

Pleural Effusions.

- 
- ▶ No Conflicts of Interest to disclose

Objectives

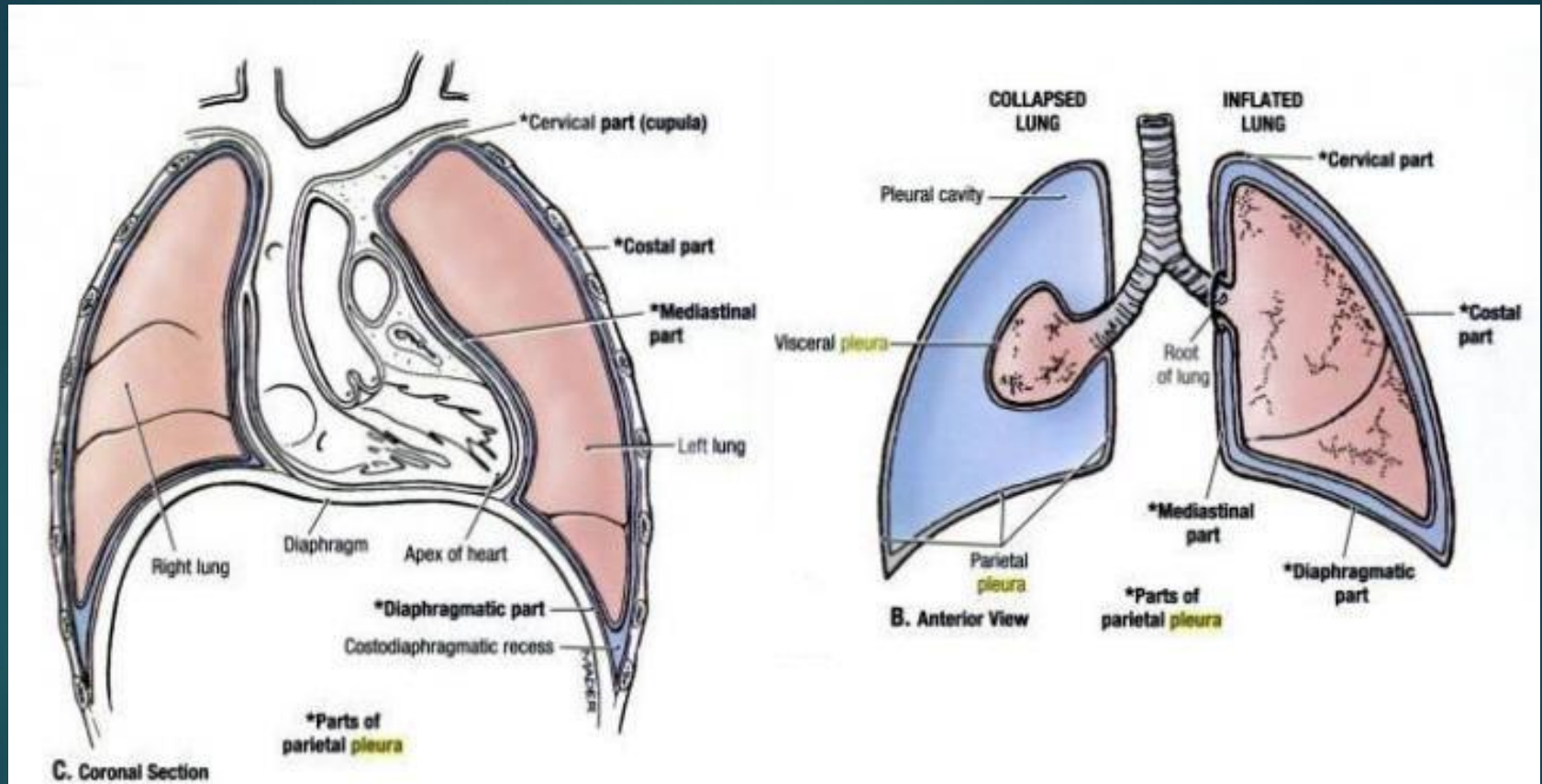
- Definition
- Normal pleural anatomy and physiology
- Pleural fluid norms
- Causes of pleural effusions
- History
- Physical examination
- Diagnosis
- Management decisions in pleural effusions
- Prognosis



Definition

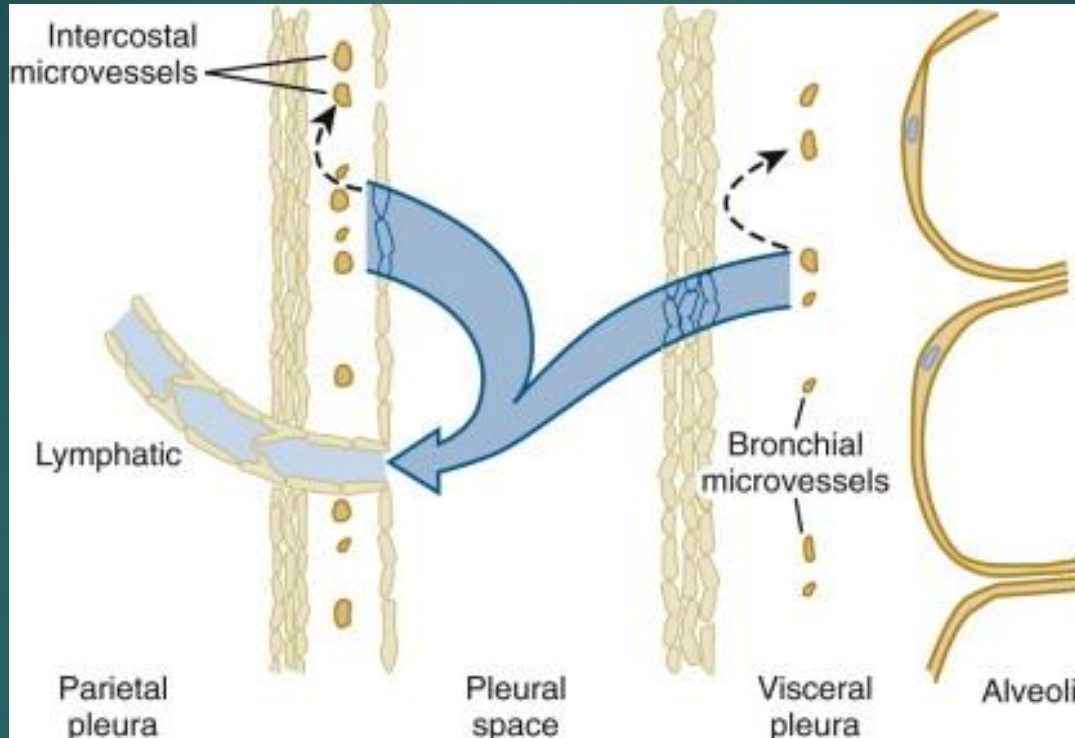
- ▶ What is “Pleural Effusion”
- ▶ Do we normally have fluids in the pleural space?
- ▶ Do we have other names for fluids in the pleural space?

Normal pleural anatomy and physiology



The two layers *combine around the root of the lung* – so the root of lung has no pleural coverage, the layers combine to form the **pulmonary ligament**, which runs inferiorly and attaches the root of the lung to the diaphragm

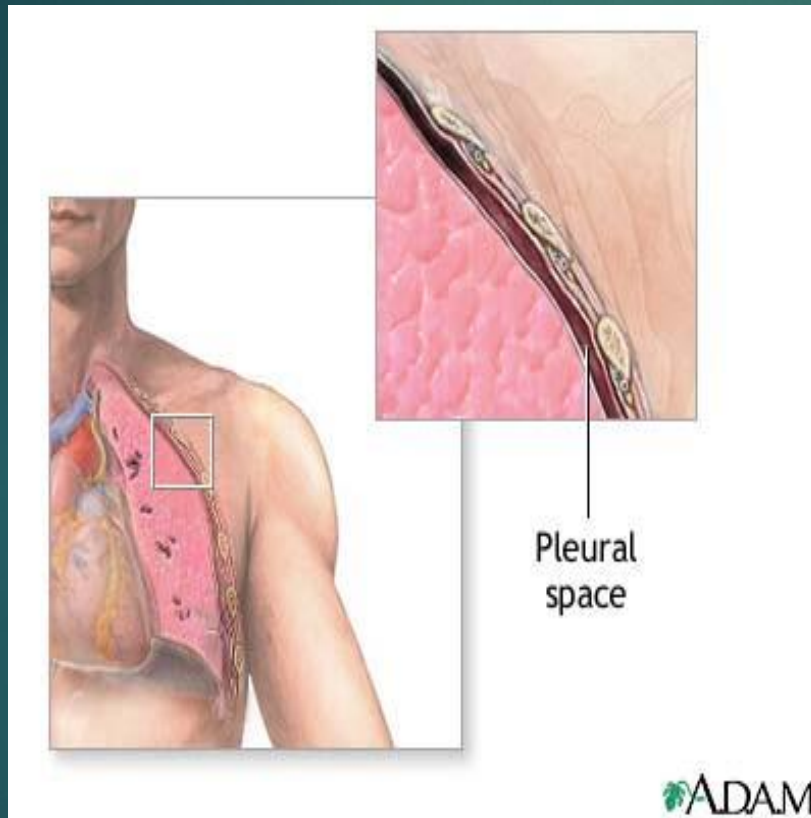
Normal pleural anatomy and physiology



Schema shows normal pleural liquid turnover. The initial microvascular filtrate in the parietal and visceral pleura is partly reabsorbed (dashed arrows). The remaining low-protein interstitial liquid flows across the leaky pleural mesothelial layers into the pleural space. The pleural liquid exits the pleural space via the parietal pleural lymphatic stomata.

(Redrawn from Staub NC, Wiener-Kronish JP, Albertine KH: Transport through the pleura: Physiology of normal liquid and solute exchange in the pleural space. In Chrétien J, Bignon J, Hirsch A [eds]: *The Pleura in Health and Disease*. New York: Marcel Dekker, 1985, p 182, by courtesy of Marcel Dekker.)

Pathophysiology



- Human body makes 0.01ml/kg/hr
- Most resorbed into bronchial veins and lung lymphatics
- 7-14cc nl state
- Low protein (1.0-1.5)
- <1,000 cells predominantly macrophages, mesothelial cells, monocytes, lymphs (10%)
- Ph 7.60-7.64

Mechanism for Pleural Fluid Formation

- ▶ Increase in hydrostatic pressure- CHF
- ▶ Decrease in oncotic pressure- hypoalbuminemia
- ▶ Increase in pleural pressure- atelectasis
- ▶ Increase in endothelial permeability- PNA
- ▶ Decrease in lymphatic drainage- malignancy
- ▶ Movement from peritoneal space- hepatic hydrothorax
- ▶ Thoracic duct rupture -lymphoma
- ▶ Iatrogenic- drug-induced

Pleural Fluid Norms

- ▶ What is the normal pleural fluid volume?
 - ▶ 0.1-0.2 mL/kg (7-14 mL for a 70 kg person)
- ▶ What is the normal cell count & differential?
 - ▶ <1000 nucleated cells/ μ L
 - ▶ Neutrophils – 2%
 - ▶ Eosinophils – 0%
 - ▶ Lymphocytes – 7-11%
 - ▶ Monocytes – 61-77%
 - ▶ Mesothelial cells – 9-30%
- ▶ What is the normal amount of protein?
 - ▶ 1.0-1.5 g/dL
- ▶ What is the normal pH?
 - ▶ 7.60 to 7.64

Transudate vs. exudate

- ▶ Light's criteria
 - ▶ Pleural fluid Total protein/serum total protein > 0.5
 - ▶ Pleural fluid LDH/serum LDH > 0.6
 - ▶ Pleural fluid LDH value $> 2/3$ upper limit of normal for serum normal values
- ▶ If meets one of these criteria, then fluid is classified as exudate.

Transudate vs. exudate

- ▶ **Transudative pleural effusions**-Basically caused by overproduction of water

CHF, Liver disease, Nephrotic syndrome, urinothorax, peritoneal dialysis, Myxedema

- ▶ **Exudative pleural effusions**-Caused by inflammation or injury to the lung/pleura

Infections, neoplasm, pulmonary embolism, collagen vascular diseases, post-surgical, uremia, asbestos exposure

Transudate vs Exudate

Any ONE of the following defines an exudate

- ▶ Light's criteria
 - ▶ Protein P/S > 0.5
 - ▶ LDH P/S > 0.6
 - ▶ LDH > 2/3 ULN
- ▶ Modified Light's Criteria
 - ▶ Pleural fluid protein > 2.9 g/dL
 - ▶ Pleural cholesterol >45 mg/dL
 - ▶ Pleural LDH > 60 % ULN

This can misidentify transudates as exudates 25% of the time.

If a transudate is expected but an exudate is found there are 2 ways to help differentiate as transudates.

- ▶ Difference between serum and pleural fluid protein >3.1g/dL
- ▶ Difference between serum and pleural fluid albumin >1.2

Can definitively diagnose via pleural fluid analysis:

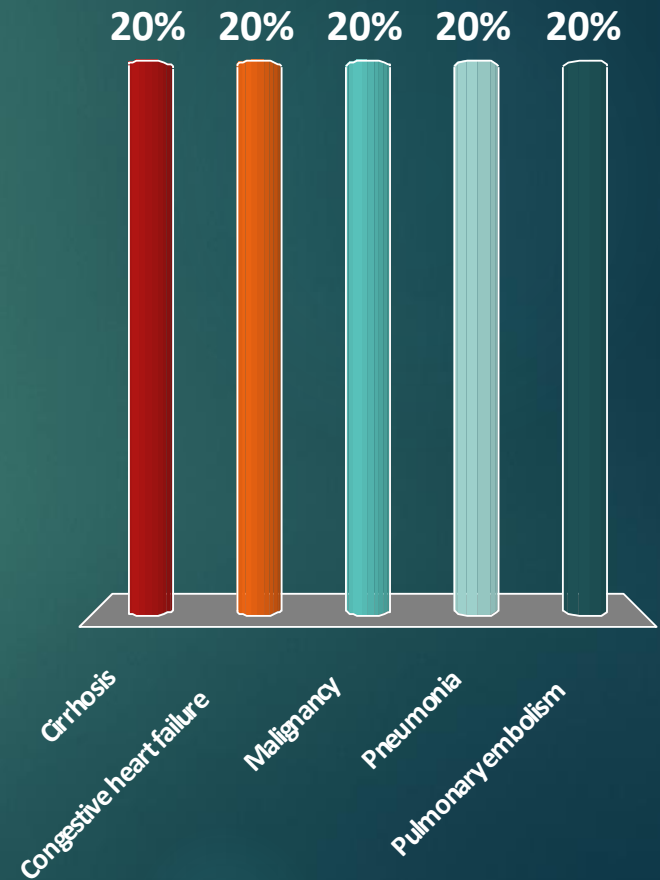
- ▶ Empyema
- ▶ Malignancy
- ▶ Lupus Pleuritis
- ▶ Tuberculous effusion
- ▶ Esophageal rupture
- ▶ Fungal effusion
- ▶ Chylothorax
- ▶ Hemothorax
- ▶ Rheumatoid pleurisy
- ▶ Biliopleural fistula
- ▶ Urinothorax
- ▶ Peritoneal dialysis
- ▶ Duopleural fistula
- ▶ Glycinothorax
- ▶ Migration of Central venous catheter



Transudates

The most common cause(s) of a pleural effusion is

- A. Cirrhosis
- B. Congestive heart failure
- C. Pneumonia
- D. Malignancy
- E. B,C,D



Evaluation: History

- ▶ Most common symptoms of dyspnea and chest pain are relatively nonspecific
- ▶ Dyspnea can present in an effusion of any size depending on parenchymal lung disease
- ▶ Importance of extensive history incld environmental exposures, recent surgery, travel, PMH, drugs

Drugs Associated with Pleural Effusion

- ▶ Bromocriptine
- ▶ Dantrolene
- ▶ Nitrofurantoin
- ▶ Mitomycin
- ▶ Cyclophosphamide
- ▶ Methotrexate
- ▶ Mesalamine
- ▶ Isoretinoin
- ▶ Procarbazine
- ▶ Practolol

TABLE 1

Causes of Pleural Effusions: History, Signs, and Symptoms

<i>Condition</i>	<i>Potential causes of the pleural effusion</i>
History	
Abdominal surgical procedures	Postoperative pleural effusion, subphrenic abscess, pulmonary embolism
Alcohol abuse or pancreatic disease	Pancreatic effusion
Artificial pneumothorax therapy	Tuberculous empyema, pyothorax-associated lymphoma, trapped lung
Asbestos exposure	Mesothelioma, benign asbestos pleural effusion
Cancer	Malignancy
Cardiac surgery or myocardial injury	Pleural effusion secondary to coronary artery bypass graft surgery or Dressler's syndrome
Chronic hemodialysis	Heart failure, uremic pleuritis
Cirrhosis	Hepatic hydrothorax, spontaneous bacterial empyema
Childbirth	Postpartum pleural effusion
Esophageal dilatation or endoscopy	Pleural effusion secondary to esophageal perforation
Human immunodeficiency virus infection	Pneumonia, tuberculosis, primary effusion lymphoma, Kaposi sarcoma
Medication use	Medication-induced pleural disease
Remote inflammatory pleural process	Trapped lung
Rheumatoid arthritis	Rheumatoid pleuritis, pseudochylothorax
Superovulation with gonadotrophins	Pleural effusion secondary to ovarian hyperstimulation syndrome
Systemic lupus erythematosus	Lupus pleuritis, pneumonia, pulmonary embolism
Trauma	Hemothorax, chylothorax, duropleural fistula

Evaluation: Physical Exam

- ▶ Less than 300cc usually not detected on PE
- ▶ ~500cc: dull to percussion, fremitus, intensity of breath sounds
- ▶ >1000cc: bulging intercostal spaces, ipsilateral chest wall expansion, dull percussion to level of scapula, fremitus, egophany
- ▶ Massive- above are accentuated but breath sounds absent

Evaluation:Radiology

- CXR- AP&Lateral
- US- to differentiate small effusions vs pleural thickening
- CT – not routinely indicated but can eval lung parenchyma/mass obscured by effusion
- Lateral Decubitus- free flowing/loculated

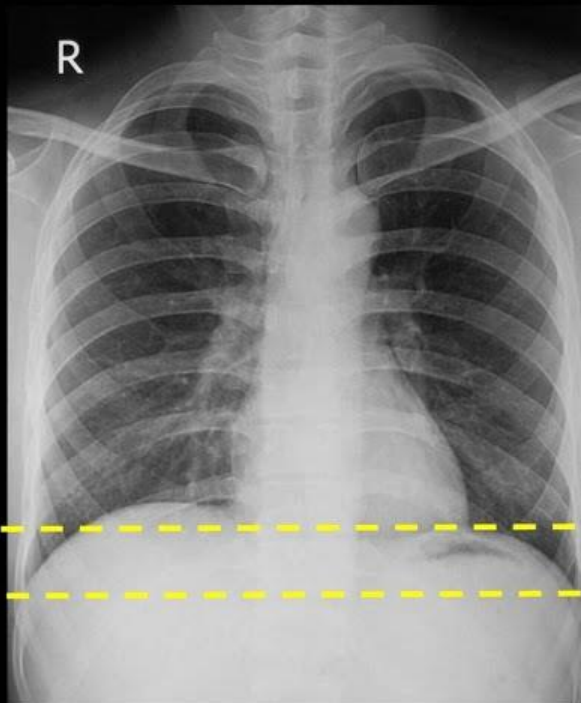
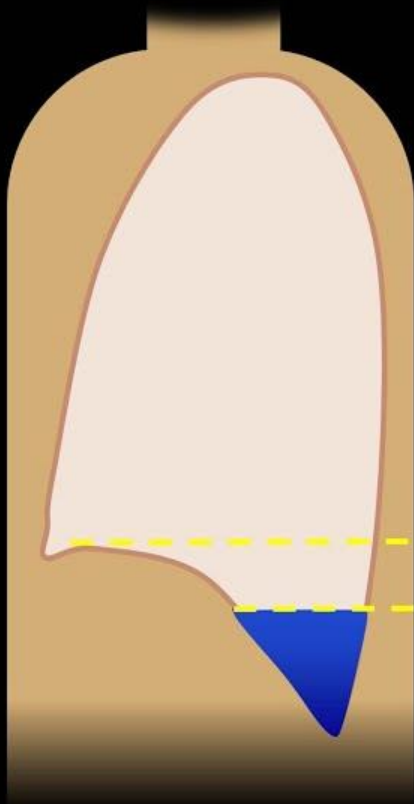
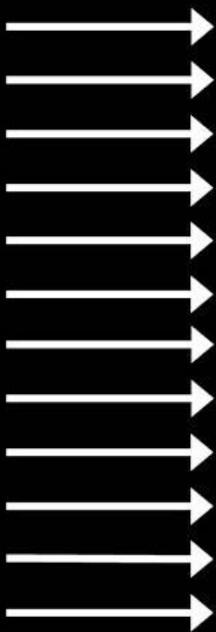






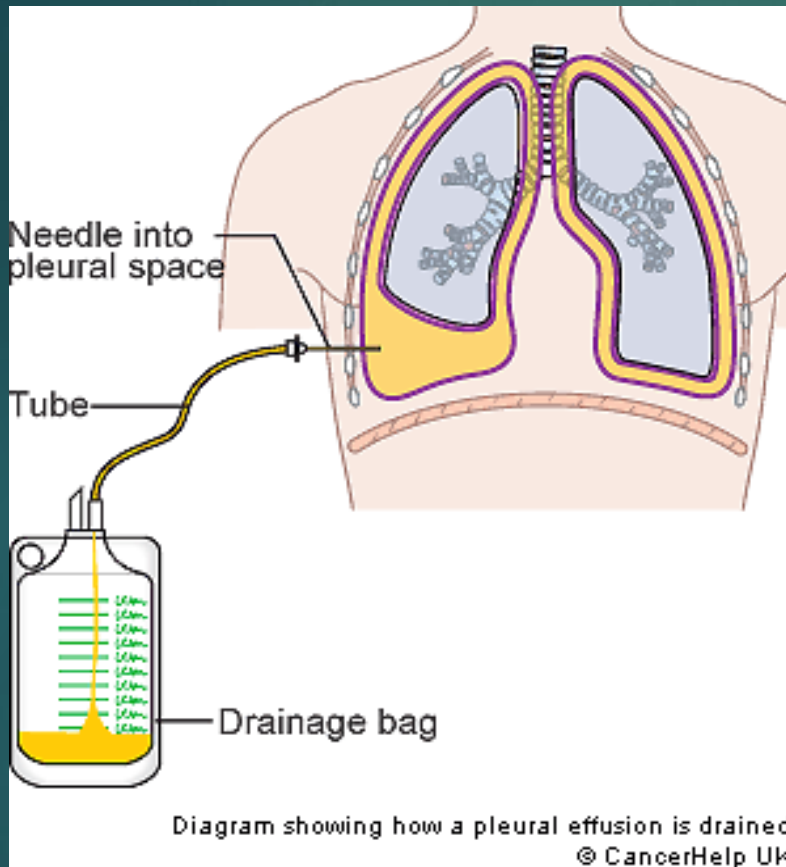
Pleural Effusions

X-rays



X ray
film

Evaluation: Thoracentesis



- ▶ First described in 1852
- ▶ Indicated in any pleural effusion of adequate size where there is no obvious cause
- ▶ Clinically useful 92%
- ▶ Diagnosis 75%

Pleural Fluid Appearance

Color	Suggested Diagnosis
Pale Yellow	Transudate
Red/Bloody	Malignancy, BAPE, PCIS, Pulmonary infarction, Trauma
White/Milky	Chylothorax/Cholesterol effusion
Brown	Chronic bloody effusion, rupture of amebic liver abscess
Black	Aspergillus
Yellow-green	Rheumatoid pleurisy
Color of tube feeds/IVF	Feeding tube/Catheter has reached pleural space

Pleural Fluid Appearance

Characteristic	Suggested Diagnosis
Water Like	Duro-pleural fistula
Urine Like	Urinothorax
Pus	Empyema
Viscous	Mesothelioma, Empyema
Debris	Rheumatoid pleurisy
Turbid	Inflammatory exudate or lipids
Anchovy paste	Amebic liver abscess rupture
Satin-like sheen	Cholesterol effusion

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Transudates

- ▶ CHF
- ▶ Hepatic hydrothorax
- ▶ Nephrotic syndrome
- ▶ Atelectasis
- ▶ Peritoneal dialysis
- ▶ Hypoalbuminemia
- ▶ Acute SVC obstruction
- ▶ Trapped lung
- ▶ Constrictive pericarditis
- ▶ Urinothorax
- ▶ Extravascular migration of central venous catheter
- ▶ Duro-pleural fistula
- ▶ Ventriculopleural shunt

Further studies for transudate

- ▶ Urinothorax
- ▶ Peritoneal dialysis
- ▶ Duopleural fistula
- ▶ Glycinothorax
- ▶ Migration of CVC

Creatinine PF/S > 1

Protein < 0.5g/dL &

PF/S glucose > 2.0

Presence of β 2-transferrin

Glycine PF > S (100-300mmol/L)

Depending on infusion

-Glucose: PF/S > 1

-Saline: PF Protein < 0.5g/dL

-Lipids: white fluid w/ high triglycerides

Table 8. Causes of Exudative Pleural Effusions**Infection**

- Bacterial pneumonia
- Tuberculous
- Parasites
- Fungal disease
- Atypical pneumonias
- Nocardia, Actinomyces
- Subphrenic abscess
- Rupture of amebic liver abscess
- Hepatic abscess
- Splenic abscess
- Viral hepatitis
- Spontaneous esophageal rupture

Malignancy

- Carcinoma
- Lymphoma
- Leukemia
- Mesothelioma
- Sarcoma (angio, Kaposi)

Inflammatory and others

- Pancreatic disease (acute; pancreaticopleural fistula)
- BAPE
- Pulmonary embolism
- Radiation therapy
- Uremic pleuritis
- Sarcoidosis
- PCIS
- Hemothorax
- ARDS

Connective tissue disease/vasculitis

- Lupus pleuritis
- Rheumatoid pleurisy
- Mixed connective tissue disease
- Churg-Strauss syndrome
- Wegener granulomatosis
- Familial Mediterranean fever

Lymphatic abnormalities

- Chylothorax
- Yellow nail syndrome
- LAM
- Noonan syndrome
- Lymphangiectasia

Movement of fluid from abdomen to pleural space

- Acute pancreatitis
- Pancreaticopleural fistula
- Meigs syndrome
- Carcinoma
- Lymphoma
- Chylous ascites

Lung entrapment

- Cholesterol effusion (TB; rheumatoid pleurisy)
- CPE/empyema
- CABG Surgery

Endocrine dysfunction

- Hypothyroidism
- Ovarian hyperstimulation syndrome

Iatrogenic

- Esophageal instrumentation
- Esophageal sclerotherapy
- Central venous catheter misplacement/migration
- Drug induced
- Enteral feeding tube misplacement into pleural space
- Leakage of percutaneous biliary drainage tube
- CABG surgery

Other diagnostic testing for pleural fluid

- Glucose
 - May be reduced in **infections or RA**
- pH
 - May be reduced in infections, malignancy, RA, esophageal rupture
 - Malignancy
- Cytology
 - Routine, AFB and fungal studies
- Cultures
 - Elevated in **esophageal rupture, pancreatitis, and malignancy**
 - Elevated in chylothorax (chylomicrons)
- Amylase
 - Elevated in **tuberculous pleuritis**, ADA < 40 U/L excludes tuberculosis
- Triglyceride
- Adenosine deaminase

Routine Additional Testing:

- ▶ pH: NL PF >7.60
- ▶ Transudates 7.45-7.55*
- ▶ Exudates 7.30-7.45
- ▶ pH <7.30 narrows diagnosis to: empyema, complicated parapneumonic effusion, chronic rheumatoid pleurisy, esophageal rupture, malignancy, tuberculous pleurisy, lupus pleuritis
- ▶ Dx with low pH are also associated with low glucose (<60mg/dL)

pH and Glucose

Diagnosis

Incidence

pH

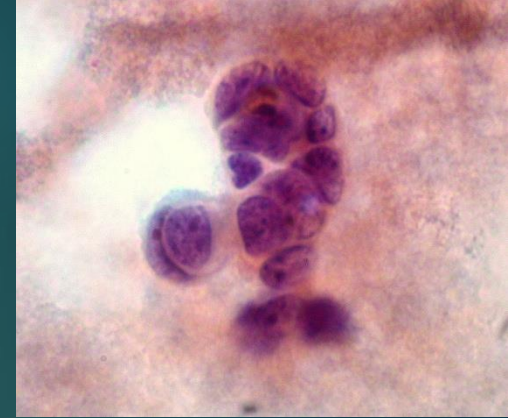
Glucose

Diagnosis	Incidence	pH	Glucose
Empyema	100%	6.00-7.20	0-40
Complicated parapneumonic	80-100%	6.90-7.29	30-50
Rheumatoid pleurisy	85%	6.85-7.05	0-50
Esophageal rupture	80-100%	6.00-7.29	0-40
Malignancy	30%	7.00-7.29	15-59
Tuberculous	20%	7.00-7.29	15-59
Lupus pleuritis	15%	7.15-7.29	30-59

Cell Count

Cell Type	Value	Differential Dx
RBC	>100,000 per mm ³	Malignancy, trauma, PE, parapneumonic effusion
Lymphocytes	>50%	Malignancy, PE, TB, Post CABG
	>80%	Post CABG, TB, Chylothorax, Yellow nail, Sarcoid, Lymphoma, Acute Lung Rejection, Chronic Rheumatoid Effusion
	>90%	TB, Lymphoma
Neutrophils	>50%	Parapneumonic effusion, PE, Abdominal disease, Acute tuberculous pleurisy (7%), Malignancy (20%), Viral infection
Eosinophils	>10%	PTX, HTX, BAPE, Parasitic, Drug induced, Fungal Disease, Churg-Strauss

Cytology



- ▶ Diagnostic yield of malignant effusion ranges from 40-90%
- ▶ Likely secondary to mechanism for effusion or type of tumor:
 - Endobronchial obstruction with atelectasis & resultant effusion
 - Commonly negative with Lymphoma, Sarcoma, Mesothelioma and + in AdenoCA

Additional testing for exudates

Amylase:

Should be ordered if pancreatic disease , malignancy or esophageal rupture suspected

Salivary amylase present in esophageal rupture and AdenoCA of lung or ovary (isoamylase), ruptured ectopic

Pancreatic pseudocyst can reach levels up to $>100,000\text{IU/L}$

Triglyceride

- ▶ Should be ordered if a whitish pleural fluid sample obtained
- ▶ If $>110\text{mg/dL}$ diagnostic of chylothorax
- ▶ If $<50\text{mg/dL}$ \Rightarrow chylothorax excluded
- ▶ If $50\text{-}110\text{mg/dL}$ then order lipoprotein electrophoresis to eval if chylomicrons present



Adenosine Deaminase (ADA)

- ▶ ADA is an enzyme found in most cells and is involved in the degradation of purines and maturation of monocyte-macrophages
- ▶ >40 IU/L has a sens 90-100% and spec 85-90% for tuberculous pleurisy
- ▶ If only lymphocytic exudates are considered specificity to >95%
- ▶ Can also be observed in RA, empyema, parapneumonic, malignant effusion

Bilirubin

- ▶ Should be ordered when a biliopleural fistula is suspected by history or greenish pleural fluid
- ▶ Complication of prolonged (7d-2months) percutaneous biliary drainage
- ▶ PF/S Bilirubin >1

Lupus Pleuritis

- ▶ ANA
- ▶ Wright stain performed on pleural fluid to evaluate for LE cells
- ▶ PF/S ANA>1 supports diagnosis
- ▶ LE Cells are diagnostic
- ▶ Specific immunofluorescent pattern of nuclear staining of either anti-IgG, anti-IgM, anti-C3 in pleural cells has been documented

Rheumatoid effusion

- ▶ Classic triad of: Glucose $<30\text{mg/dL}$, LDH $>1000\text{IU/L}$, pH 7.00 (Infxn exclud)
- ▶ RF $>1:320$
- ▶ Cytology is characteristic- large, elongated tadpole-shaped cells with background granular material

Undiagnosed exudates...


- ▶ Bronchoscopy should be considered if hemoptysis, infiltrates, mass is present
- ▶ Bx- had been recommended for undiagnosed exudates when TB or malignancy suspected

A 58-year old man is evaluated for dyspnea and is found to have a moderate sized right-sided pleural effusion. He undergoes a thoracentesis with the following findings.


Appearance	Serosanguinous
pH	7.48
Protein	5.8g /dL (serum protein 7.2g/dL)
LDH	285 IU/L (serum LDH 320 IU/L)
Glucose	66 mg/dL
WBC	3800/mm ³
RBC	24,000/mm ³
PMNs	10%
Lymphocytes	80%
Mesothelial cells	10%
Cytology	Lymphocytosis with chronic inflammation and no malignant cells or organisms identified

Which of the following is an unlikely cause of the pleural effusion in this patient?

- A. Cirrhosis
- B. Lung cancer
- C. Mesothelioma
- D. Pulmonary embolism
- E. Tuberculosis



A 62 year-old woman is admitted to the hospital with a community acquired pneumonia with a 4-day history of fever, cough, and right-sided pleuritic chest pain. The admission chest x-ray identifies a right lower and middle lobe infiltrate with an associated effusion.



All of the following indicate a complicated effusion that may require tube thoracostomy EXCEPT:

- A. Loculated fluid
- B. Pleural fluid pH less than 7.2
- C. Pleural fluid glucose greater than 60 mg/dL
- D. Positive Gram stain or culture of the pleural fluid
- E. Frank pus on thoracentesis

Indicators of complicated parapneumonic pleural effusion

Empyema-positive Gram stain of fluid or gross pus noted on thoracentesis

Multiple septations or loculations noted on ultrasound or CT chest

pH < 7.2 indicates complicated infection, < 7.0 will likely need drainage/decortication

Pleural fluid glucose < 60 mg/dL

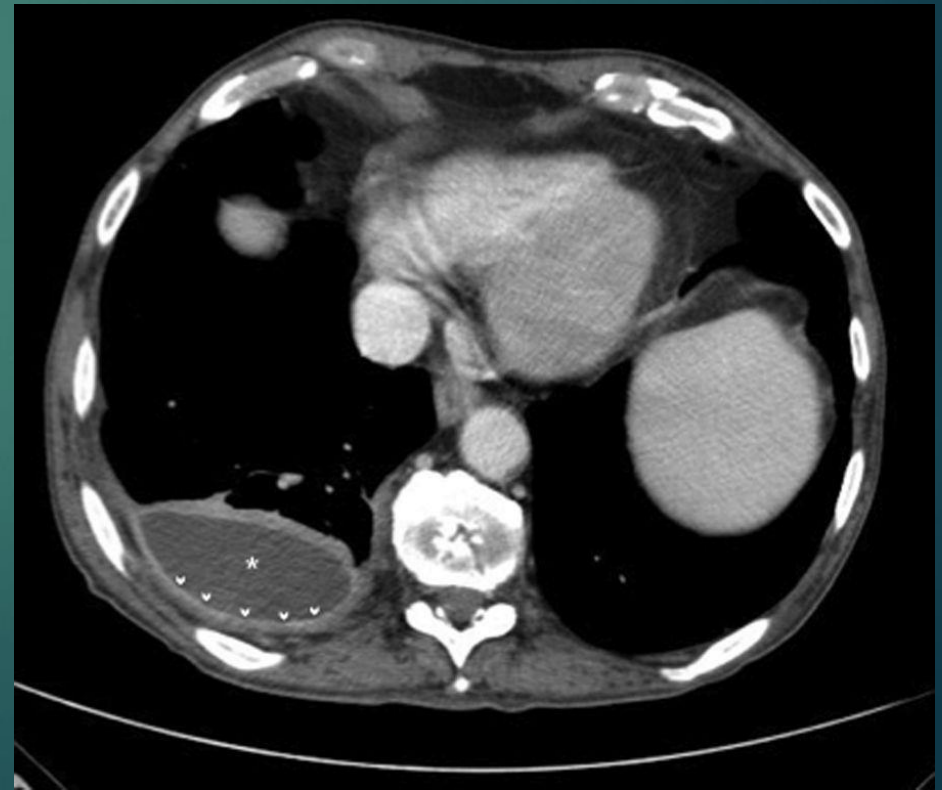
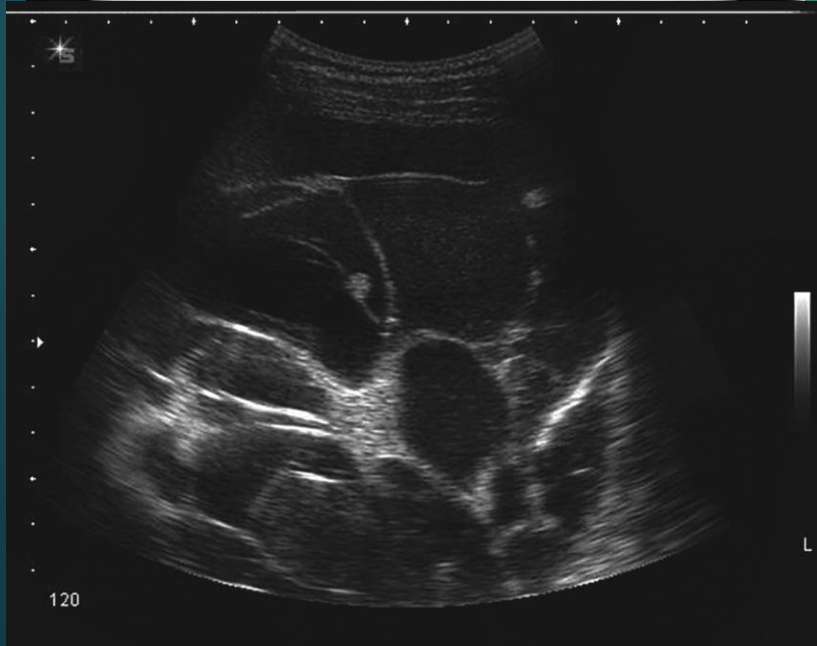
Treatment is **drainage** and antibiotic therapy.

Includes either repeat thoracentesis, percutaneous catheter drainage, chest tube thoracostomy or possible surgical decortication. Can use **intrapleural thrombolytics** to help facilitate drainage.

Early intervention improves outcomes.


Radiology of complicated pleural effusion

- Shows pocket of fluid or mass
- CT shows split pleura with some contrast enhancement of the parietal pleura
- **Ultrasound** images can show septations in the fluid



Malignant pleural effusions

- ▶ Poor prognosis – median survival 6-9 months (except breast, lymphoma, ovarian)
- ▶ **Diagnosis: Pleural fluid cytology x 2 (yield on second thoracentesis goes up slightly)**
- ▶ Thoracoscopic biopsy
- ▶ Management: Repeat thoracentesis, indwelling pleural catheters, pleurodesis, surgery



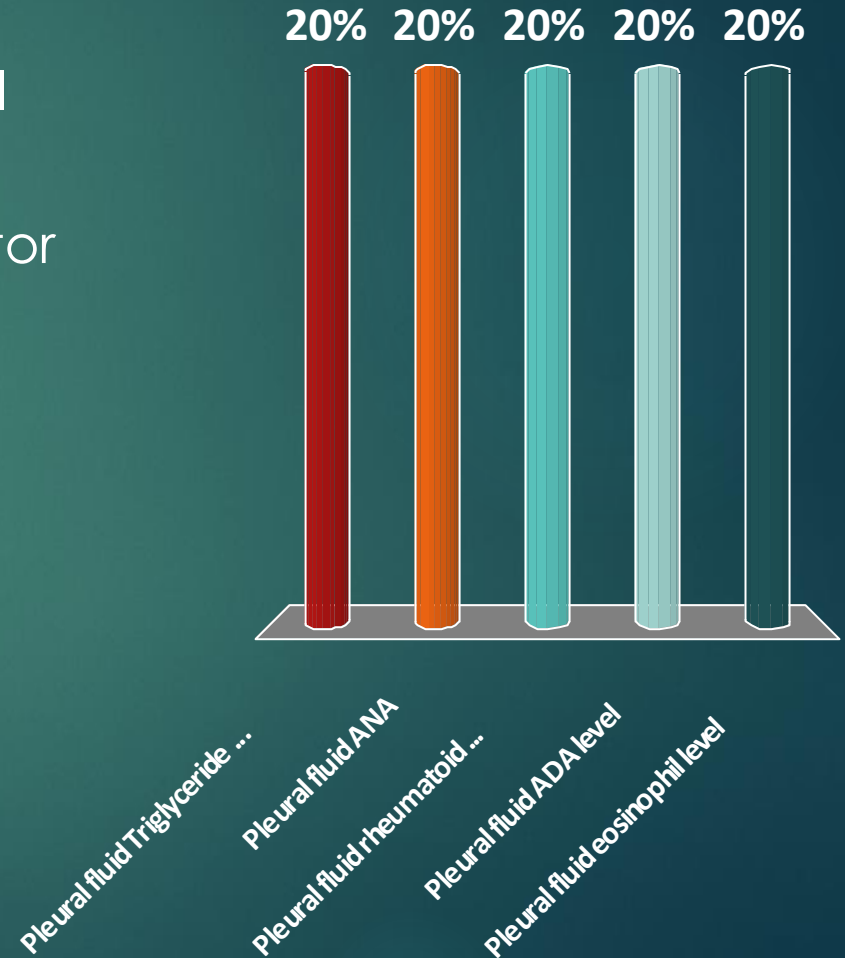
42 year old man with a history of arthritis develops a cough and some increased dyspnea. Physical exam reveals bilateral wrist swelling and subcutaneous nodules. There are decreased breath sounds over the left chest and CXR shows a moderate sized pleural effusion.

Thoracentesis reveals

- Protein 3.8 g/dl (Serum 6.8)
- LDH 400 IU/L (serum 280)
- Glucose 25 mg/dl
- pH 7.0

Additional diagnostic testing to help with diagnosis should include

- A. Pleural fluid Triglyceride level
- B. Pleural fluid ANA
- C. Pleural fluid rheumatoid factor
- D. Pleural fluid ADA level
- E. Pleural fluid eosinophil level



Pleural effusions associated with collagen vascular diseases

Rheumatoid Arthritis

- Usually occurs after arthritis has been present for years
- Associated with subcutaneous nodules
- More common in men with RA
- Can be associated with other pulmonary manifestations such as pulmonary nodules
- Does not tend to respond to treatment of RA
- Can have cholesterol crystals

Lupus Pleuritis

- Usually preceded by arthritis and arthralgias
- May be associated with drug induced lupus –INH, hydralazine, phenytoin, procainamide
- Frequently have pleuritic pain
- Diagnosis is based primarily on clinical picture
- Pleural fluid ANA not particularly sensitive or specific for diagnosis
- Drug induced disease resolves with stopping offending agent
- Responds to steroid therapy

24 year old woman presents with several weeks of increasing cough and dyspnea. She denies chest pain, fever or chills. She has noted some weight loss but is unable to quantify it well. Physical exam reveals decreased breath sounds over the right chest with dullness to percussion and decreased tactile fremitus. A CXR reveals large mediastinal mass and right sided pleural effusion. She has no previous history of any trauma or recent surgery to the chest. She takes NSAIDs for dysmenorrhea. You perform a thoracentesis revealing turbid fluid. Pleural fluid analysis shows triglycerides of 600



The most likely diagnosis is

- A. Drug induced pleural effusion
- B. Bronchogenic carcinoma
- C. Lymphoma
- D. Empyema
- E. Rheumatoid arthritis

Chylothorax and Pseudochyolous effusions

Chylothorax-presence of chyle in the pleural space.

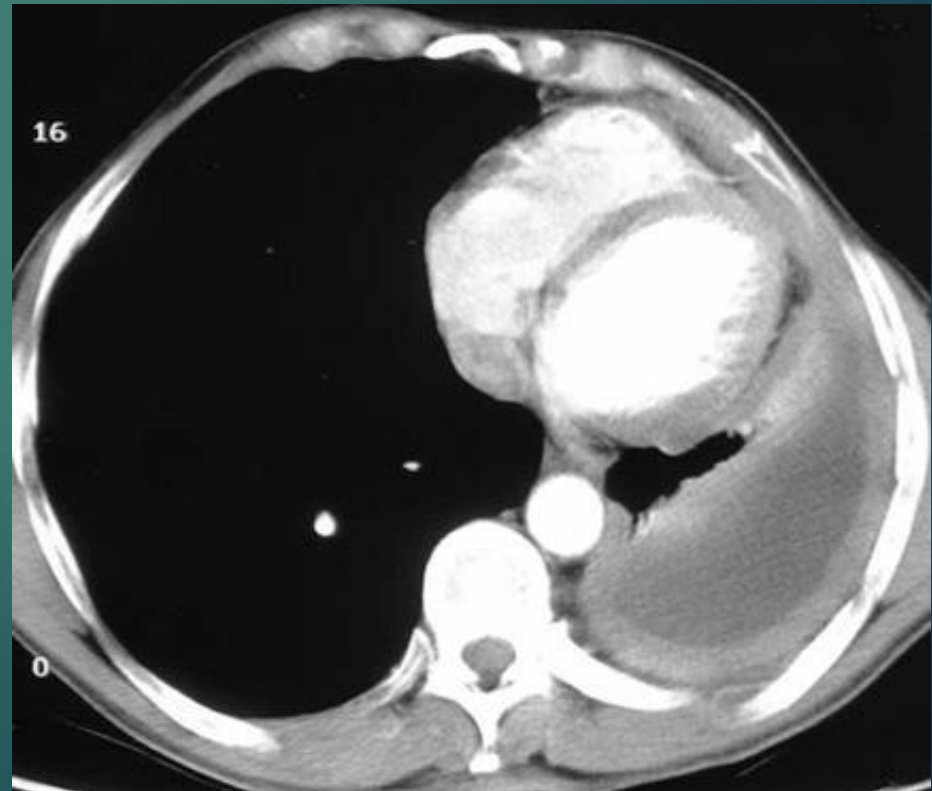
Triglyceride level > 110mg/dL

- **Trauma** to thoracic duct(surgery)
- Non-traumatic causes related to malignancy-
lymphoma
- Difficult to treat. Use a **low fat diet**. Limit use of thoracentesis and chest tube drainage
- Treatment of lymphoma or other malignancy with XRT and/or chemotherapy
- Embolization of the thoracic duct or ligation may be options

Pseudochyolous effusion-presence of **cholesterol** in the pleural space, Cholesterol level >250 mg/dL. May have cholesterol crystals

- **Chronic effusions**
- **Tuberculous** pleurisy
- **Rheumatoid arthritis**
- Thoracentesis may have limited benefit because of the chronicity of the process causing trapped lung.

- 68 year old man, previously worked at a paper mill for 20 years where he applied insulation to large industrial boilers, however, he stopped when he was 50. presents with complaint of increased cough and dyspnea over the past three months. He has also had some dull continuous chest discomfort over the right side of his chest
- Physical exam reveals decreased breath sounds and dullness to percussion over the right chest
CT chest reveals-



Most likely diagnosis:

- ▶ A. Yellow Nail syndrome
- ▶ B. Loculated empyema
- ▶ C. Tuberculous pleuritis
- ▶ D. Chylothorax
- ▶ E. Mesothelioma

Pleural malignancy

- ▶ Adenocarcinoma is most common diagnosis and is metastatic. Usually related to lung cancer, but also can be seen in breast or other adenocarcinomas.
- ▶ Treatment is usually palliative though some malignancies may respond better to chemotherapy. (Breast and Lymphoma)
- ▶ Mesothelioma is a primary neoplasm involving the pleura. Related to previous asbestosis exposure. Mesothelin levels in pleural fluid may suggest diagnosis.
- ▶ Can treat localized mesothelioma with surgical excision but most disease is extensive. Cisplatin/pemetrexed can be used for treatment.

Asbestos related pleural disease

- Can cause disease many years after exposure
- Pleural effusion is more likely with heavier exposure history
- Associated with recurrent pleural effusions that may resolve without evidence of disease or may cause pleural fibrosis
- May cause calcified pleural plaques.
- Diagnosis of benign pleural disease is a diagnosis of exclusion. Monitor for up to two years. **Eosinophils** may be noted in fluid, also hemorrhagic effusion.



▶ Management and Prognosis