PLEURAL EFFUSION

Prof. G. Zuliani

Anatomy of pleural membrane and pleural space

- Pleural membrane consists of parietal pleura and visceral pleura
- A space situated between parietal and visceral pleura is the pleural space
- It is normally filled with 5 -10 milliliter of serous fluid

Anatomy of pleural membrane and pleural space

Parietal pleura is receiving its blood supply from the systemic circulation (high pressure) and containing sensory nerve ending (pain)

Visceral pleura is receiving its blood supply from the (low-pressure) pulmonary circulation and containing no sensory nerve fibers

The mechanisms that lead to the accumulation of pleural fluid

1. Increased **hydrostatic pressure** in microvascular circulation
2. Decreased **oncotic pressure** in microvascular circulation
3. Increased **permeability** of the microvascular circulation
4. Impaired **lymphatic drainage** from the pleural space
5. **Movement of fluid** from peritoneal space

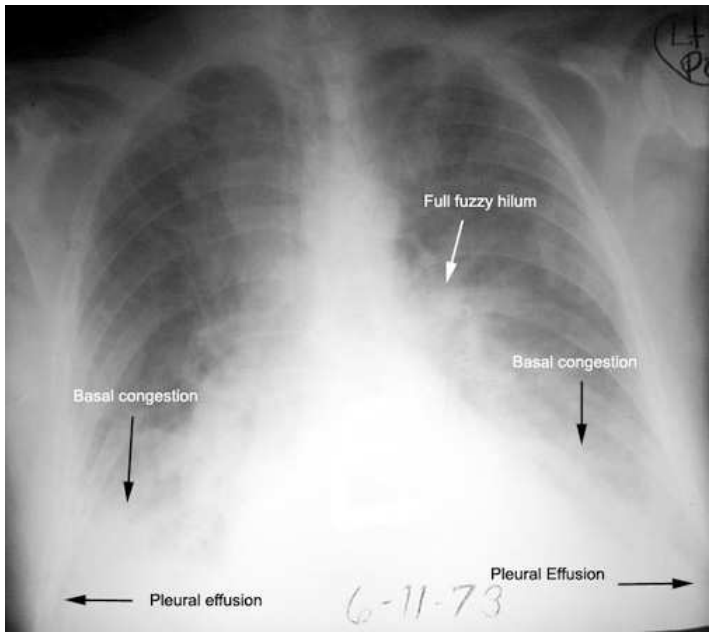
Two kinds of pleural effusions: transudates and exudates

	Transudate	Exudate
• Cause	non-inflammatory	inflammatory, tumor
• Apperance	light yellow	yellow, purulent
• Specific gravity	<1.018	>1.018
• Coagulability	unable	able
• Rivalta test	negative	positive
• Protein content	< 30g/L	> 30g/L
• P to S Prot	< 0.5	> 0.5
• LDH	< 200 I U/L	> 200 I U/L
• P to S LDH	< 0.6	> 0.6
• Cell count	$< 100 \times 10^{6}$/L	$> 500 \times 10^{6}$/L
• Differential cell	Lymphocyte	Different

1. Transudative Pleural effusions

- Congestive heart failure
- Cirrhosis (more often right side)
- Nephrotic syndrome
- Pulmonary embolism
- Myxedema
- Superior vena cava obstruction
- Peritoneal dialysis

Congestive heart failure

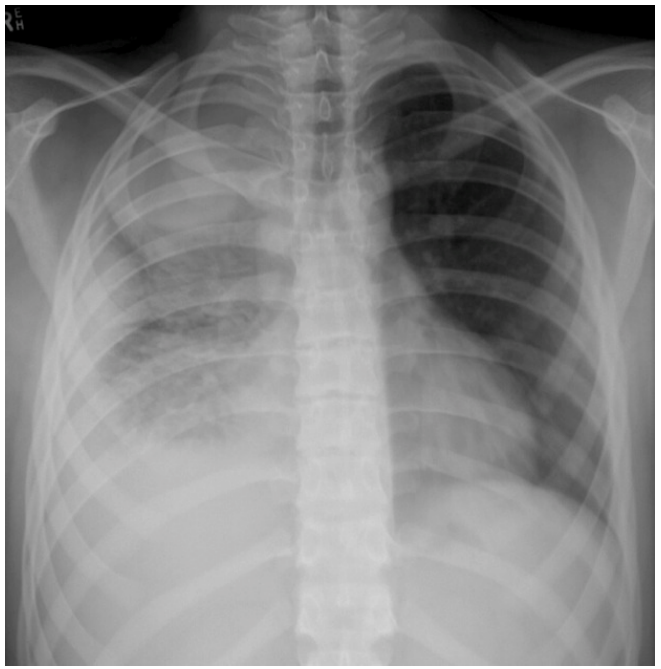


2. Exudative Pleural Effusions

- Neoplastic diseases
  - Metastatic disease
  - Mesothelioma
- Infectious diseaseS (pneumonia-pleuritis)
  - Bacterial infections
  - Fungal infections
  - Viral infections
  - Tuberculosis
  - Parasitic infections

Characteristics of a complicated parapneumonic effusion

- Glucose < 60 mg/dL
- pH < 7.2
- Positive culture
- Pleural LDH > 3x the upper limit for serum
- Pleural fluid is often ***loculated***



2. Exudative Pleural Effusions

- Pulmonary embolization (PE)
- Gastrointestinal disease
  - Esophageal perforation (Booherave syndrome)
  - Pancreatic diseases
  - Intra-abdominal abscesses
  - After abdominal surgery
  - Endoscopic variceal sclerotherapy
  - After liver transplant

2. Exudative Pleural Effusions

- Collagen-vascular diseases

  - Rheumatoid pleuritis
  - Systemic lupus erythematosus
  - Drug-induced lupus
  - Immunoblastic lymphadenopathy
  - Sjögren's syndrome
  - Wegener's granulomatosis
  - Churg-Strauss syndrome

RA and SLE

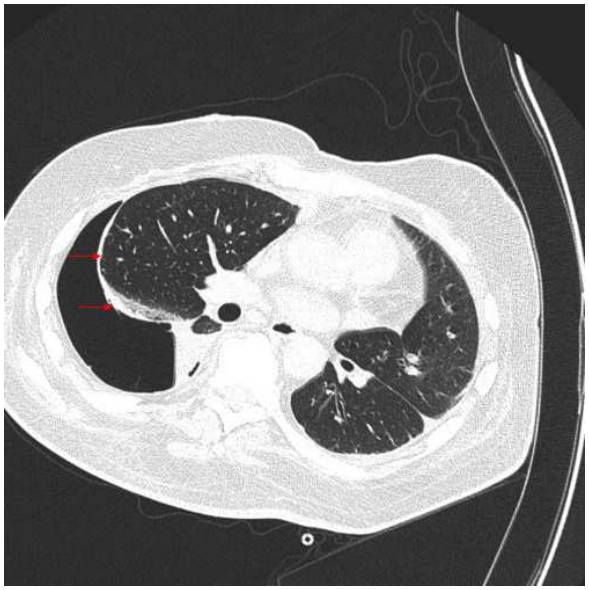
Characteristics	RA	SLE
Incidence	3%-7%	15%-44%
Effusion	Exudate	Exudate
Glucose	< 20 mg/dl: 63% < 50 mg/dl: 83%	> 70 mg/dl
C4	Low	Low
Pleural immunology	R.Fact +	LE cells or + ANA
Treatment	NSAID/Steroids	Steroids
Response	Variable response	Excellent

2. Exudative Pleural Effusions

- Post-coronary artery bypass surgery (left side)
- Asbestos exposure
- Sarcoidosis
- Uremia
- Meigs' syndrome
- Yellow nail syndrome … (pleural effusions, lymphoedema, and yellow dystrophic nails)

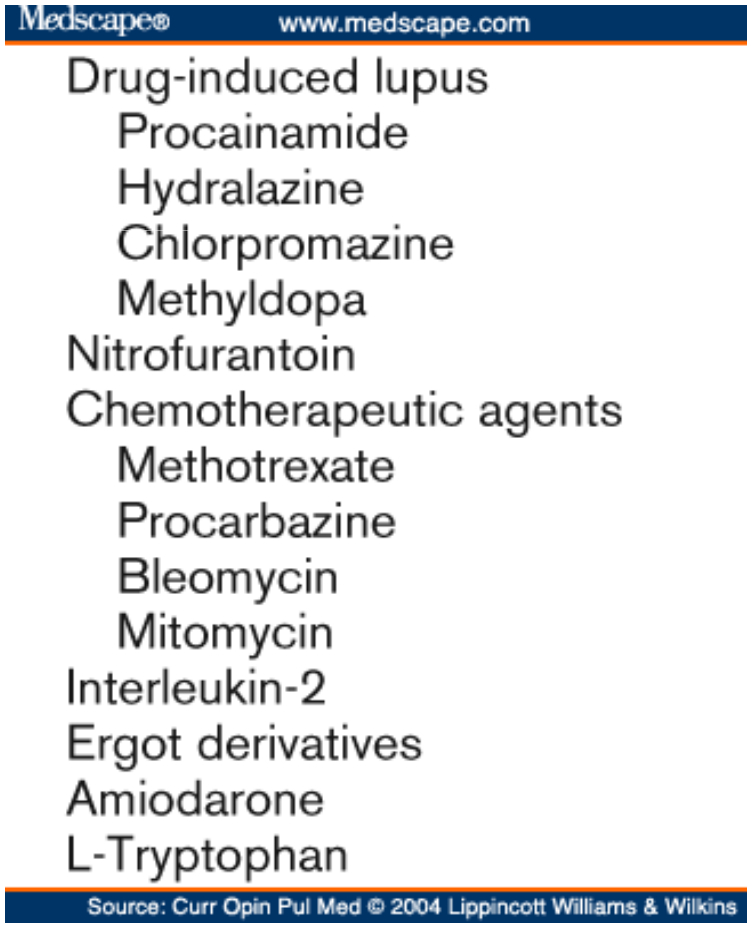
2. Exudative Pleural Effusions

- **Trapped lung:** unexpandable lung due to visceral or **pleural** restriction can result from malignant and non-malignant disease
- Neoplasia
- Radiation therapy
- Pericardial disease
- Iatrogenic injury
- Sarcoidosis
- Hemothorax
- Chylothorax



2. Exudative Pleural Effusions

- Drug-induced pleural disease



Haemorrhagic effusion

1. Trauma
2. Tumor
3. Pulmonary infarction
4. TBC
5. Spontaneous pneumothorax

Hemothorax

- Pleural fluid hematocrit greater that 50% that of peripheral blood
- Causes
  - Traumatic (penetrating or non-penetrating)
  - Iatrogenic (thoracic surgery or line placement)
  - Non traumatic (from metastatic pleural disease),
  - Spontaneous rupture of an intrathoracic vessel, bleeding disorders
  - Complication of anticoagulant therapy

- Treatment is immediate chest tube (both to evacuate the fluid and monitor for additional bleeding) and selective arteriography.

Chylous effusion

1. Trauma
2. Tumors
3. TBC
4. Thrombosis of the left subclavian vein

Chylous Pleural Effusion

- Defined by the presence of chyle (lymph) in the pleural space

- Diagnosis
  - Appearance often milky. Must differentiate chylous from chyliform effusion. "*Chyliform effusion"* has elevated cholesterol and occurs in long standing effusions.

  - Chemical confirmation
    - Triglyceride > 110 mg/dL
    - If triglyceride is between 50-110 mg/dL, send fluid for lipoprotein electrophoresis. Chylomicrons confirms a chylothorax
    - If triglyceride is < 50, it is not chylous

Neoplastic disease of the pleura

- Lung 36%
- Breast 25%
- Lymphoma 10%
- Ovary 5%
- Stomach 2%
- Unknown 7%

Sahn, SA: In Fishman, JA 9ed): Fishman's Pulmonary Diseases and Disorders, 3rd ed. McGraw Hill, NY

Fluid Tests for Cancer

- Cytology is fast, efficient, and minimally invasive
- Establishes the diagnosis in more than 70% of cases of metastatic adenocarcinoma
- Not routinely warranted in young patients with evidence of acute illness.
- Less efficient in the diagnosis of: mesothelioma squamous cell carcinoma, lymphoma, and sarcoma
- If cytology is negative: thoracoscopy
- If lymphoma is suspected, flow cytometry can establish the diagnosis (clonal cell population)

Empyema

- Pulmonary infection
- TBC
- Trauma
- Esophageal rupture

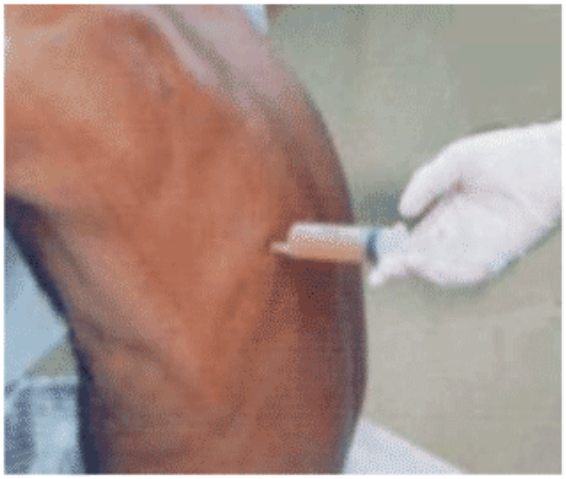
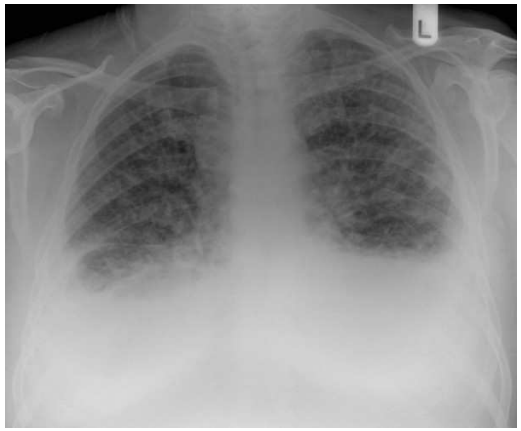
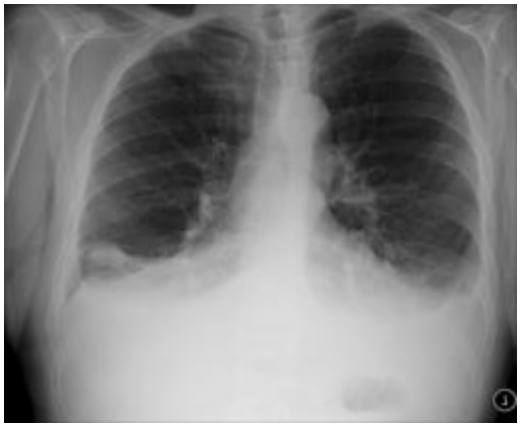


Figure 1. Diagnostic thoracocentesis producing purulent pleural fluid

Bilateral pleural effusion

1. Generalized salt and water retention:
   - ***congestive heart failure***
   - ***nephrotic syndrome***
2. Ascites (more often right side)
3. Pulmonary infarction
4. Lupus erythematosus, rheumatoid arthritis
5. TBC





Causes of Pleural Effusion

1. Congestive heart failure	500,000
2. Pneumonia	300,000
3. Malignancy	200,000
4. Pulmonary embolism	150,000
5. Viral	100,000
6. Cirrhosis with ascites	50,000
7. GI disease	25,000
8. Collagen-vascular disease	6,000
9. Tuberculosis	2,500
10. Asbestos	2,000
11. Mesothelioma	1,500

Light, RW: Pleural Diseases (3rd) edition, Philadelphia: Lea & Febiger

Clinical signs of Pleural Effusion

- **dyspnea, cough**
- **tachipnea**
- **pleural pain**
- fever, weight loss
- dullness on percussion, decreased tactile fremitus
- decreased transmission of breath and vocal sounds
- occasionally: pleural friction sound in its early stage (dry pleurisy)

How to Approach

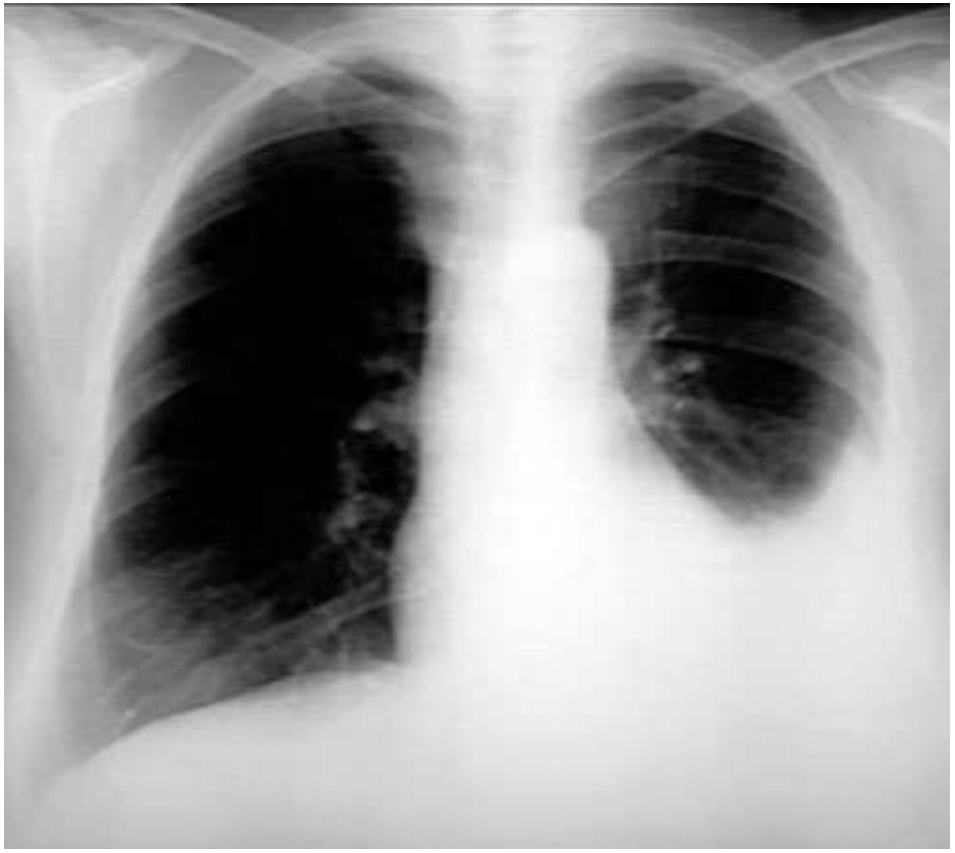
- The diagnostic workup of a patient with a pleural effusion will depend on the probable causes of the condition in that patient
- ***History and physical examination are critical***

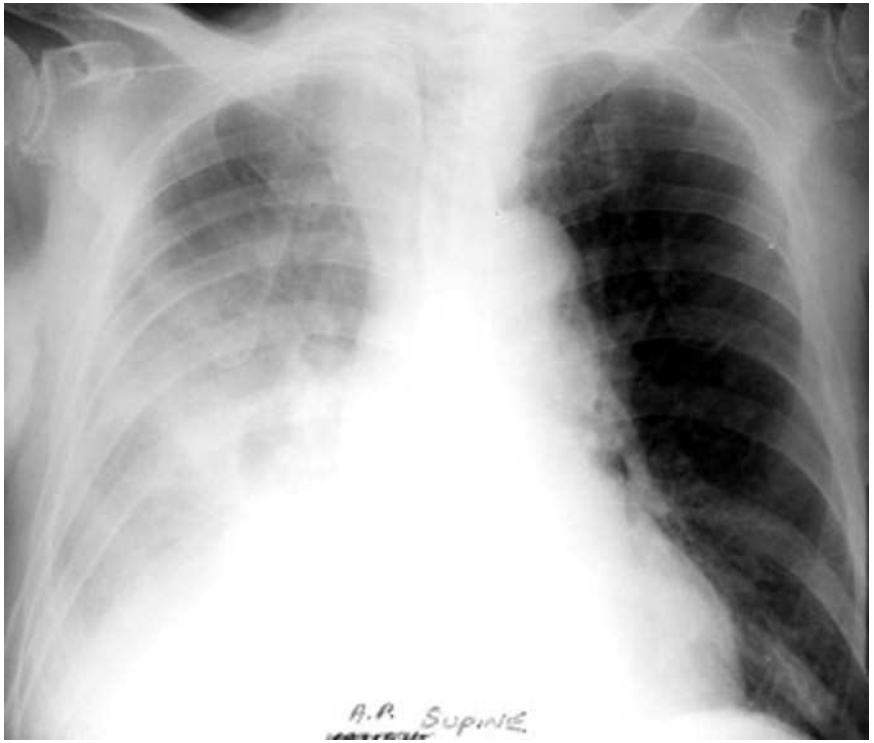
- History should focus at least on the most common etiologies along with occupational, ***smoking, drug exposure*** (prescription, OTC and illicit), ***travel history, sick contacts***, hospitalizations, transfusions, health maintenance status, immunizations.

Diagnostic procedures

Chest X-Ray examination

- blunting of the normally sharp costophrenic angle
- a concave shadow with its highest margin along the pleural surface
- shift of the mediastinum and the tracheas toward the normal side

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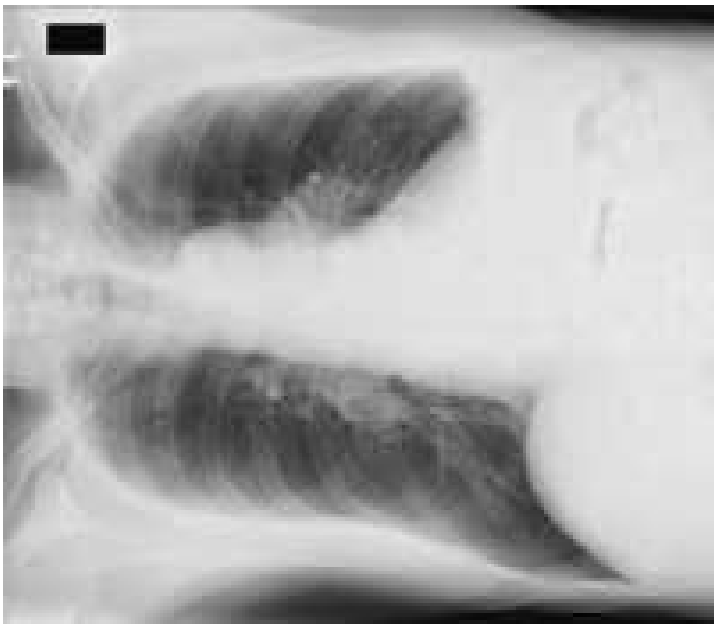
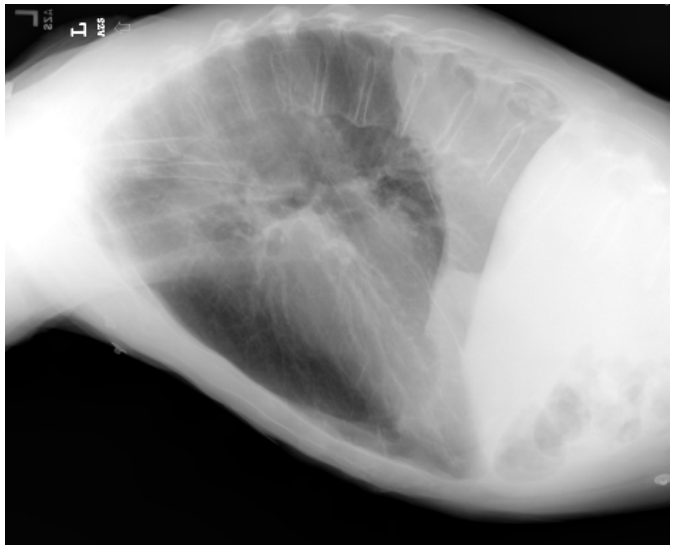
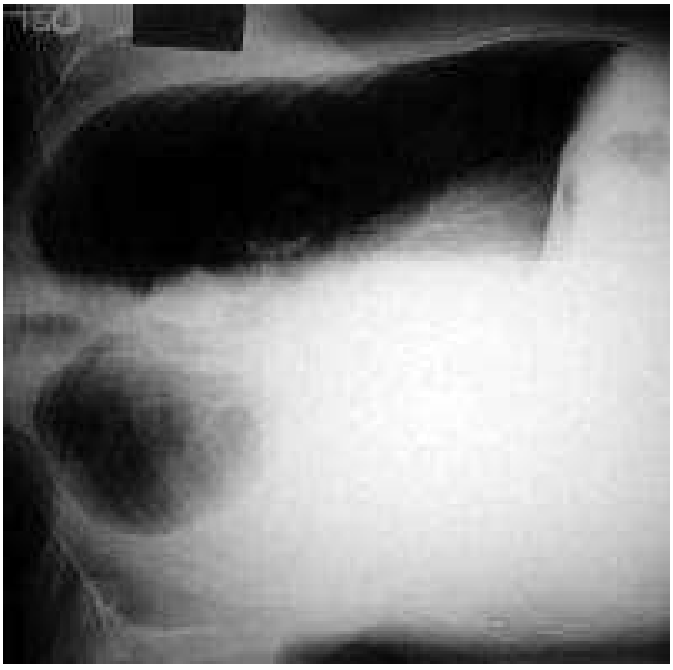


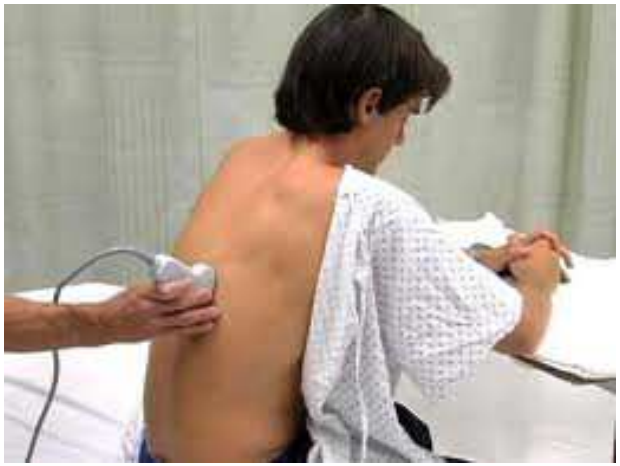




Diagnostic procedures

Ultrasonic examination

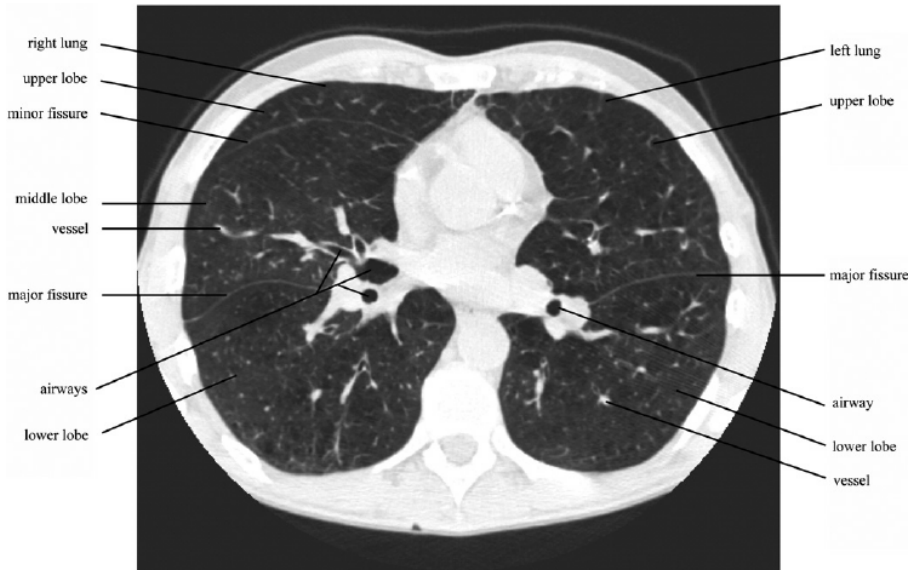
To localize a small pleural effusion, to quantify an effusion, and to determine the correct site for performing of a thoracentesis

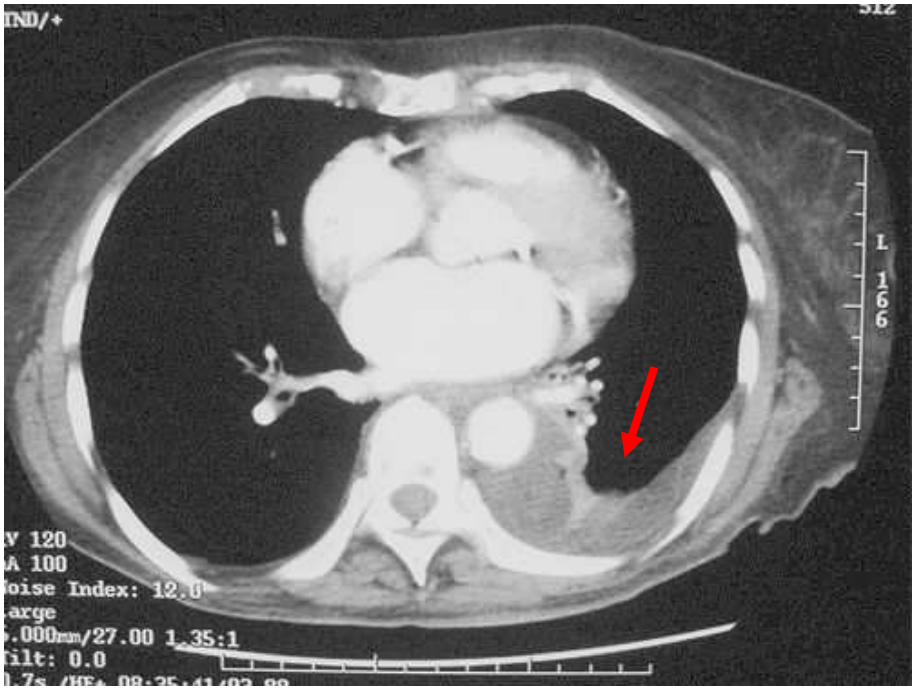


Diagnostic procedures

TC scan of the thorax

To visualize lungs, pleura, mediastinum, heart, pericardium, bones

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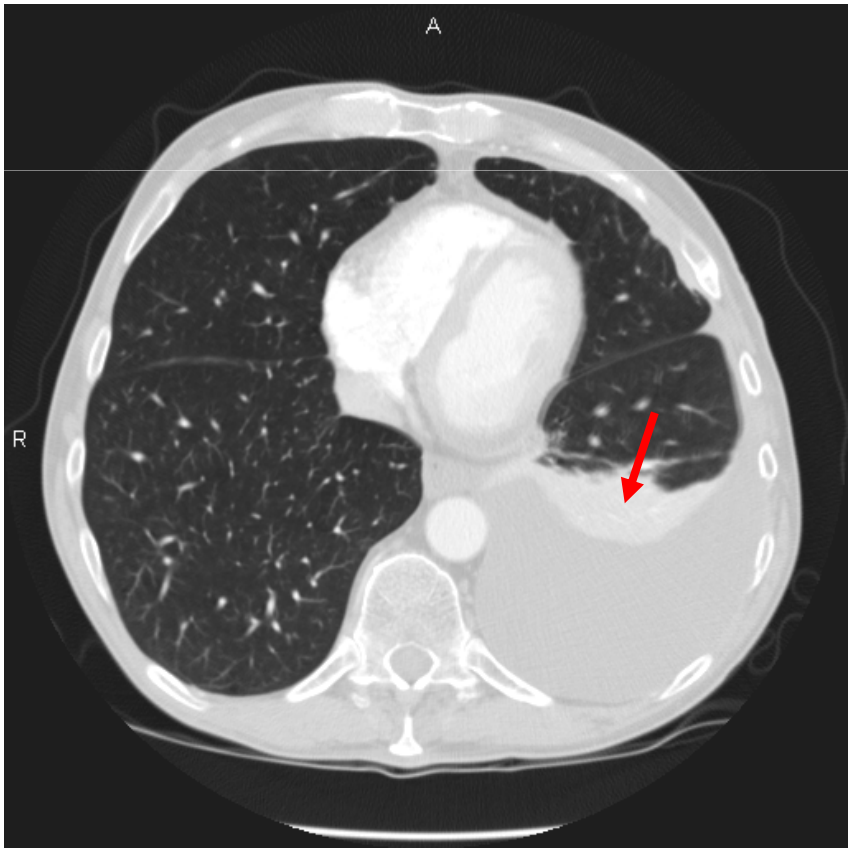
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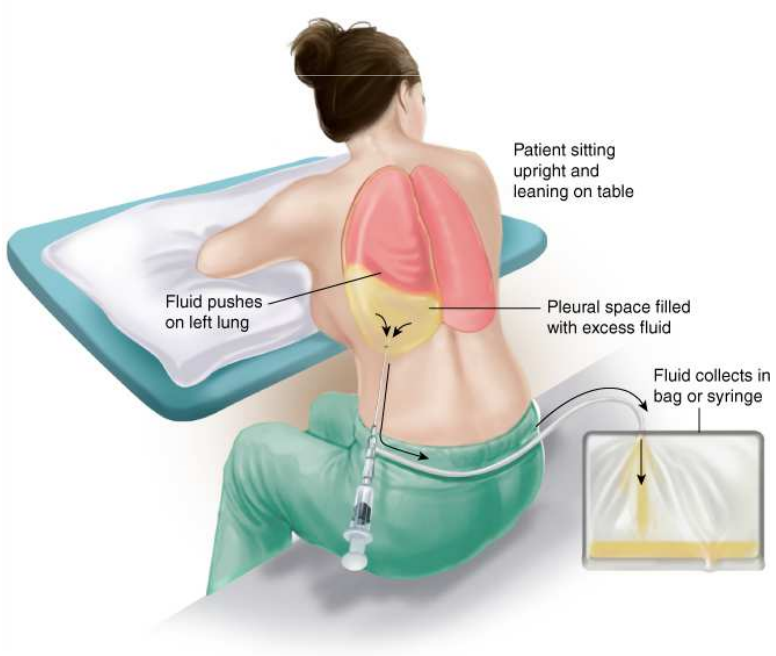
Diagnostic procedures

Thoracentesis

To aspirate the effusion for laboratory examination:

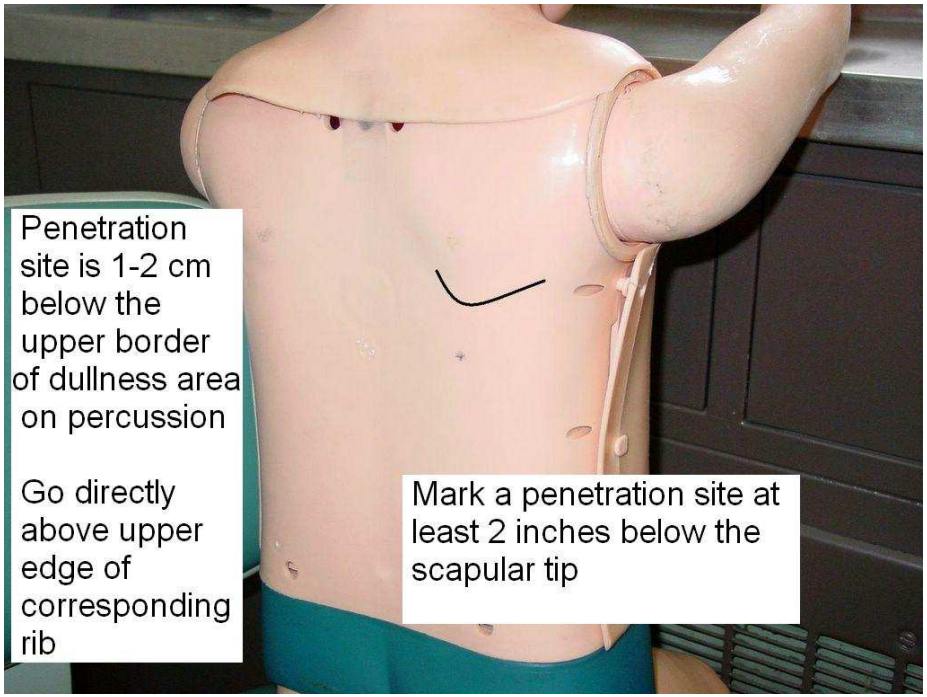
- **Appearance**
- **Specific gravity**
- **Protein content**
- **Cell counts**
- **Glucose**
- **LDH lipid content**
- **Rheumatoid factor**
- **Lupus pleuritis cells**
- **Gram stain and culture**
- **Cytologic examination**



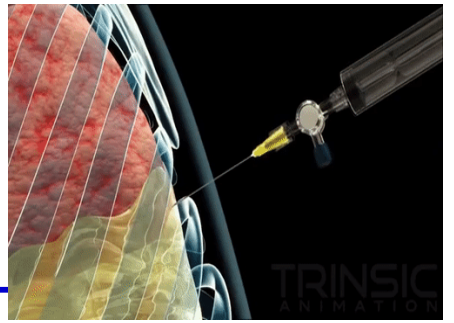
Source: McKean S, Ross JJ, Dressler DD, Brotman DJ, Ginsberg JS: *Principles and Practice of Hospital Medicine*: www.accessmedicine.com

Diagnostic thoracentesis

- It is indicated if the effusion monolateral, clinically significant, with no known cause.



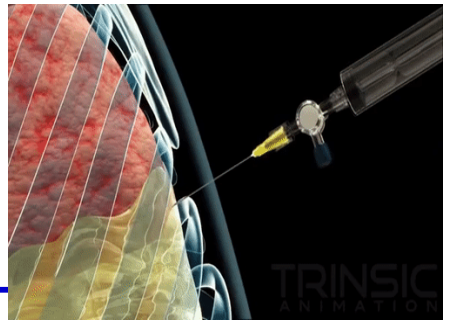
Thoracentesis



- Also indicated in a patient with **CHF** if any of the following are present:

✓ **Unilateral** effusion, particularly if it is left-sided
✓ Bilateral effusions, but are of **disparate sizes**
✓ There is evidence of **pleurisy** or **fever**
✓ The **cardiac silhouette appears normal** on CXR
✓ NO response to **diuretics** in 48-72 hrs.
✓ The alveolar-arterial oxygen gradient is widened out of proportion to the clinical setting

Thoracentesis



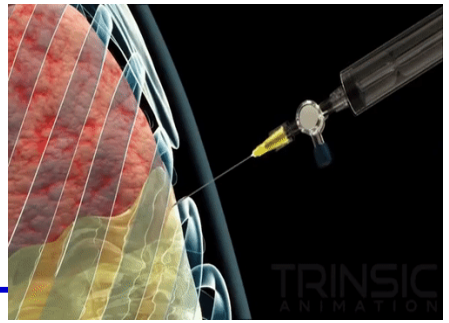
Contraindications

Absolute: none

Relative include:

- Patient on *anticoagulation or with bleeding diathesis*
- Very small volume of fluid
- Patients in *mechanical ventilation* are at high risk for tension pneumothorax or persistent airleak
- Active skin infection at the port of entry

Thoracentesis



- Post-procedure CXR

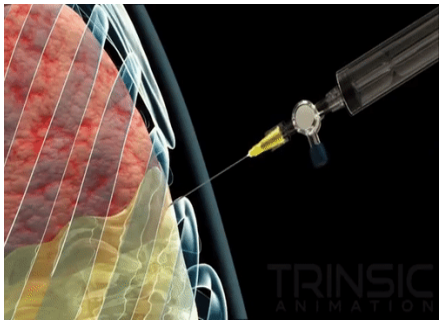
  Indicated only if air is obtained during the procedure or if cough, pain or dyspnea develops

- Complications: pain, bleeding (hematoma, hemothorax, hemoperitoneum), pneumothorax, empyema, vasovagal events, soft tissue infection, spleen or liver puncture (!), and adverse reactions to lidocaine or topical antiseptic solutions

Two kinds of pleural effusions: transudates and exudates

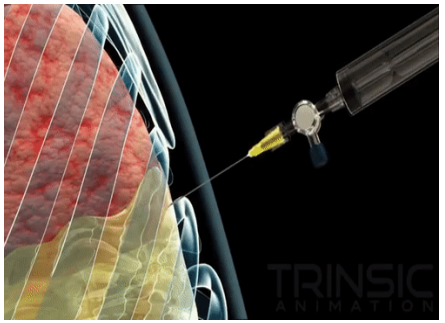
	Transudate	Exudate
• Cause	non-inflammatory	inflammatory, tumor
• Apperance	light yellow	yellow, purulent
• Specific gravity	<1.018	>1.018
• Coagulability	unable	able
• Rivalta test	negative	positive
• Protein content	<30g/L	>30g/L
• P/S Prot ratio	< 0.5	> 0.5
• LDH	< 200 I U/ L	> 200 I U/L
• P/S LDH ratio	< 0.6	> 0.6
• Cell count	$< 100 \times 10^6$/ L	$> 500 \times 10^6$ /L
• Differential cell	Lymphocyte	Different

Glucose Level



- Low glucose concentration (< 60 mg/dL) indicates a complicated **parapneumonic** or a **malignant** effusion.
- less common are hemothorax, tuberculosis, rheumatoid pleuritis,
- more rarely, Churg–Strauss syndrome, and lupus pleuritis

LDH Level



- The LDH level correlates with the ***degree of inflammation*** and *should be measured each time* fluid is sampled from an effusion whose cause has not been determined.
- *Increasing LDH* with repeated thoracentesis suggests that the degree of *inflammation is increasing*, and a diagnosis should be aggressively pursued.
- Conversely, if the *LDH decreasing* with repeated thoracentesis, a less aggressive diagnostic approach may be considered.

Table 5. Initial Evaluation of Pleural Fluid

Quality	*Test indicated*	*Interpretation*
Appearance		
Bloody	Hematocrit	< 1 percent: nonsignificant 1 to 20 percent: cancer, pulmonary embolus, or trauma > 50 percent peripheral hematocrit: hemothorax
Cloudy or turbid	Centrifugation	Turbid supernatant: chylothorax
Odor		
Putrid	Stain and culture	Possible anaerobic infection
Distinguishing transudate from exudate		
Light's criteria		Fluid is exudate if it meets one or more of the following criteria: Ratio of pleural fluid protein level to serum protein level > 0.5 Ratio of pleural fluid LDH level to serum LDH level > 0.6 Pleural fluid LDH level > two thirds the upper limit of normal for serum LDH level
Confirmation of Light's criteria assessment*		Fluid is exudate if: Serum albumin level – pleural fluid albumin level ≤ 1.2 g per dL (12 g per L)

Sensitivity of Tests to Distinguish Exudative from Transudative Effusions

TABLE 3. SENSITIVITY OF TESTS TO DISTINGUISH EXUDATIVE FROM TRANSUDATIVE EFFUSIONS.*

TEST	SENSITIVITY FOR EXUDATE	SPECIFICITY FOR EXUDATE
	%	
Light's criteria (one or more of the following three)	98	83
Ratio of pleural-fluid protein level to serum protein level >0.5	86	84
Ratio of pleural-fluid LDH level to serum LDH level >0.6	90	82
Pleural-fluid LDH level >two thirds the upper limit of normal for serum LDH level	82	89
Pleural-fluid cholesterol level >60 mg/dl (1.55 mmol/liter)	54	92
Pleural-fluid cholesterol level >43 mg/dl (1.10 mmol/liter)	75	80
Ratio of pleural-fluid cholesterol level to serum cholesterol level >0.3	89	81
Serum albumin level − pleural-fluid albumin level ≤1.2 g/dl	87	92

*LDH denotes lactate dehydrogenase.

Light R. N Engl J Med 2002

Diagnostic evaluation of the pleura

- Video-assisted thoracic surgery (thoracoscopy)
- Thoracotomy

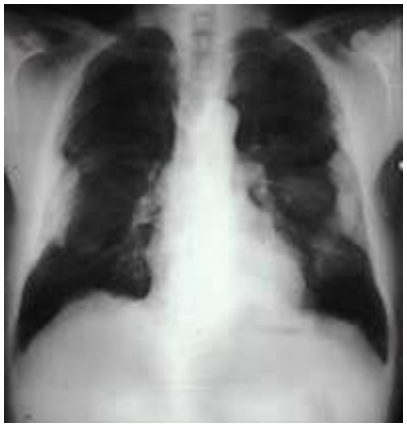
Asbestos-related Pleural Disease

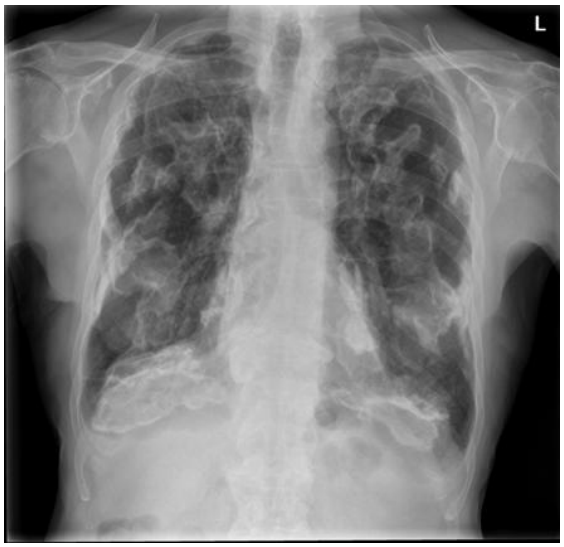
- Initially described in 1950's
- Is the most common pleuro-pulmonary abnormality related to asbestos during the first 20 yrs after exposure:

- **Exudative Pleural Effusion**
- exposure to asbestos
- exclusion of other causes
- exclusion of malignancy

Asbestos-related Pleural Disease

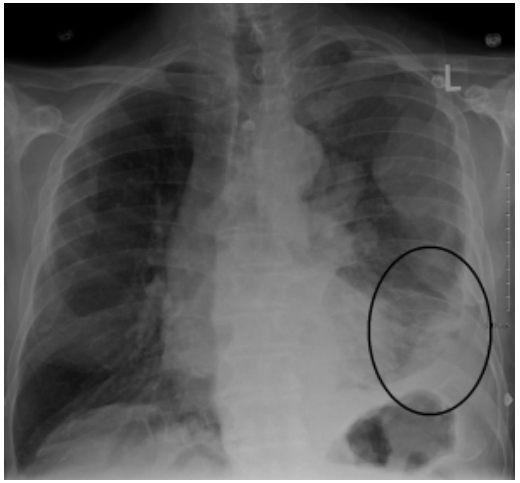
1. **Benign asbestos pleural effusion** (10-20 year latency)
2. **Pleural plaques** (20-30 year after latency)
3. **Mesothelioma** (30-40 year latency)
4. **Diffuse pleural fibrosis**
5. **Rounded atelectasis**





Mesothelioma

- Associated with asbestos exposure (even very modest exposures)
  - Latency of 30-40 years
- No association with smoking habit
- Difficult diagnosis by cytology; therefore, usually a ***pleural biopsy*** is recommended
- Three histological subtypes
  - Epithelial
  - Sarcomatous
  - Mixed



Tuberculous Pleuritis

- Acute illness in 60% of cases; chronic illness in 30% of cases
- **Unilateral effusion**
- 1/3 will have parenchymal disease
- Exudative, lymphocyte predominant effusion

Diagnosis of Tuberculous Pleuritis

- PPD (tuberculosis skin test) may be negative in up to 30%
- Culture
- Pleural fluid for:
  - Polymerase chain reaction (PCR) for tuberculous DNA
  - Adenosine deaminase (ADA)
  - Interferon-gamma
- Biopsy

Table 4. Findings Associated with Selected Causes of Pleurisy

Diagnosis	*History*	*Physical examination*	*Selected diagnostic test results*
Connective tissue disorders	Prior diagnosis of systemic lupus erythematosus, rheumatoid arthritis, or other connective tissue disorder should raise suspicion, but pleuritic chest pain may be initial presentation Fever; arthritis or arthralgias	Decreased breath sounds	Chest radiography: small to moderate unilateral or bilateral effusion PFA: exudative effusion (rheumatoid arthritis characterized by low glucose level [< 40 mg per dL (2.2 mmol per L)], elevated lactic dehydrogenase level [> 700 U per L], and low pH [< 7.2]) Abnormal disease-specific serologic markers
Drug-induced pleuritis	Use of drug known to cause drug-induced pleural disease or drug-induced lupus pleuritis*	Possible decreased breath sounds, pleural friction rub	Chest radiography: may be normal or demonstrate infiltrate, pleural effusion, or pleural thickening PFA: exudative effusion
Familial Mediterranean fever	Recurrent episodes of fever (one to four days) associated with abdominal, chest, or joint pain or erysipelas-like skin disease Mediterranean descent Family history of familial Mediterranean fever	Normal between episodes During episodes: temperature of 100 to 104°F (38 to 40°C) and signs of serositis (e.g., peritoneal irritation, pleural and/or pericardial friction rub) Other possible findings: joint swelling, unilateral erythema over extensor surface of leg, ankle, or foot	Increased acute phase reactants (ESR, CRP, WBC, fibrinogen) Positive mutation analysis for *MEFV* gene
Post–cardiac injury syndrome†	Recent myocardial infarction, cardiac procedure, or chest trauma Fever, dyspnea, pleuropericardial pain	Pleural and/or pericardial friction rub; decreased breath sounds	Chest radiography: may reveal pleural effusion PFA: exudative effusion Elevated ESR, leukocytosis Electrocardiographic abnormalities similar to pericarditis (see Table 3)
Tuberculous pleuritis	Exposure to environment with high risk of *Mycobacterium tuberculosis* Cough, low-grade fever, weight loss, fatigue Human immunodeficiency virus infection	Unilaterally decreased breath sounds	Chest radiography: small to moderate unilateral pleural effusion, often without associated infiltrate PFA: exudative effusion with elevated adenosine deaminase levels (> 40 to 60 U per L [670 to 1,000 nkat per L]) Caseous granulomas on pleural biopsy Culture positive for *M. tuberculosis* on induced sputum, pleural fluid culture, or pleural biopsy Negative PPD result does not exclude diagnosis
Viral pleurisy	Recent respiratory illness or undifferentiated febrile illness	Rapid, shallow respirations; pleural friction rub	Chest radiography: normal

PFA = pleural fluid analysis; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; WBC = white blood cell count; PPD = purified protein derivative.

**—Drugs known to cause pleural disease include amiodarone (Cordarone), bleomycin (Blenoxane), bromocriptine (Parlodel), cyclophosphamide (Cytoxan), methotrexate, methysergide (Sansert; not available in the United States), minoxidil (Loniten), mitomycin (Mutamycin), oxyprenolol (Apsolox; not available in the United States), practolol (Eraldin; not available in the United States), procarbazine (Matulane), and sclerotherapeutic agents. Drugs that may cause lupus pleuritis include hydralazine (Apresoline), procainamide (Pronestyl), and quinidine.*

†—Post–cardiac injury syndrome includes post–myocardial infarction syndrome (Dressler's syndrome) and postpericardiotomy syndrome (postcommissurotomy syndrome).

The undiagnosed effusion

- ***No known etiology*** found in a substantial percentage of patients with effusions !
- If the effusion persists despite conservative treatment, **thoracoscopy** could be considered, since it has a high yield for cancer or tuberculosis.
- If thoracoscopy is unavailable, alternative invasive approaches are **needle biopsy** and **open biopsy** of the pleura.
- ***No diagnosis is ever established for about 15 % of patients despite invasive procedures.***

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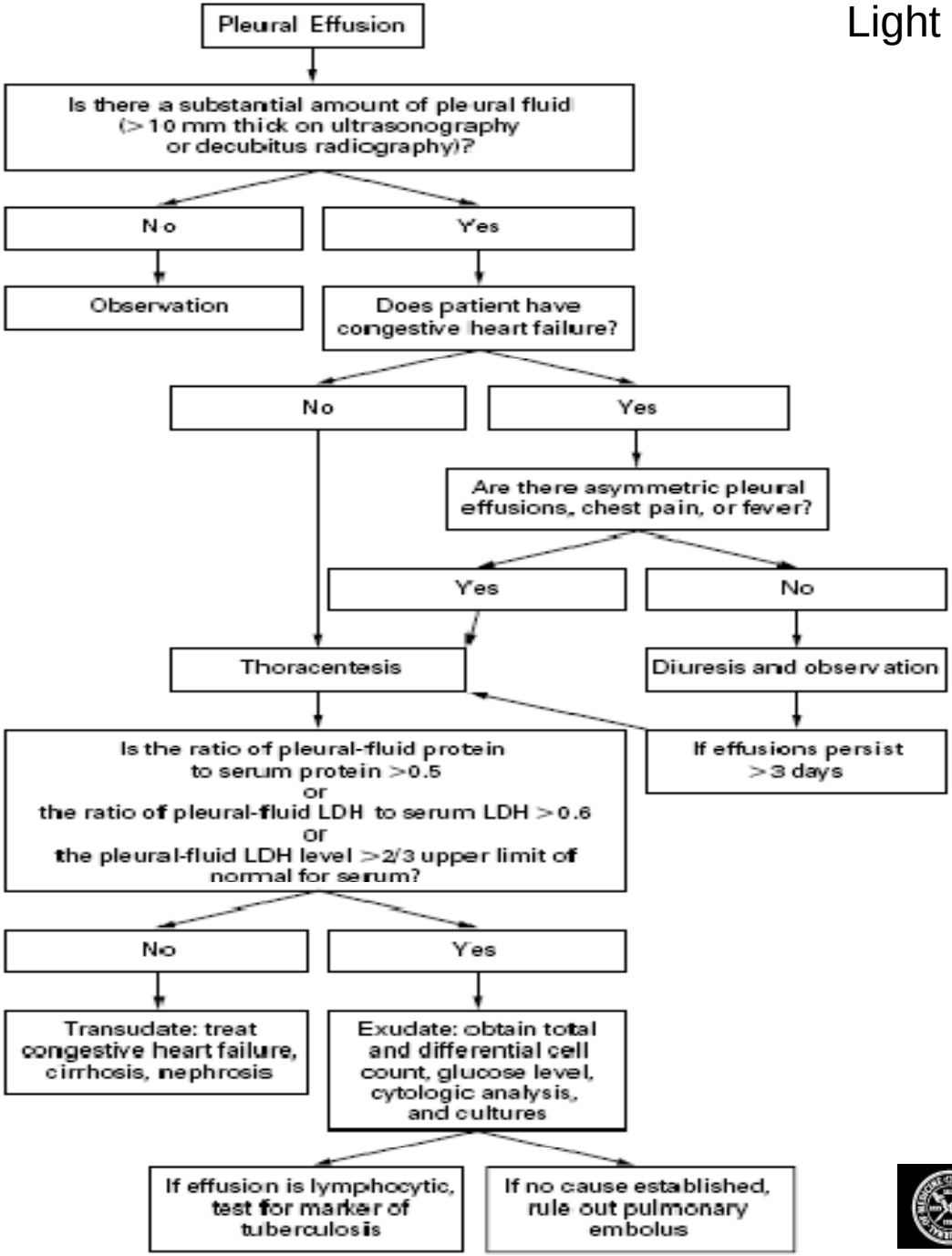

Pleuritis – treatment

Treatment

Management of pleurisy has two primary goals: (1) control the pleuritic chest pain, and (2) treat the underlying condition. To achieve pain control, nonsteroidal anti-inflammatory drugs (NSAIDs) commonly are prescribed as the initial therapy. Narcotic analgesics may be required to relieve severe pleuritic chest pain; however, NSAIDs do not suppress respiratory efforts or cough reflex and are the preferred first-line agent.