)

A parapneumonic effusion with a low pleural fluid pH (≤7.15) indicates a high likelihood of necessity for pleural space drainage [50-52]. (See "Epidemiology, clinical presentation, and diagnostic

evaluation of parapneumonic effusion and empyema in adults".)

**Amylase** — Although not routinely tested in pleural fluid samples, amylase measurements can assist when pancreatic or esophageal etiologies of an effusion appear possible. The finding of an amylase-rich pleural effusion, defined as either a pleural fluid amylase greater than the upper limits of normal for serum amylase or a pleural fluid to serum amylase ratio greater than 1, narrows the differential diagnosis of an exudative effusion to the following major possibilities:

- Acute pancreatitis
- Chronic pancreatic pleural effusion
- Esophageal rupture
- Malignancy

Pleural fluid amylase, however, has low discriminative value for differentiating benign from malignant effusions so it is not routinely performed for this reason.

Other rare causes of an amylase-rich pleural effusion include pneumonia, ruptured ectopic pregnancy, hydronephrosis, and cirrhosis [53]. Pancreatic disease is associated with pancreatic isoenzymes, while malignancy and esophageal rupture are characterized by a predominance of salivary isoenzymes [53]. One case report observed an increase in pleural fluid salivary amylase isoenzymes in a patient with a pleural effusion due to multiple myeloma [54].

**Adenosine deaminase** — Measurement of adenosine deaminase (ADA) may be helpful to distinguish between malignant and tuberculous pleurisy when an exudative effusion is lymphocytic, but initial cytology and smear and culture for tuberculosis are negative [55-58]. The level of ADA is typically greater than 35 to 50 U/L in tuberculous pleural effusions [56,59] and less than 40 U/L in 94 percent of malignant pleural effusions [60]. The most common diagnostic threshold used to establish tuberculous pleural effusions is a value greater than 40 U/L [58]. False negative and false positive ADA results do occur, so ADA results need to be considered in the context of other features of the patient's clinical presentation [59]. ADA testing may be more valuable for ruling in the diagnosis of tuberculous pleurisy in geographic locations with high prevalence of tuberculosis, although the negative predictive value of ADA testing remains high in lower tuberculosis prevalence regions [61-63]. Coexisting conditions, however, that cause exudative pleural effusions, such as uremic pleuritis, decrease the diagnostic utility of ADA even in high tuberculosis prevalence regions [64]. For patients with neutrophil-predominant pleural effusions and elevated pleural fluid ADA levels, the presence of coexisting nodular lung lesions supports a diagnosis of tuberculous pleurisy while the presence of intrapleural loculations supports a diagnosis of parapneumonic effusion [65].

Some studies suggest greater diagnostic value of pleural fluid interferon gamma (T.SPOT.TB and/or QuantiFERON assays) in differentiating malignant from tuberculous lymphocytic exudates, but the

lower cost and ready availability of ADA testing has promoted its use in this setting [66,67]. For pleural fluid interferon gamma testing, primary studies [68-72] report varying diagnostic utility and a meta-analysis identifies problems with the quality of primary studies and inadequate diagnostic performance of pleural fluid interferon gamma testing to allow it to serve as a standalone test [73]. (See "Tuberculous pleural effusion".)

**N-terminal pro-BNP** — Multiple studies have demonstrated that natriuretic peptides in the blood and pleural fluid, such as N-terminal pro-brain natriuretic peptide (NT-proBNP), brain natriuretic peptide (BNP), and midregion pro-atrial natriuretic peptide (MR-proANP) are diagnostic markers for heart failure [74-83]. Measuring pleural fluid NT-proBNP, however, has questionable added value as compared with blood NT-proBNP levels, which are elevated in heart failure and have a high degree of correlation with pleural NT-proBNP results [23]. Moreover, a meta-analysis suggests that additional high quality primary studies are needed to evaluate the diagnostic accuracy of pleural fluid natriuretic peptides [82], and conditions other than heart failure can increase pleural fluid levels in critically ill patients [83]. Blood NT-proBNP testing is useful for diagnosing a cardiogenic pleural effusion in patients whose pleural fluid appears exudative (eg, due to diuresis). (See "Natriuretic peptide measurement in heart failure".)

**Procalcitonin** — Interest in serum procalcitonin as a diagnostic and prognostic marker for patients with bacterial tissue infections and sepsis [84] has directed attention to a possible value for pleural fluid procalcitonin in differentiating parapneumonic or tuberculous pleural effusions from other causes of exudative effusions and also for differentiating parapneumonic from tuberculous pleural effusions. However, studies have not demonstrated sufficient diagnostic utility of pleural fluid procalcitonin in these settings to recommend its use [85-87].

**Cytology** — Cytological analysis of pleural fluid can establish the diagnosis of malignant pleural effusions, but the test has an overall sensitivity of approximately 60 percent [88], which may increase by 15 percent with a second thoracentesis pleural fluid sample [89]. The sensitivity of pleural fluid cytology varies depending on the histological type of the underlying malignancy; among patients with lung cancer, for instance, cytology has a sensitivity of 78 percent for adenocarcinoma, 53 percent for small cell carcinoma, and 25 percent for squamous cell carcinomas [88]. The diagnostic yield of pleural fluid cytology does not appear to depend on the volume of fluid sent for cytological smear and cell block analysis [90]. Further details are provided separately. (See "Selection of modality for diagnosis and staging of patients with suspected non-small cell lung cancer", section on 'Pleural (T2, T3, M1a)' and "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Thoracentesis'.)

**Cancer-related biomarkers** — Multiple biomarkers are expressed by cancer cells or their environment. Modern immunohistochemistry techniques can detect these biomarkers in pleural fluid

and provide opportunities to diagnose pleural malignancies when the results of standard cytology are noncontributory. Although promising, clinical applicability of cancer-related biomarkers to establish a diagnosis of pleural malignancy is limited by the lack of standardized laboratory analysis methodologies and a shortage of studies that validate positive studies.

No single pleural fluid biomarker is accurate enough for routine use in the diagnostic evaluation of pleural effusion [91]. Measuring a panel of tumor markers (eg, carcinoembryonic antigen [CEA], carbohydrate antigen [CA] 125, CA 15-3, CA 19-9, cytokeratin fragment CYFRA 21-1) in pleural fluid has also been examined [92,93]. At levels that provide 100 percent specificity, individual sensitivities are less than 30 percent and a combination of four markers (CEA, CA 125, CA 15-3, and CYFRA 21) only reached 54 percent sensitivity in one study [93]. Similar results were reported in two meta-analyses that looked at various combinations of pleural fluid tumor markers [92,94]. A meta-analysis observed that the combination of CEA, CYFRA 21-1, and CA19-9 had a sensitivity for adenocarcinoma-associated malignant effusions of 95.06 percent, with an area under the receiver operating curve (AUC) of 0.95 [95].

Mesothelin is a glycoprotein that is highly over expressed in malignant mesothelioma cells [96]. Mesothelin levels measured in serum and pleural fluid may provide adjuvant diagnostic values with high specificity but low sensitivity for patients with suspected mesothelioma [97]. The role of soluble mesothelin-related peptides (SMRPs) in the diagnosis of pleural mesothelioma is discussed separately. (See "Presentation, initial evaluation, and prognosis of malignant pleural mesothelioma", section on 'Biomarkers under investigation'.)

**Nucleated cells** — The total pleural fluid nucleated cell count is virtually never diagnostic. There are, however, some settings in which the count may be helpful:

- Counts above 50,000/microL are usually found only in complicated parapneumonic effusions, including empyema
- Exudative effusions from bacterial pneumonia, acute pancreatitis, and lupus pleuritis usually have total nucleated cell counts above 10,000/microL [98]
- Chronic exudates, typified by tuberculous pleurisy and malignancy, typically have nucleated cell counts below 5000/microL [98]

The timing of thoracentesis in relation to the acute pleural injury determines the predominant cell type. The early cellular response to pleural injury is neutrophilic. As the time from the acute insult lengthens, if the pleural injury in not ongoing, the effusion develops a mononuclear predominance.

**Lymphocytosis** — Pleural fluid lymphocytosis, particularly with lymphocyte counts representing 85 to 95 percent of the total nucleated cells, suggests tuberculous pleurisy, lymphoma, sarcoidosis, chronic rheumatoid pleurisy, yellow nail syndrome, or chylothorax [1,99]. Malignant pleural effusions will be lymphocyte-predominant in over one-half of cases; however, the percentage of lymphocytes is usually between 50 and 70 percent [99]. Some drug-induced pleural effusions, such as those caused by dasatinib [100], are lymphocyte predominant. (See "Tuberculous pleural effusion" and "Primary effusion lymphoma" and "Etiology, clinical presentation, and diagnosis of chylothorax".)

**Eosinophilia** — Pleural fluid eosinophilia (defined by pleural fluid eosinophils representing more than 10 percent of the total nucleated cells) occurs with both malignant and benign etiologies of pleural effusions [101]. The differential diagnosis of pleural fluid eosinophilia includes [101-104]:

- Pneumothorax
- Hemothorax
- Pulmonary infarction
- Benign asbestos pleural effusion
- Parasitic disease
- Fungal infection (coccidioidomycosis, cryptococcosis, histoplasmosis)
- Drugs
- Catamenial pneumothorax with pleural effusion
- Malignancy (carcinoma, lymphoma, myeloma)
- Tuberculous pleurisy
- Parapneumonic effusions
- Chronic eosinophilic pneumonia

Two studies have noted that the presence or absence of eosinophilia provides no diagnostic value for ruling in or out a malignant pleural effusion [105,106]. Another case series of 6801 pleural fluid analyses from 3942 patients noted no discriminative properties of pleural fluid eosinophilia defined as >10 percent eosinophils for malignancy but some diagnostic value with a higher cut off point of >15 percent pleural fluid eosinophils (sensitivity and specificity 66 percent and 68 percent respectively). (See "Pleural fluid eosinophilia".)

**Mesothelial cells** — Mesothelial cells are found in small numbers in normal pleural fluid, are prominent in transudative pleural effusions, and are variable in exudative effusions. The major clinical significance of mesothelial cells in exudates is that tuberculosis is unlikely if there are more than 5 percent mesothelial cells [99,107,108].

## DIFFERENTIAL DIAGNOSIS

A listing of most of the causes of pleural effusion, differentiated by whether the fluid is transudative or exudative, is given in the tables ( table 1 and table 2). The evaluation of pleural effusions of undetermined etiology after the above evaluation is discussed separately. (See "Diagnostic evaluation of pleural effusion in adults: Additional tests for undetermined etiology".)

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Pleural effusion".)

## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5$^{th}$ to 6$^{th}$ grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10$^{th}$ to 12$^{th}$ grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Pleural effusion (The Basics)")
- Beyond the Basics topics (see "Patient education: Thoracentesis (Beyond the Basics)")

## SUMMARY AND RECOMMENDATIONS

- Analysis of pleural fluid can help to establish a diagnosis or at least limit the differential diagnoses in the majority of patients who undergo the thoracentesis ( table 1). (See 'Introduction' above.)
- Characteristics of the gross appearance of pleural fluid that are helpful in identifying the cause of the effusion are listed in the table ( table 2). (See 'Gross appearance' above.)

- An important initial step in the analysis of pleural fluid is to ascertain whether the fluid is a transudate or an exudate. Transudates are largely due to imbalances in hydrostatic and oncotic pressures in the chest ( table 3). Exudates are caused by a variety of mechanisms, including infection, malignancy, immunologic responses, lymphatic abnormalities, noninfectious inflammation, and trauma ( table 4). (See 'Characterization' above.)

- According to Light's traditional criteria (calculator 1), if at least one of the following three criteria is present, the fluid is defined as an exudate (see 'Diagnostic criteria' above):

  - Pleural fluid protein/serum protein ratio greater than 0.5

  - Pleural fluid lactate dehydrogenase (LDH)/serum LDH ratio greater than 0.6

  - Pleural fluid LDH greater than two-thirds the upper limits of the laboratory's normal serum LDH

- Other sets of criteria, called the two and three test rules have been developed to avoid needing simultaneous measurement of LDH or protein in the serum. (See 'Diagnostic criteria' above.)

- A low pleural fluid glucose concentration (less than 60 mg/dL [3.33 mmol/liter]) or a pleural fluid/serum glucose ratio less than 0.5 narrows the major differential diagnoses to rheumatoid pleurisy, tuberculous pleurisy or other infection, lupus pleuritis, malignant effusion, and esophageal rupture. A pleural fluid/serum glucose ratio greater than 1 suggests the presence of the infusion of glucose-containing intravenous fluids or intraperitoneal dialysate into the pleural space. (See 'Glucose' above.)

- The measurement of cholesterol, triglycerides, amylase, creatinine, and pH can provide useful additional information in selected patients. (See 'Cholesterol' above and 'Triglycerides' above and 'pH' above and 'Amylase' above.)

- Measurement of adenosine deaminase may be helpful when an effusion is lymphocytic and the initial smear and culture for tuberculosis are negative. The level of adenosine deaminase (ADA) is typically greater than 40 U/L in tuberculous pleural effusions but can be elevated to this level in other clinical conditions. (See 'Adenosine deaminase' above.)

- Predominant populations of neutrophils, lymphocytes, or eosinophils in the pleural fluid can help narrow the diagnostic possibilities. (See 'Nucleated cells' above.)

- Pleural fluid cytological examination has a sensitivity of 60 percent for pleural malignancy. The sensitivity varies depending on the histopathology of the underlying malignancy. (See 'Cytology'

above and "Procedures for tissue biopsy in patients with suspected non-small cell lung cancer", section on 'Thoracentesis'.)

- The evaluation of pleural effusions of undetermined etiology after the above evaluation is discussed separately. (See "Diagnostic evaluation of pleural effusion in adults: Additional tests for undetermined etiology".)



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## GRAPHICS

### Diagnoses established "definitively" by pleural fluid analysis

| Disease | Diagnostic pleural fluid tests |
|---|---|
| Empyema | Observation (pus, putrid odor), positive culture |
| Malignancy | Positive cytology |
| Tuberculous pleurisy | Positive AFB stain, culture |
| Esophageal rupture | High salivary isoenzyme form of amylase, low pH (often as low as 6), ingested vegetable or meat fragments |
| Fungal-related effusions | Positive fungal stain, culture |
| Chylothorax | Triglycerides >110 mg/dL, chylomicrons by lipoprotein electrophoresis |
| Cholesterol effusion | Cholesterol >200 mg/dL with a cholesterol to triglyceride ratio >1, cholesterol crystals under polarizing light |
| Hemothorax | Ratio of pleural fluid to blood hematocrit >0.5 |
| Urinothorax | Pleural fluid creatinine to serum ratio always >1 but diagnostic if >1.7 |
| Peritoneal dialysis | Protein <0.5 mg/dL and pleural fluid to serum glucose ratio >1 in peritoneal dialysis patient |
| Extravascular migration or misplacement of a central venous catheter | Pleural fluid to serum glucose ratio >1, pleural fluid gross appearance mirrors infusate (eg, milky white if lipids infused) |
| Rheumatoid pleurisy | Cytologic evidence of elongated macrophages and distinctive multinucleated giant cells (tadpole cells) in a background of amorphous debris |
| Glycinothorax | Measurable glycine after bladder irrigation with glycine-containing solutions |
| Cerebrospinal fluid leakage into pleural space | Detection of beta-2 transferrin |
| Parasite-related effusions | Detection of parasites |

Graphic 50027 Version 4.0

## Observations of pleural fluid helpful in diagnosis

| | Suggested diagnosis |
|---|---|
| **Color of fluid** | |
| Pale yellow (straw) | Transudate, some exudates |
| Red (bloody) | Malignancy, benign asbestos pleural effusion, postcardiac injury syndrome, or pulmonary infarction in absence of trauma |
| White (milky) | Chylothorax or cholesterol effusion |
| Brown | Long-standing bloody effusion; rupture of amebic liver abscess |
| Black[1-4] | Aspergillus niger, Rhizomes oryzae, metastatic melanoma, pancreaticopleural fistula, crack cocaine use, bronchogenic adenocarcinoma, esophageal perforation during treatment with activated charcoal, chronic hemothorax |
| Yellow-green | Rheumatoid pleurisy |
| Dark green | Biliothorax |
| Color of: | |
| Enteral tube feeding | Feeding tube has entered pleural space |
| Central venous catheter infusate | Extravascular catheter migration |
| **Character of fluid** | |
| Pus | Empyema |
| Viscous | Mesothelioma |
| Debris | Rheumatoid pleurisy |
| Turbid | Inflammatory exudate or lipid effusion |
| Anchovy paste | Amebic liver abscess |
| **Odor of fluid** | |
| Putrid | Anaerobic empyema |
| Ammonia | Urinothorax |

*References:*

1. *Chhabra A, Mukherjee V, Chowdhary M, et al. Black Pleural Effusion: A Unique Presentation of Metastatic Melanoma. Case Rep Oncol 2015; 8:222.*
2. *Huang TY, Tsai MJ. Education and imaging. Gastrointestinal: black pleural effusion induced by pancreaticopleural fistula. J Gastroenterol Hepatol 2013; 28:1798.*
3. *Jayakrishnan B, Dildar B, Rizavi DM, et al. Black pleural effusion. Lancet 2015; 386:e7.*
4. *Saraya T, Light RW, Takizawa H, Goto H. Black Pleural Effusion. Am J Med 2013; 126:641.e1.*

Graphic 74757 Version 2.0

## Causes of transudative pleural effusions

| Causes of transudative effusions | Comment |
|---|---|
| **Processes that *always* cause a transudative effusion** | |
| Atelectasis | Caused by increased intrapleural negative pressure |
| Cerebrospinal fluid leak into pleural space | Thoracic spinal surgery or trauma and ventriculopleural shunts |
| Heart failure | Acute diuresis can result in borderline exudative features |
| Hepatic hydrothorax | Rare without clinical ascites |
| Hypoalbuminemia | Edema liquid rarely isolated to pleural space |
| Iatrogenic | Misplaced intravenous catheter into the pleural space; post Fontan procedure |
| Nephrotic syndrome | Usually subpulmonic and bilateral |
| Peritoneal dialysis | Acute massive effusion develops within 48 hours of initiating dialysis |
| Urinothorax | Caused by ipsilateral obstructive uropathy or by iatrogenic or traumatic GU injury |
| **Processes that *may* cause a transudative effusion, but *usually* cause an exudative effusion** | |
| Amyloidosis | Often exudative due to disruption of pleural surfaces |
| Chylothorax | Most are exudative effusions |
| Constrictive pericarditis | Bilateral effusions |
| Hypothyroid pleural effusion | From hypothyroid heart disease or hypothyroidism per se |
| Malignancy | Usually exudative, but 3 to 10 percent transudative possibly due to early lymphatic obstruction, obstructive atelectasis, or concomitant disease (eg, heart failure) |
| Pulmonary embolism | Most are exudative effusions |
| Sarcoidosis | Stage II and III disease |
| Superior vena caval obstruction | May be due to acute systemic venous hypertension or acute blockage of thoracic lymph flow |
| Nonexpandable lung* | A result of remote or chronic inflammation |

GU: genitourinary.
* Trapped and entrapped lung are examples of nonexpandable lung. While trapped lung typically causes a transudative pleural effusion, entrapped lung is typically associated with an exudative effusion.

Graphic 73530 Version 8.0

## Causes of exudative pleural effusions

| Infectious |
| --- |
| Bacterial pneumonia |
| Tuberculous pleurisy |
| Parasites |
| Fungal disease |
| Atypical pneumonias (viral, mycoplasma) |
| Nocardia, Actinomyces |
| Subphrenic abscess |
| Hepatic abscess |
| Splenic abscess |
| Hepatitis |
| Spontaneous esophageal rupture |
| Cholecystitis |
| **Iatrogenic or trauma** |
| Central venous catheter misplacement/migration |
| Drug-induced (eg, nitrofurantoin, dantrolene, methysergide, dasatinib, amiodarone, interleukin-2, procarbazine, methotrexate, clozapine, phenytoin, beta blocker, ergot drugs) |
| Esophageal perforation |
| Esophageal sclerotherapy |
| Enteral feeding tube in pleural space |
| Radiofrequency ablation of pulmonary neoplasms |
| Hemothorax |
| Chylothorax |
| **Malignancy-related** |
| Carcinoma |
| Lymphoma |
| Mesothelioma |
| Leukemia |
| Chylothorax |
| Paraproteinemia (multiple myeloma, Waldenstrom's macroglobulinemia) |
| Paramalignant effusions |
| **Other inflammatory disorders** |
| Pancreatitis (acute, chronic) |
| Benign asbestos pleural effusion |
| Pulmonary embolism |
| Radiation therapy |
| Uremic pleurisy |
| Sarcoidosis |

| Increased negative intrapleural pressure with accompanying pleural malignancy or inflammation |
| --- |
| Lung entrapment |
| Cholesterol effusion (eg, due to tuberculosis, rheumatoid arthritis) |
| **Connective tissue disease** |
| Lupus pleuritis |
| Rheumatoid pleurisy |
| Mixed connective tissue disease |
| Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) |
| Granulomatosis with polyangiitis (Wegener's) |
| Familial Mediterranean fever |
| **Endocrine dysfunction** |
| Hypothyroidism |
| Ovarian hyperstimulation syndrome |
| **Lymphatic abnormalities** |
| Malignancy |
| Chylothorax (eg, yellow nail syndrome, lymphangioleiomyomatosis, lymphangiectasia) |
| **Movement of liquid from abdomen to pleural space** |
| Pancreatitis |
| Pancreatic pseudocyst |
| Meigs' syndrome |
| Chylous ascites |
| Malignant ascites |
| Subphrenic abscess |
| Hepatic abscess (bacterial, amebic) |
| Splenic abscess, infarction |
| **Miscellaneous** |
| Pulmonary vein stenosis |
| Endometriosis |
| Drowning |
| Electrical burns |
| Capillary leak syndrome |
| Extramedullary hematopoiesis |

| |
|---|
| Postcardiac injury syndrome |
| Acute respiratory distress syndrome (ARDS) |

Graphic 54055 Version 10.0