

Pleural Disease

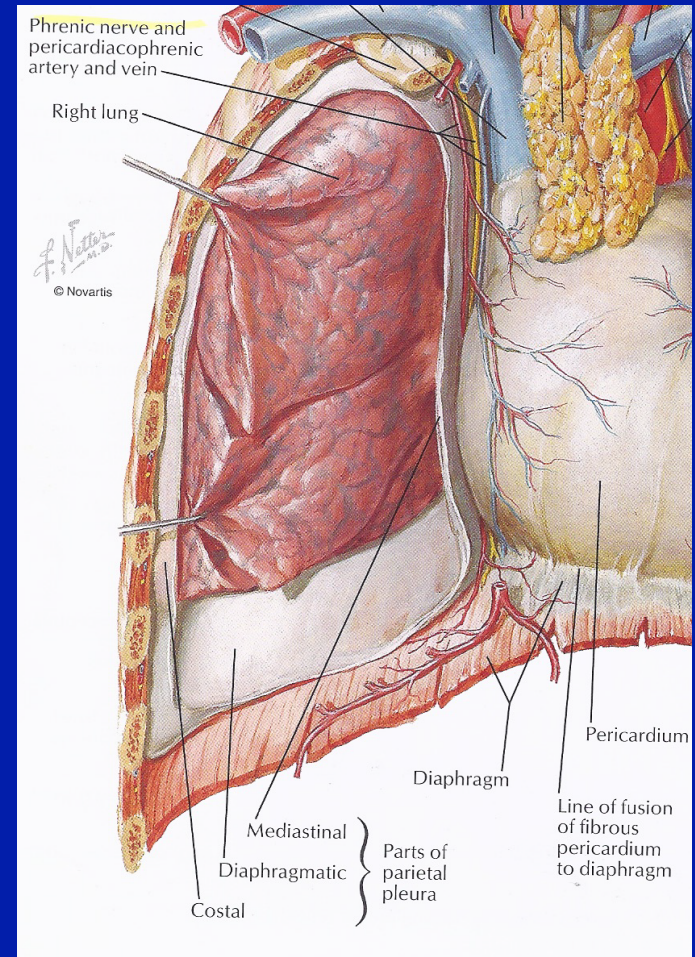
Meghan Fitzpatrick, MD

Pleural Disease: Objectives

- Review the anatomy and physiology of the pleural space
- Review diagnosis and management of common disorders of the pleura
 - Pleural effusion
 - Pneumothorax
 - Pleural Tumors

Pleural Anatomy

- Visceral and parietal pleura surround the lung and line thoracic cavity, respectively
- Single layer of mesothelial cells, with underlying layer of connective tissue containing vasculature, lymphatics, nerves



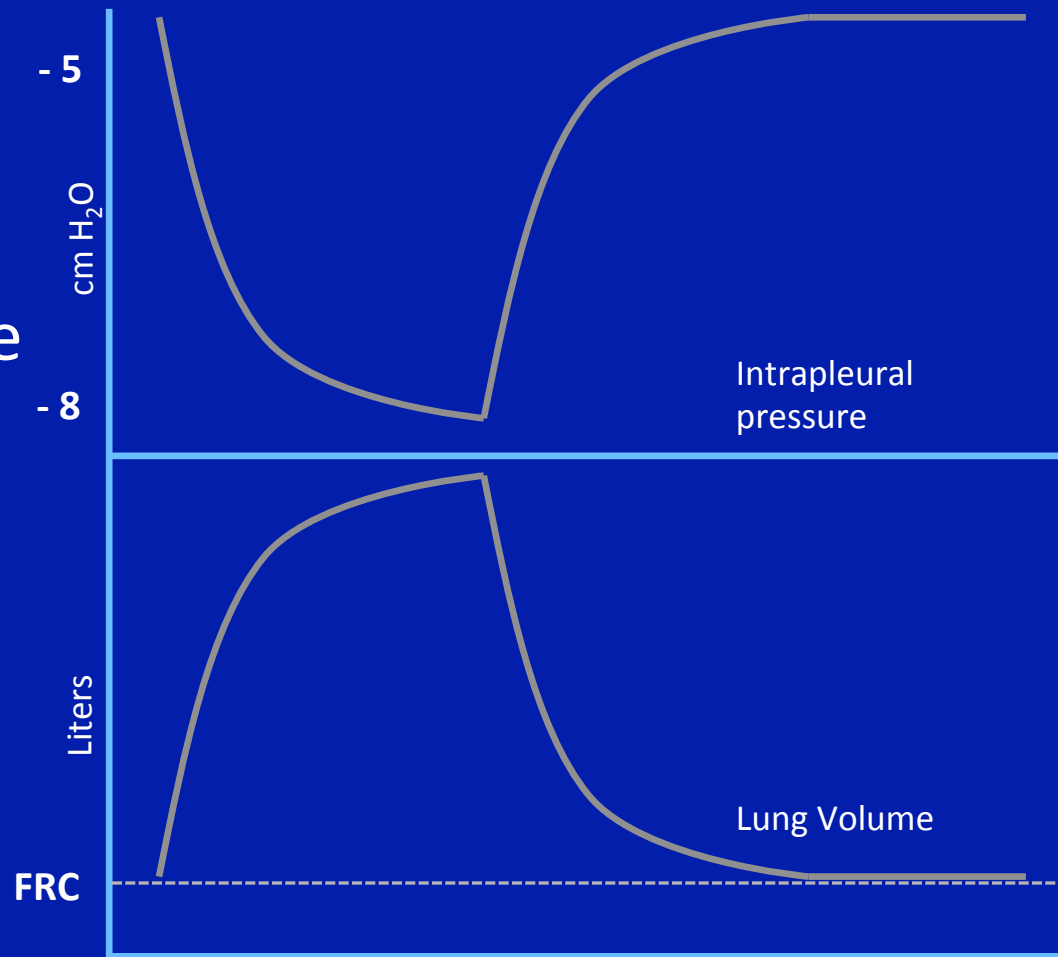
Netter F. Atlas of Human Anatomy, 2nd edition. 1997, Plate 200.

Pleural Anatomy

- Both parietal and visceral pleura in humans are supplied by systemic circulation
- Lymphatics are present in both visceral and parietal pleura, but fluid from the pleural space is primarily absorbed by the parietal pleural lymphatics
- Pain fibers are located on parietal pleura only

Pleural Physiology

- Pleural space pressure in a spontaneously breathing person is a negative pressure space (with exception of during forced exhalation)



Pleural Physiology: Fluid Transfer

- 2-20 mL of fluid in each pleural space, continuously filtered via pleural capillaries
- Fluid flow for every capillary system can be described using the Starling equation

$$Q_f = K_f * [(P_{CAP} - P_{PL}) - \sigma (\pi_{CAP} - \pi_{PL})]$$

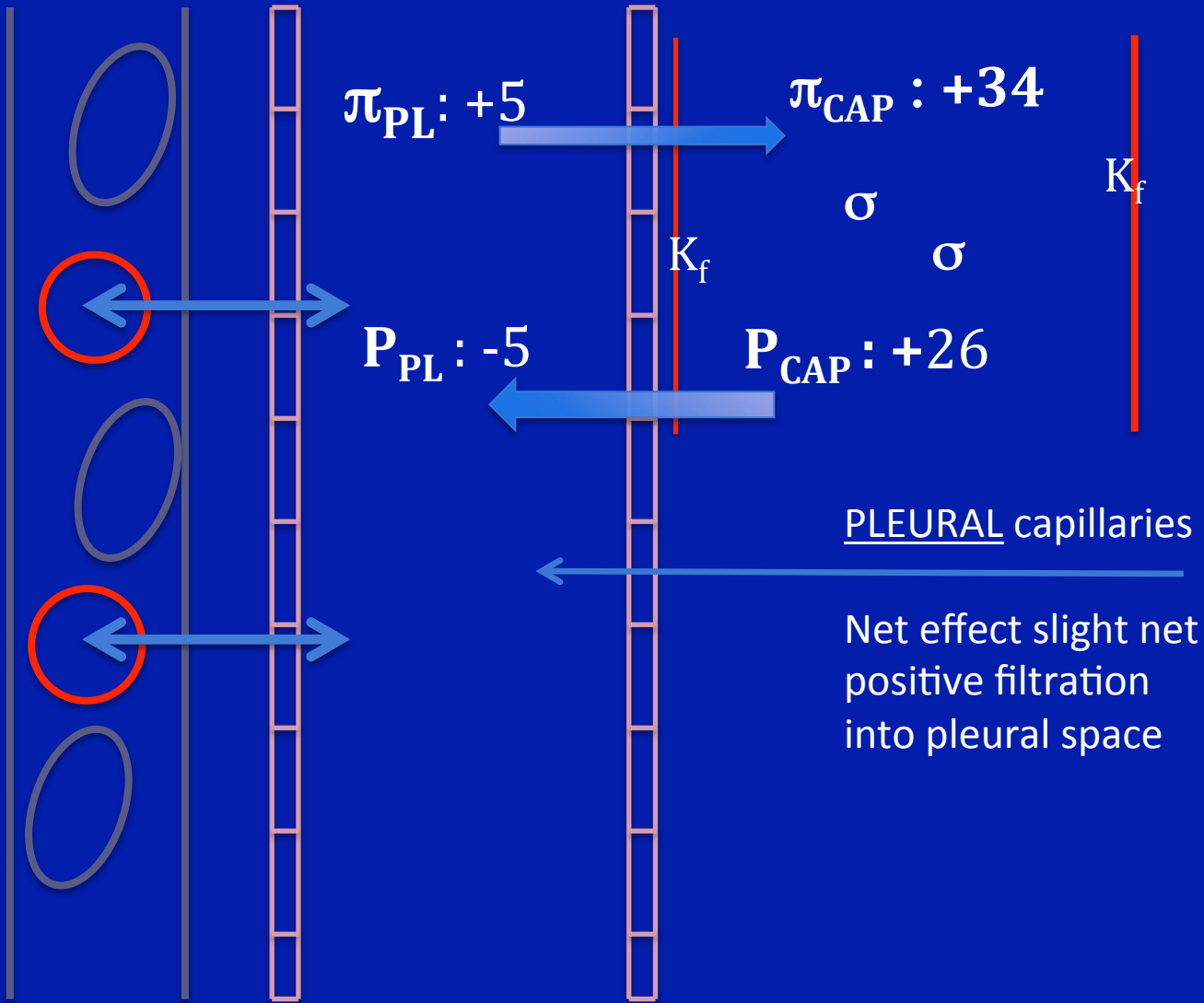
Q_f : fluid flow (into pleural space)

P : hydrostatic pressures, π : oncotic pressures

K_f : filtration coefficient (capillary permeability)

σ : reflection coefficient (ability of the capillary to retain solute)

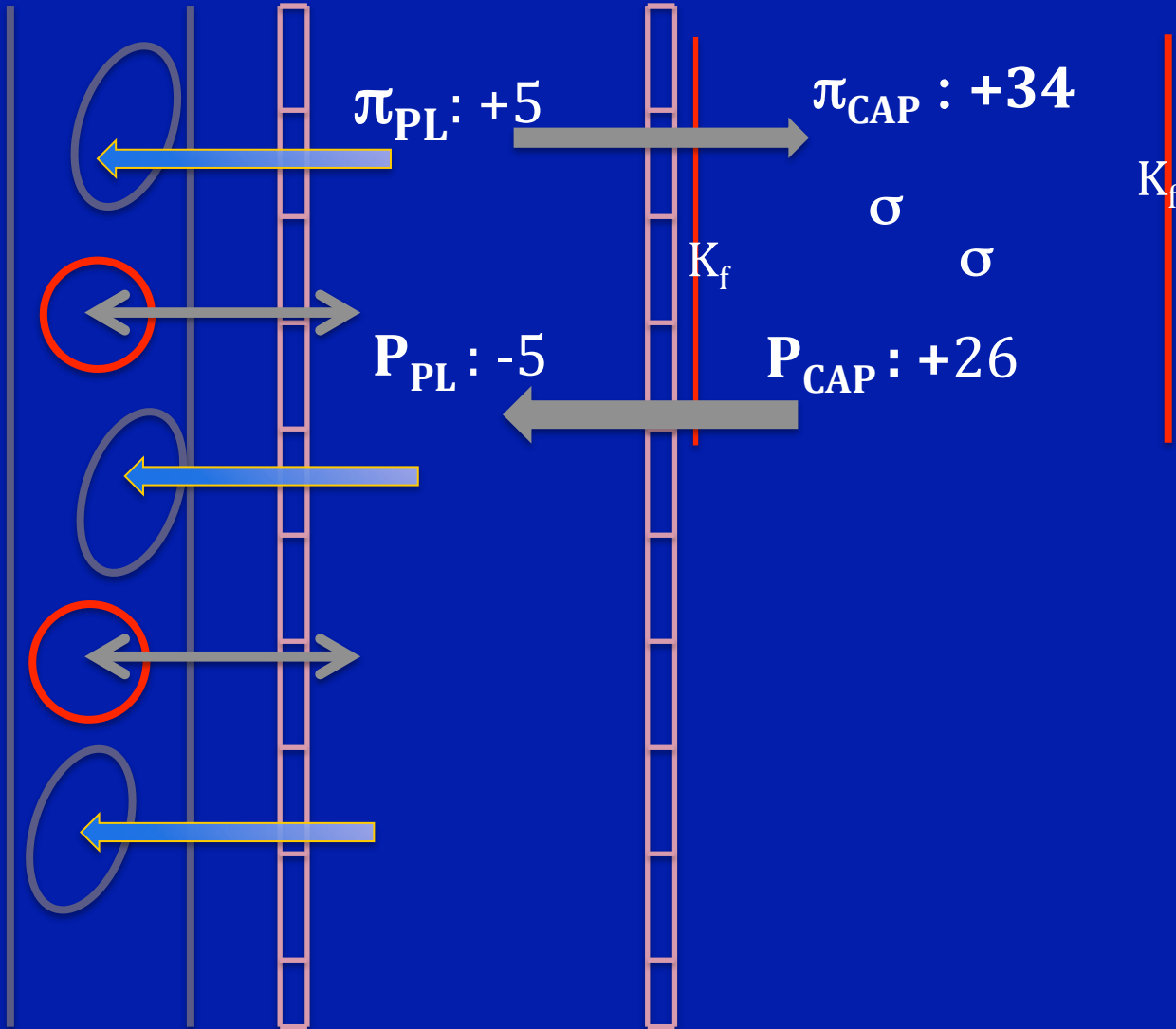
Filtration: $Q_f = K_f * [(P_{CAP} - P_{PL}) - \sigma (\pi_{CAP} - \pi_{PL})]$



PLEURAL capillaries

Net effect slight net positive filtration into pleural space

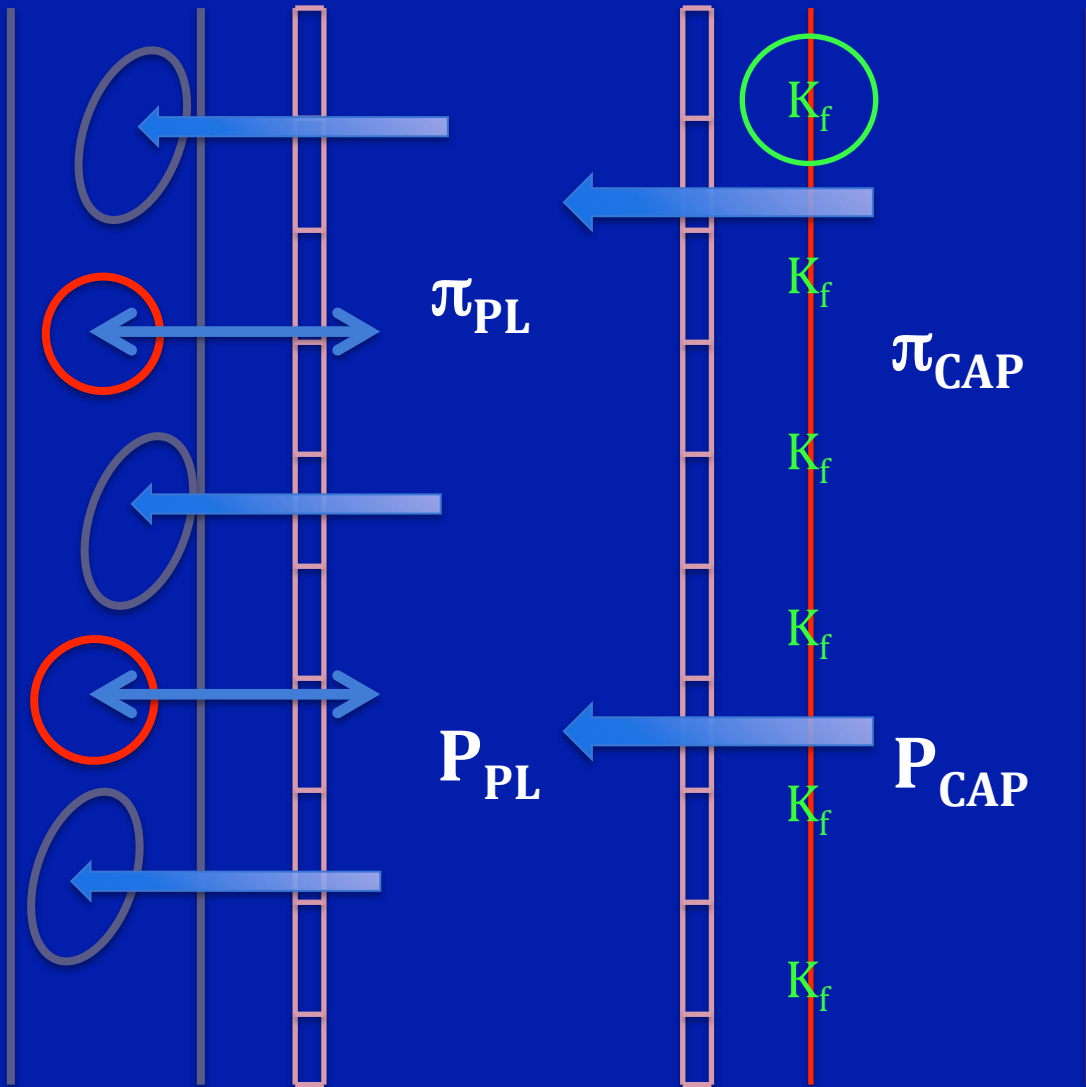
Parietal Pleural Lymphatics Absorb Fluid, Solute, and Cells from the Pleural Space



What Leads to Excess Pleural Fluid Collection?

- Multiple Mechanisms ...

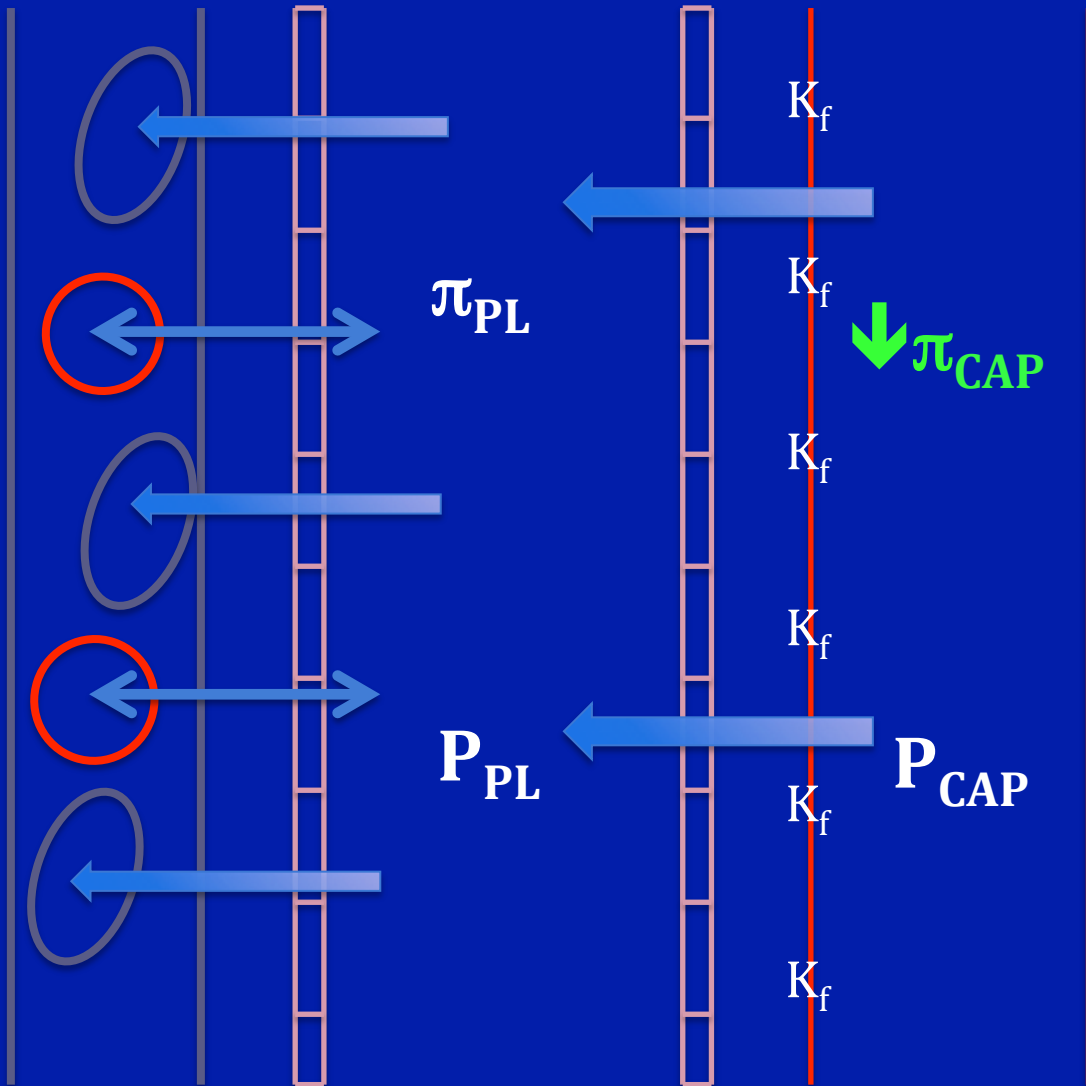
Filtration: $Q_f = K_f * [(P_{CAP} - P_{PL}) - \sigma (\pi_{CAP} - \pi_{PL})]$



Increased Pleural Capillary Permeability:

- Pleural Inflammation
- Infection
- Connective Tissue Disease
- Malignancy

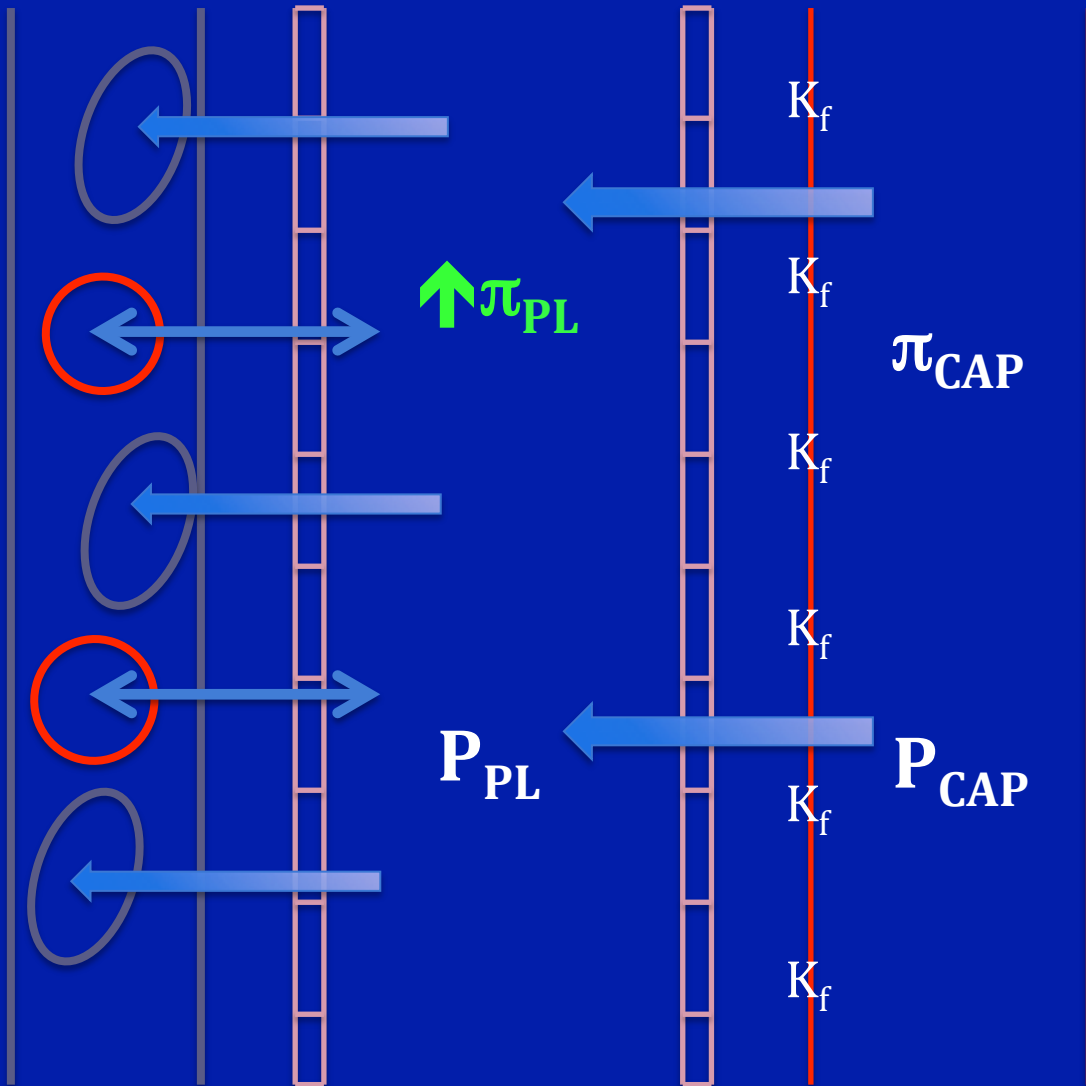
Filtration: $Q_f = K_f * [(P_{CAP} - P_{PL}) - \sigma (\pi_{CAP} - \pi_{PL})]$



Decreased capillary oncotic pressure:

- Hypoalbuminemia
- Nephrotic syndrome

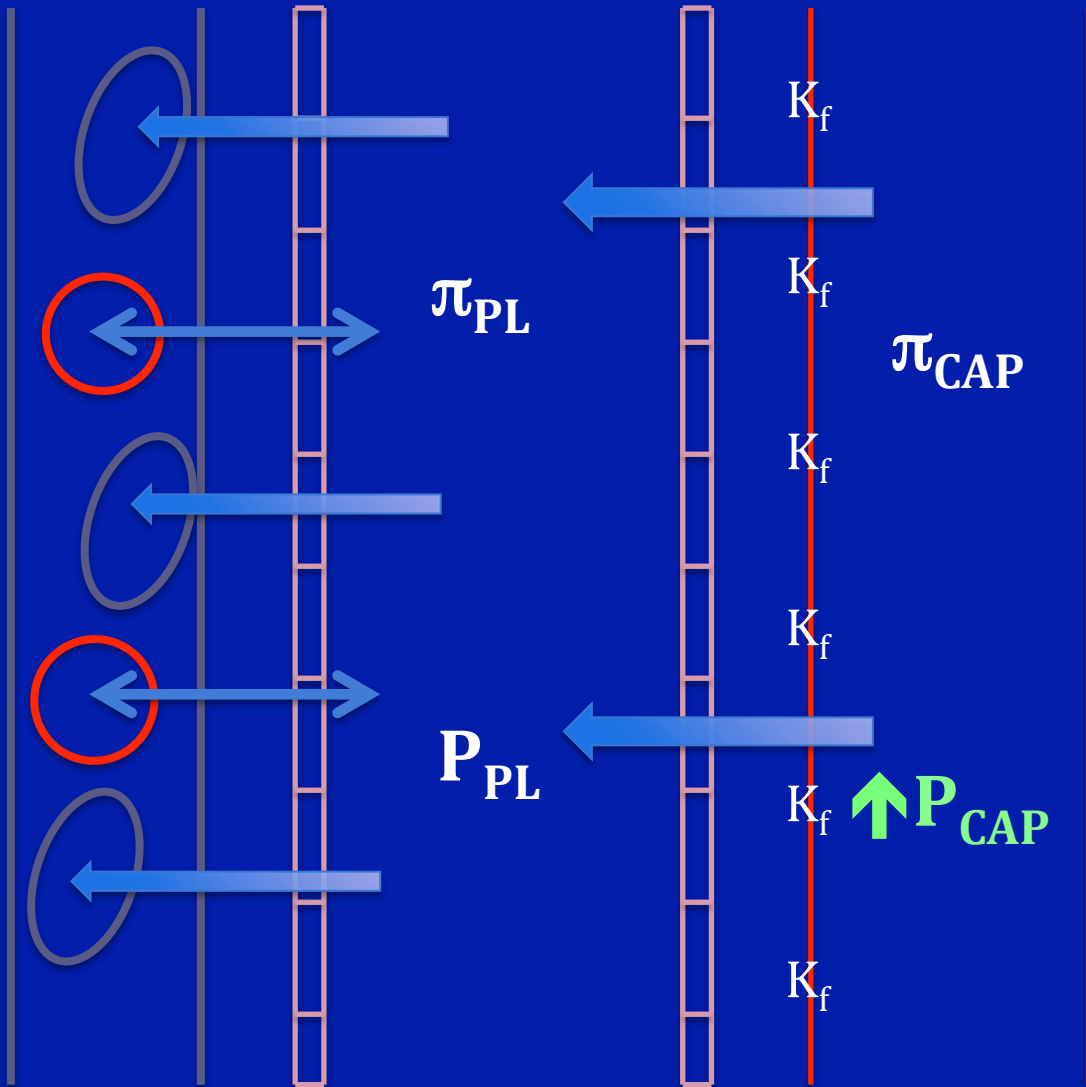
Filtration: $Q_f = K_f * [(P_{CAP} - P_{PL}) - \sigma (\pi_{CAP} - \pi_{PL})]$



Increased pleural oncotic pressure:

- not usually significant
- occasionally with hemothorax

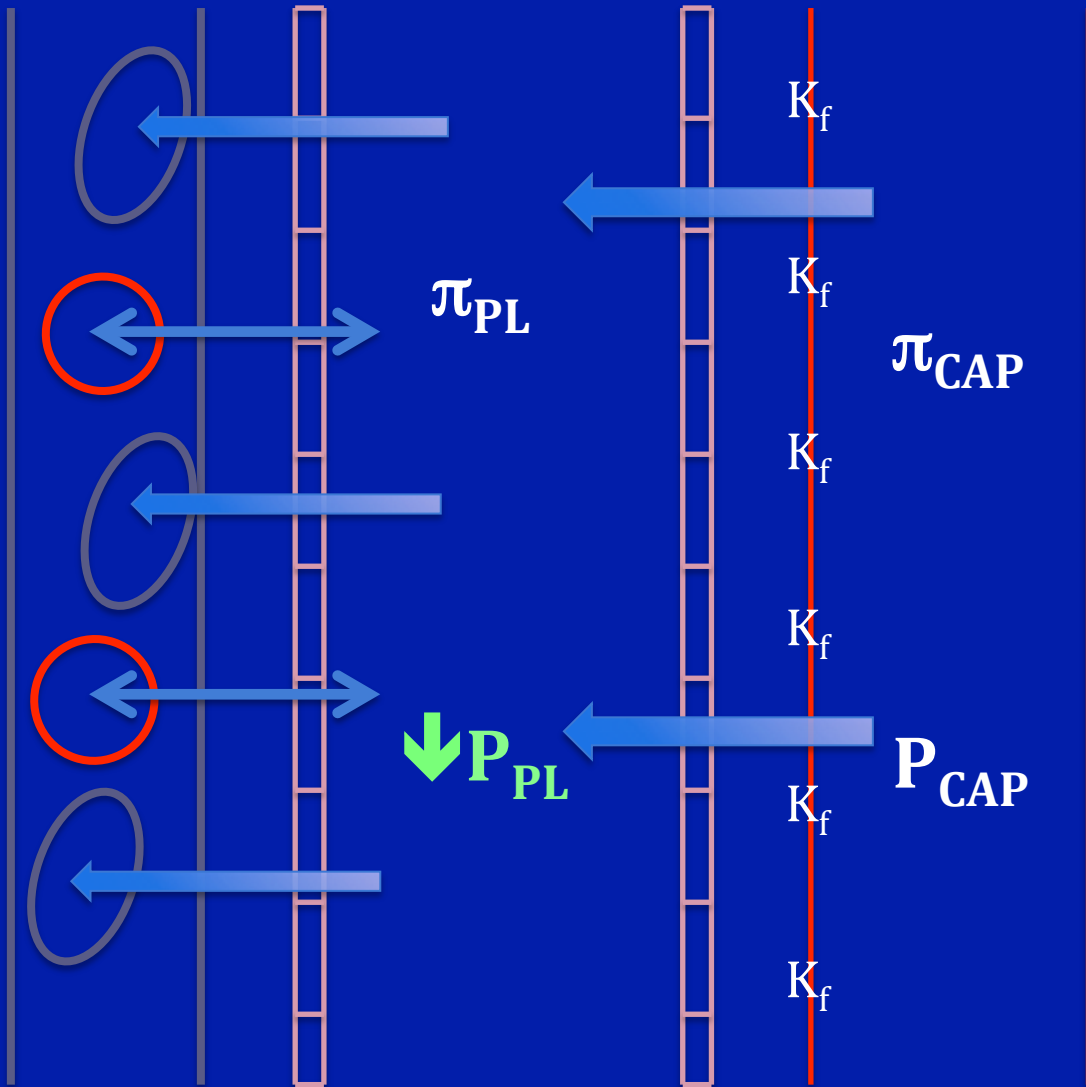
Filtration: $Q_f = K_f * [(P_{CAP} - P_{PL}) - \sigma (\pi_{CAP} - \pi_{PL})]$



Increased Pleural Capillary Hydrostatic Pressure:

- Right or Left LV Failure (CHF)
- Volume Overload
- Superior Vena Cava Syndrome

Filtration: $Q_f = K_f * [(P_{CAP} - P_{PL}) - \sigma (\pi_{CAP} - \pi_{PL})]$



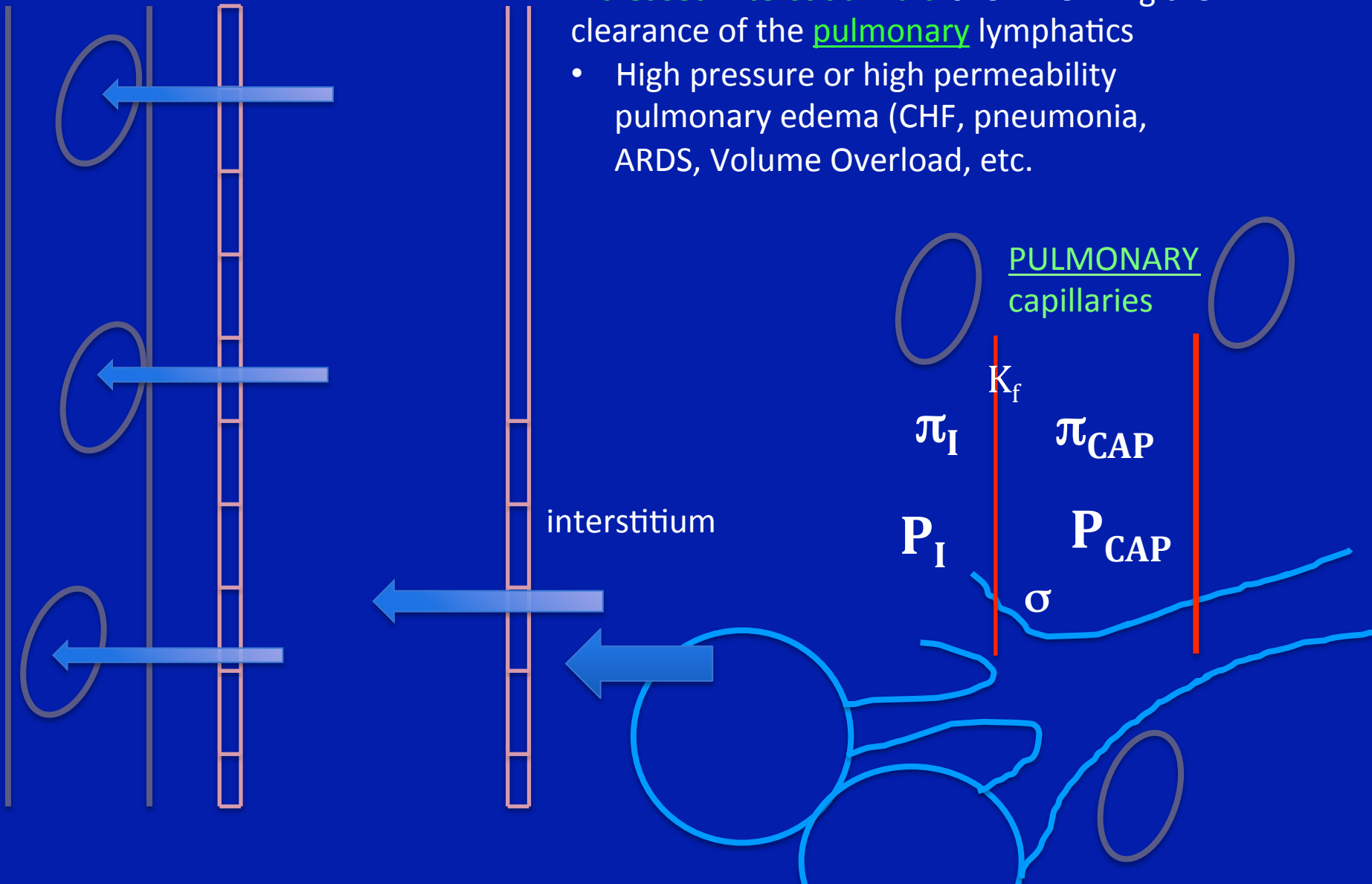
Decreased pleural hydrostatic pressure:

- Lung atelectasis

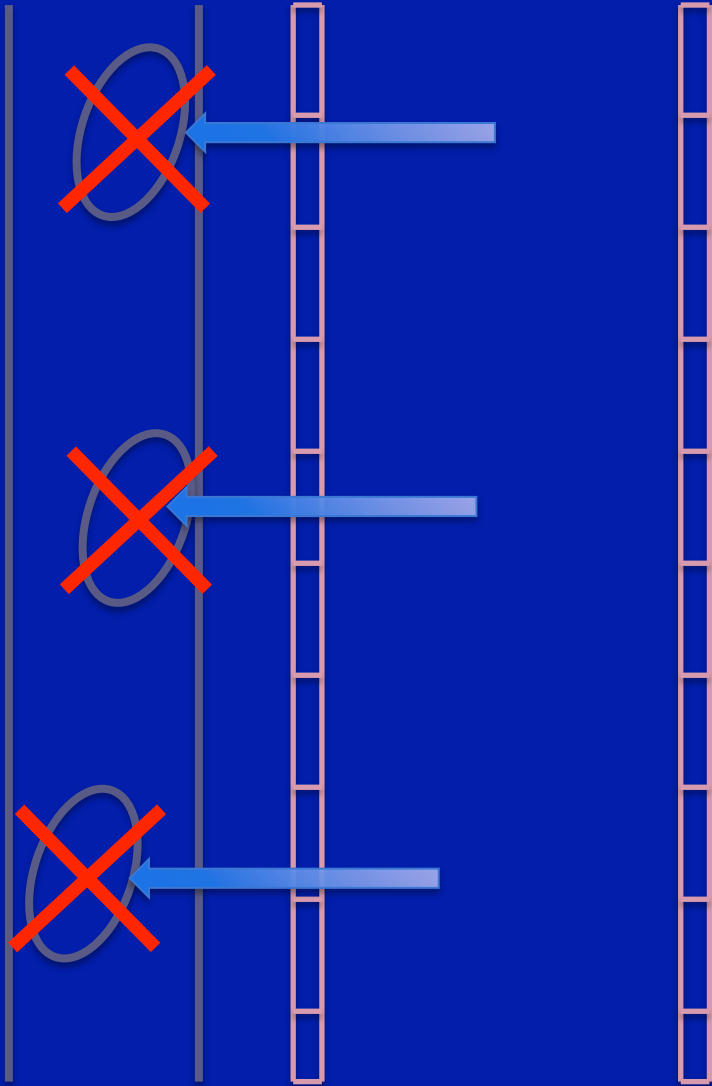
Filtration: $Q_f = K_f * [(P_{CAP} - P_I) - \sigma (\pi_{CAP} - \pi_I)]$

Increased interstitial fluid overwhelming the clearance of the pulmonary lymphatics

- High pressure or high permeability pulmonary edema (CHF, pneumonia, ARDS, Volume Overload, etc.)



Decreased Lymphatic absorption



- Lymphatic obstruction
 - Malignancy
 - Connective Tissue Disease
 - Empyema
- Markedly elevated systemic venous pressures

Pleural Effusion Pathogenesis: Summary

Multiple Mechanisms:

- 1) Increased pulmonary interstitial fluid from alveolar/pulmonary capillary leak (pulmonary circulation) into interstitial spaces of lung, then into the pleural space
- 2) Pleural capillary (systemic circulation) Starling changes
- 3) Obstruction of parietal lymphatic drainage
- 4) Breach of pleural space to another fluid-filled compartment

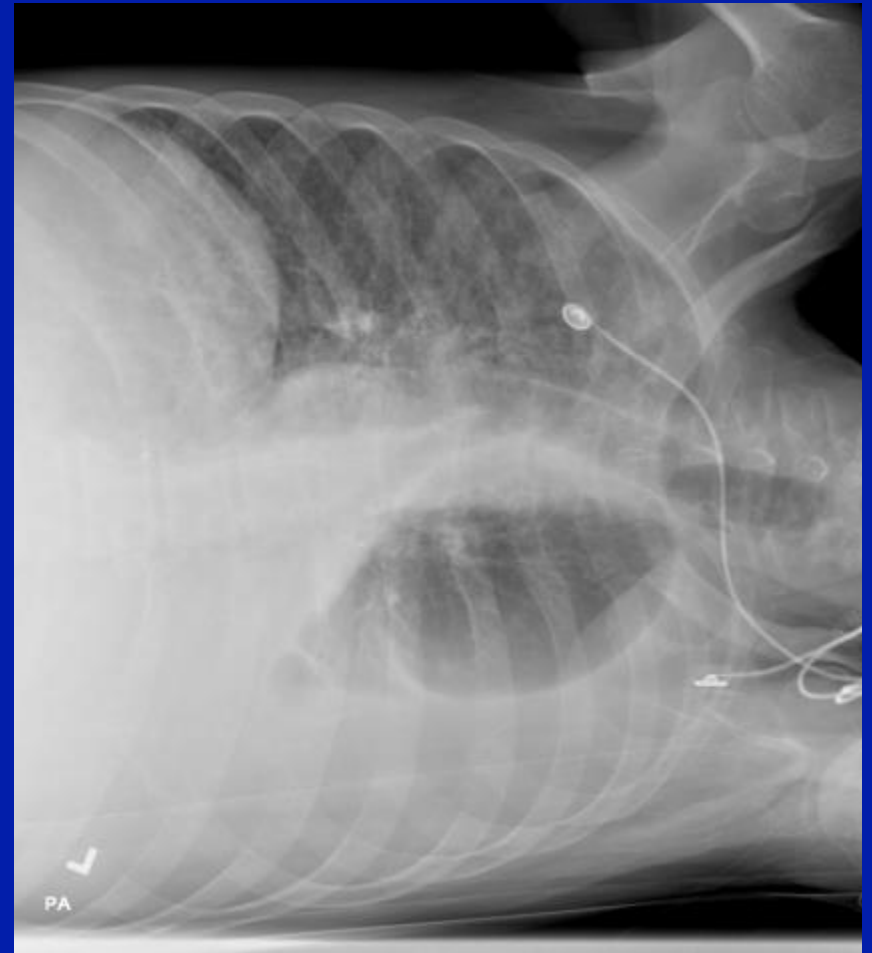
Pleural Effusion Clinical: Background

- More than 1,000,000 cases annually in U.S.
- Physical exam findings reflect fluid interposed between the chest wall and the lung: dullness to percussion, decreased tactile fremitus, diminished breath sounds
- Appears on CXR at a volume of 200 mL in PA projection and 50 mL on lateral – decubitus views, ultrasound, or CT enhance detection

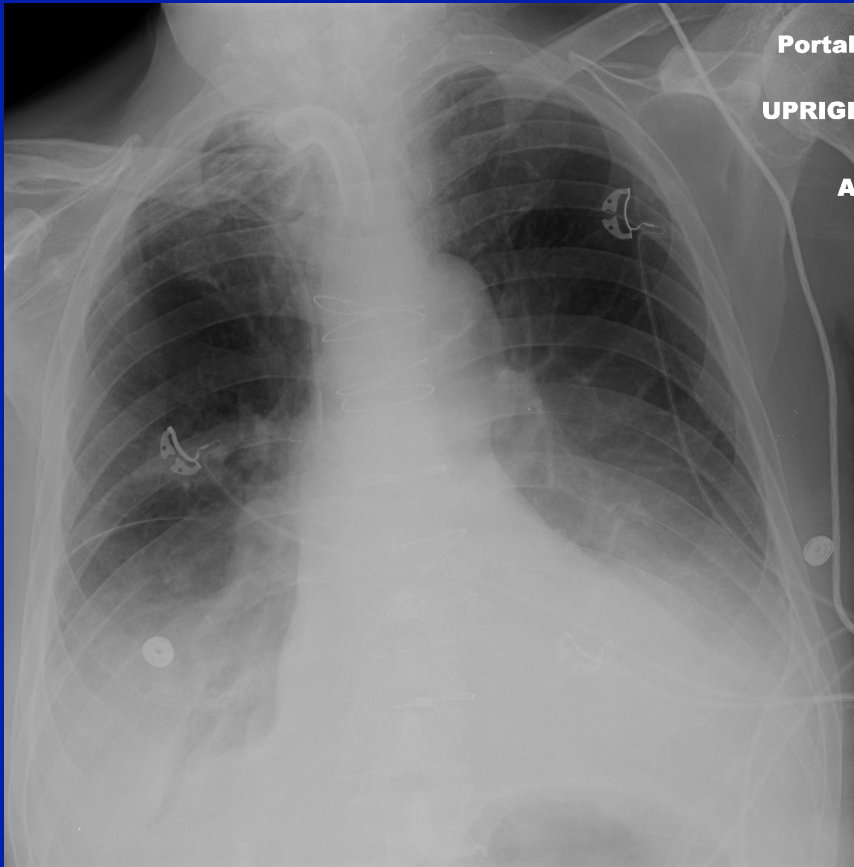
L pleural effusion: PA/lat



L pleural effusion: PA, L decubitus



Case 1: 76 yo male with dyspnea



- Progressive dyspnea following aortic valve surgery
- Peripheral edema noted at hip
- Generalized weakness, failure to thrive

Case 1: 76 yo male with dyspnea

- Diagnostic thoracentesis for fluid analysis, with associated bloodwork
 - Fluid protein = 1.6, Fluid LDH = 54
 - Serum protein = 6.1, Serum LDH = 132
- How is the fluid characterized?
 - A. Exudate
 - B. Transudate

Transudate v Exudate

- Transudates result from a systemic process (most commonly CHF, hepatic disease, and renal disease) in the setting of normal pleura and rarely require further diagnostic testing of the pleural fluid
- Exudates develop in setting of lung and/or pleural pathology

Transudate versus Exudate

- Important to differentiate
 - Narrows differential diagnosis
 - Exudate indicates need for further diagnostic testing of the pleural fluid
- Light's Criteria (only need 1)
 1. Pleural Protein:Serum Protein > 0.5
 2. Pleural LDH:Serum LDH > 0.6
 3. Pleural LDH $> 2/3$ of Upper Limit Normal Serum

Case 1: 76 yo male with dyspnea

1. Pleural Protein:Serum Protein > 0.5
 - $1.6/6.1 = 0.26$
2. Pleural LDH:Serum LDH > 0.6
 - $54/132 = 0.41$
3. Pleural LDH $> 2/3$ of Upper Limit Normal Serum
 - ULN serum = 171; 54 not $> 2/3$

Meets none of Light's Criteria; thus is a
TRANSUDATE and requires no further fluid
testing

Transudate: Limited Differential

Common

- Congestive Heart Failure
- Cirrhosis
- Nephrotic syndrome
- Hypoalbuminemia

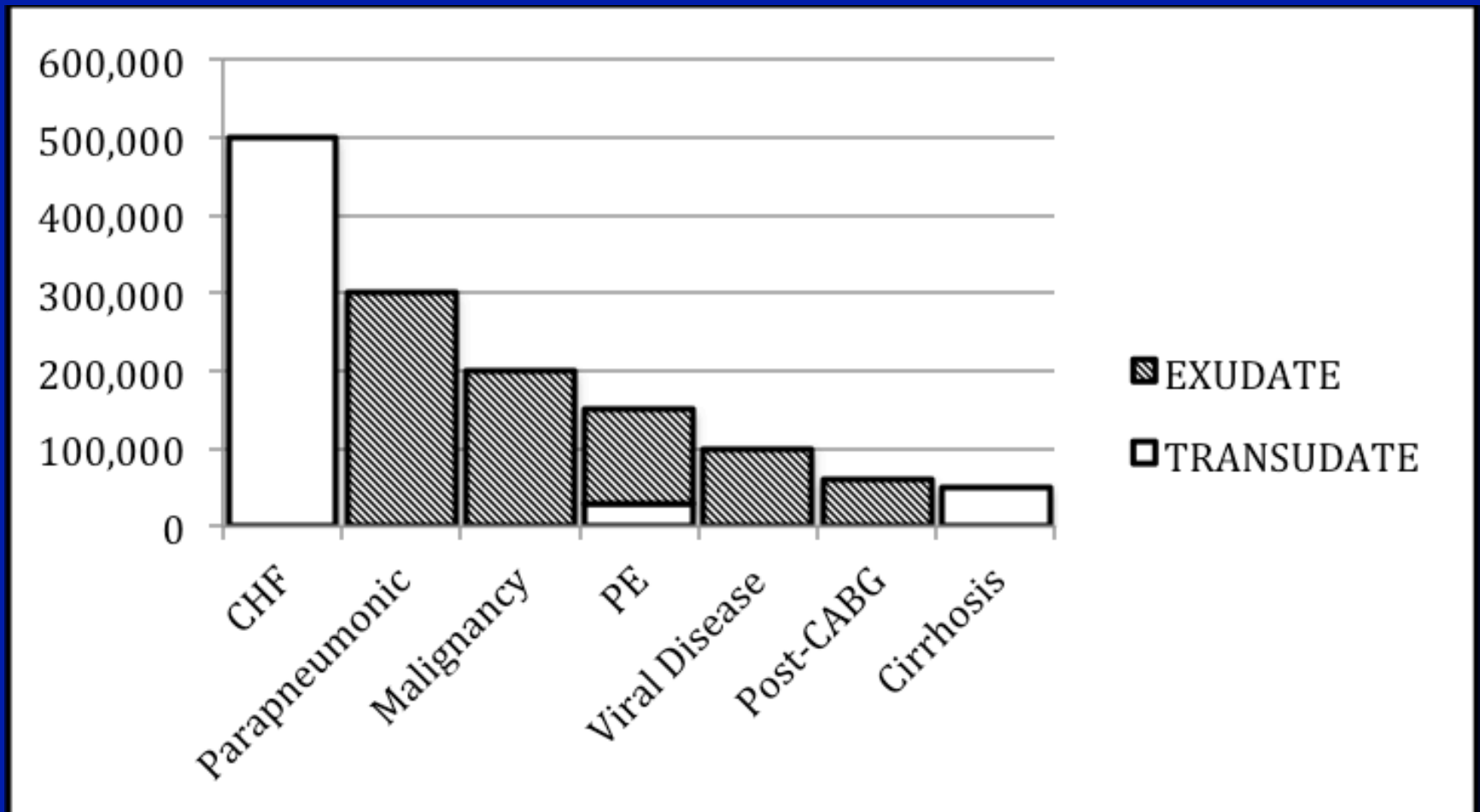
Less Common

- PE (usually exudate)
- Associated with peritoneal dialysis
- Urinothorax
- CSF Leak

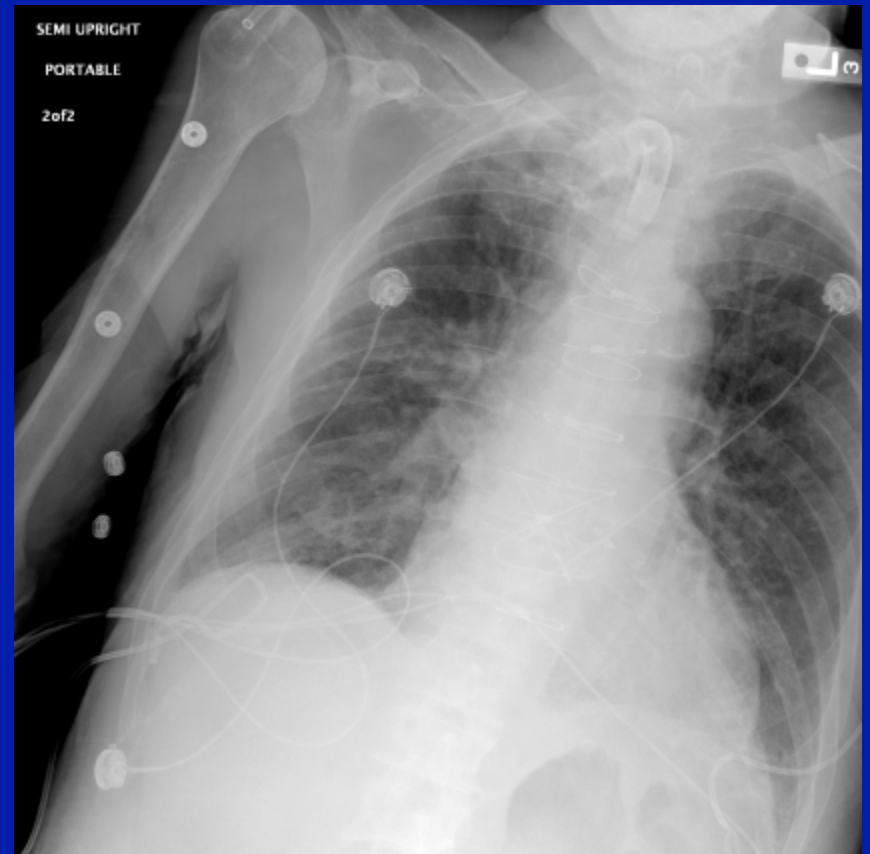
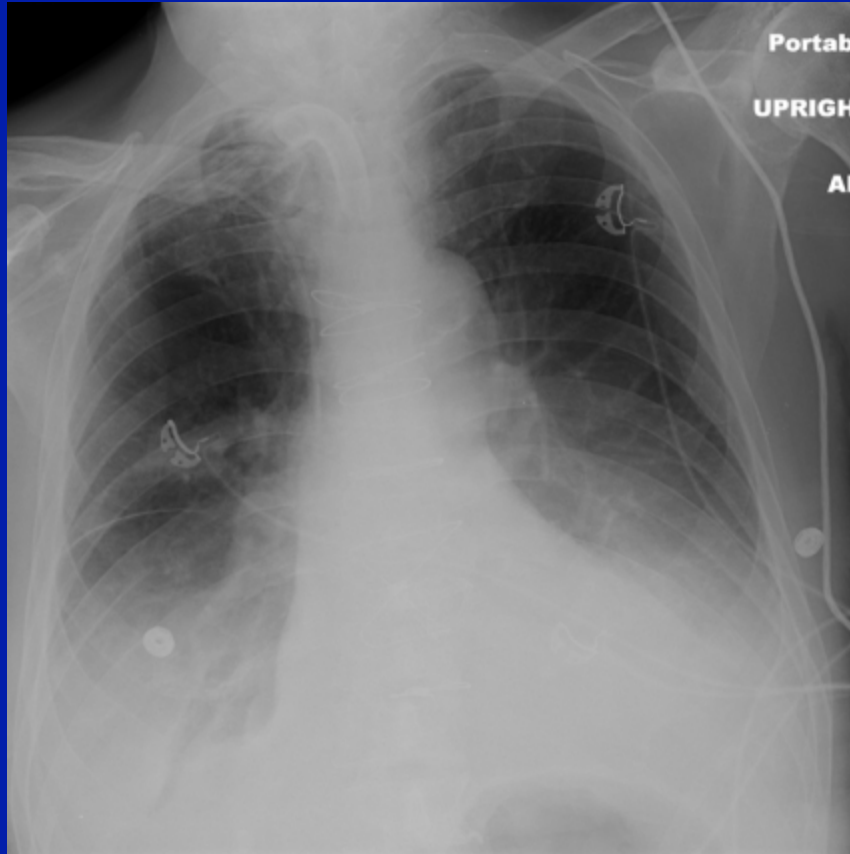
- Treatment: Treat underlying cause
- May require drainage if very large, but likely to recur if underlying cause not addressed.

Case 1: 34 yo male with unilateral exudative effusion

Most Common Causes of Pleural Effusion in the United States



Case 1: 76 yo male with dyspnea



Case 2: 34 yo male with dyspnea



- 2 weeks of worsening dyspnea on exertion
- Intermittent cough productive of brown sputum, R sided chest pain
- Fevers, chills, anorexia
- Recent hospitalization for intoxication

Case 2: 34 yo male with dyspnea

- Diagnostic thoracentesis for fluid analysis, with bloodwork
 - Fluid protein = 3, Fluid LDH = 12,000
 - Serum protein = 7, Serum LDH = 246
- How is the fluid characterized?
 - A. Exudate
 - B. Transudate

Case 2: 34 yo male with dyspnea

1. Pleural Protein:Serum Protein > 0.5

- $3/7 = 0.43$

2. Pleural LDH:Serum LDH > 0.6

- $12,000/246 = 48$

3. Pleural LDH $> 2/3$ of Upper Limit Normal Serum

- $12,000 \gggg 171$

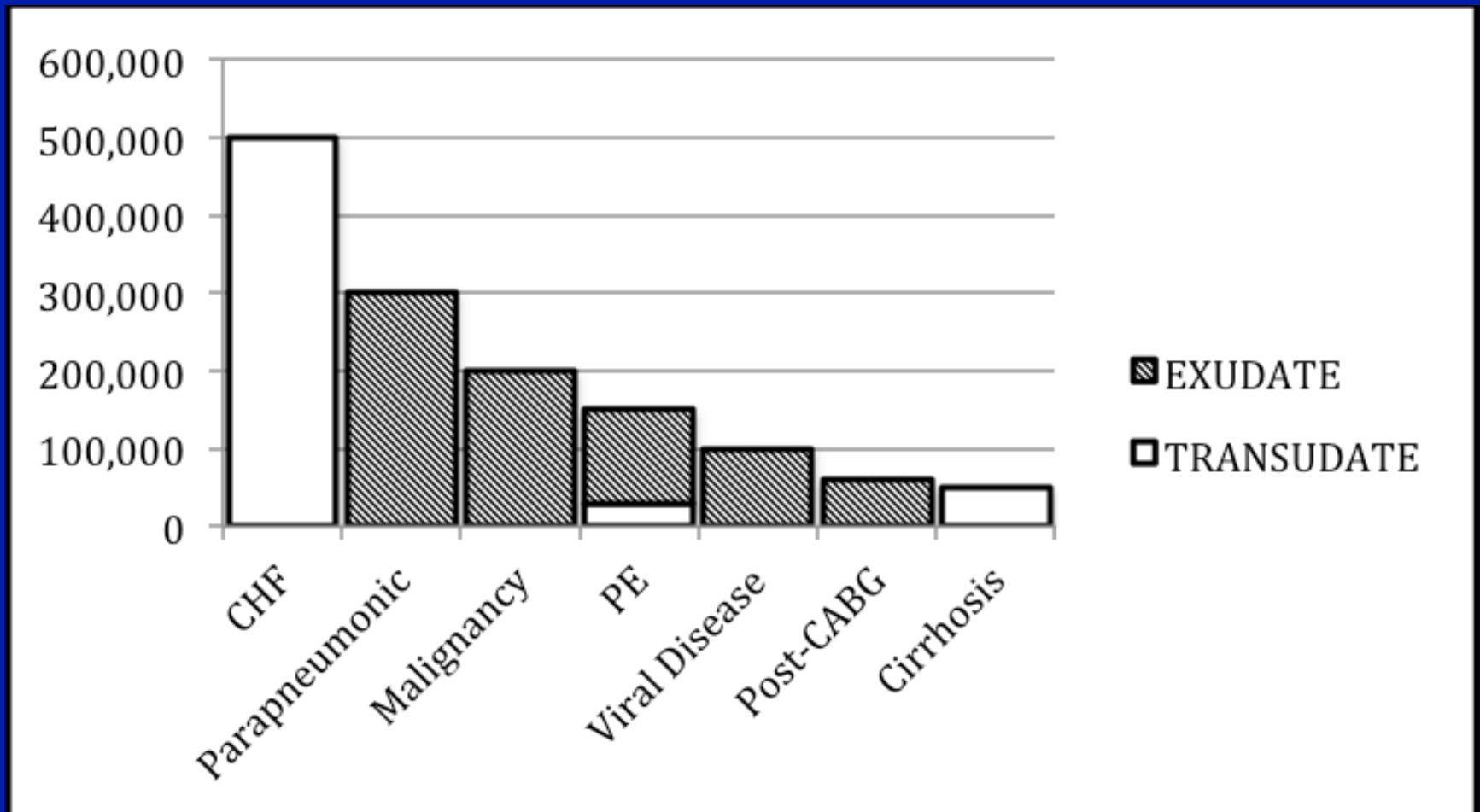
Meets 2 of 3 of Light's Criteria (only needed one); thus is an EXUDATE and requires further diagnostic testing

Case 2: 34 yo male with unilateral exudative effusion

- What is the most likely cause of his exudative effusion?
 - A. Pneumonia
 - B. Pulmonary Embolism
 - C. Malignancy
 - D. Congestive Heart Failure

Case 1: 34 yo male with unilateral exudative effusion

Most Common Causes of Pleural Effusion in the United States



Parapneumonic Effusion

- Most common cause of exudative effusion in United States
- Complicates 40-60% of bacterial pneumonia
- Parapneumonic effusion, especially empyema, associated with increased mortality
- Common Organisms:
 - CAP: *Streptococcus*, *Staphylococcus*, anaerobes (*Fusobacterium*, *Bacteroides*, *Peptostreptococcus*)
 - HCAP: *Staph* (MRSA), gram-negative aerobes (*E.coli*, *Pseudomonas*, *Klebsiella*)
- Higher mortality with gram-negatives, *Staph*, and hospital-acquired

Case 2: 34 yo male with unilateral exudative effusion

- You obtain further appropriate fluid studies in your patient, resulting with the following:
 - appearance: purulent
 - pH = 7.0; glucose < 10, WBC = unobtainable; gram stain: many WBC, few organisms
 - cytology: negative, AFB: negative
- What is the classification of this effusion?
 - A. Uncomplicated parapneumonic
 - B. Complicated parapneumonic
 - C. Empyema

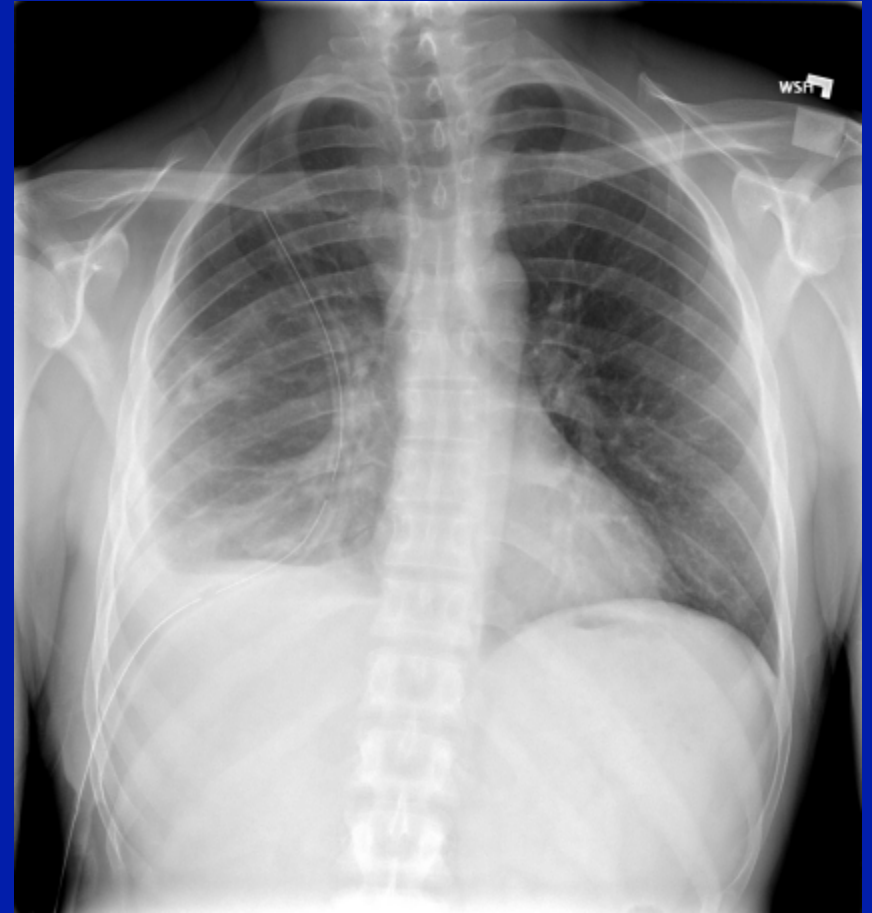
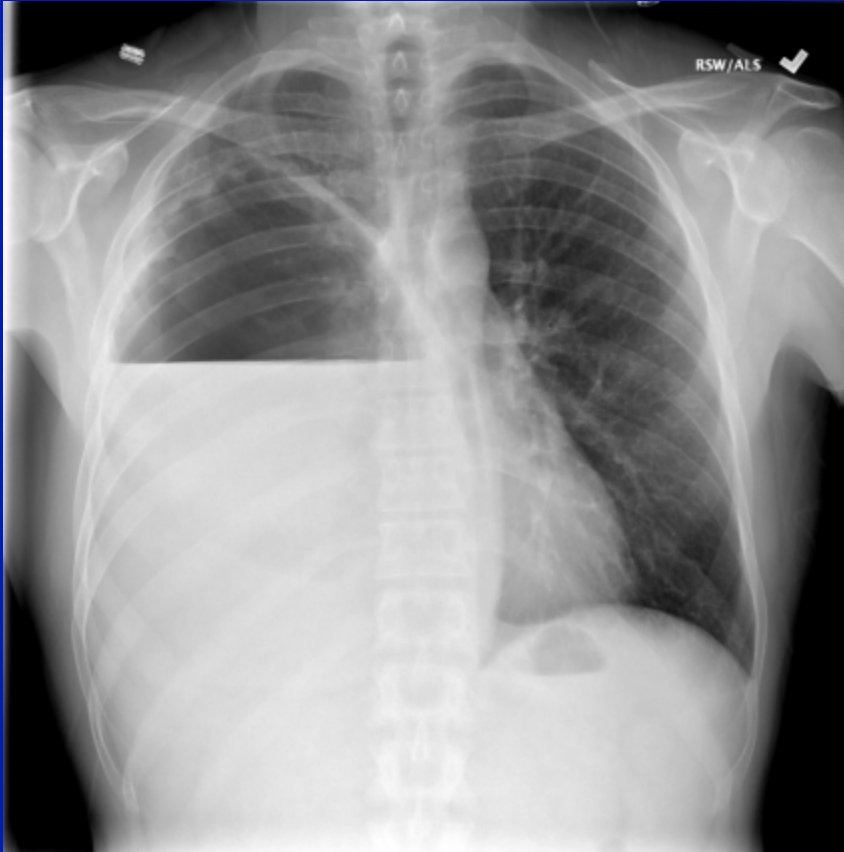
Classification of Parapneumonic Effusion

	Uncomplicated	Complicated	Empyema
Imaging characteristics	Free-flowing	Loculated, septated, or with associated pleural thickening. May also be free-flowing; imaging characteristics do not rule out complicated effusion	Any of the characteristics of complicated, or dense fluid/air locules suggestive of pus
Appearance			Frank pus
Gram stain/Culture	Negative	May be positive	+/- positive gram stain, culture may be positive
pH	> 7.2	< 7.2	< 7.0
Glucose	> 60	< 60	< 60
LDH	< 3X serum UNL	> 3X serum UNL	> 3X serum UNL (usually very high)

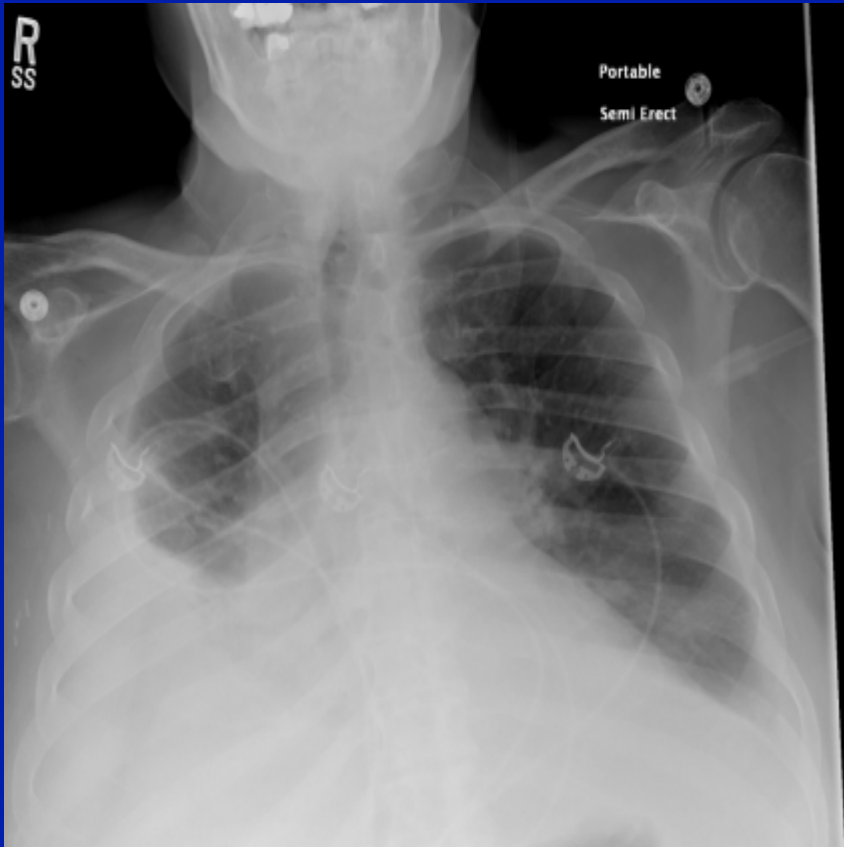
REQUIRE DRAINAGE

- Cannot differentiate uncomplicated from complicated effusion without sampling the fluid.
- Parapneumonic effusions of adequate size (> 10 mm on decubitus film) must be sampled, and complicated parapneumonic effusions must be drained.
- Don't forget ANTIBIOTICS!

Case 2: 34 yo male with empyema



Case 3: 82 yo male with dyspnea



- Subacute onset of dyspnea on exertion, now at rest
- Fatigued and frail
- Histories include R breast cancer, CHF, and gallstone requiring biliary surgery 2 months prior to admission

Case 3: 82 yo male with dyspnea

- Diagnostic thoracentesis for fluid analysis, with bloodwork
 - Fluid protein = 5.5, Fluid LDH = 148
 - Serum protein = 7.1, Serum LDH = 139
- Exudate – now what?

Undifferentiated exudate: Routine Studies

Study	Indication
Appearance	Frank pus: empyema Frank blood: possible hemothorax (send Hct) Milky: chylothorax
Culture and Gram Stain	Eval Infection. Send in culture bottles
Cytology	Eval Malignancy
Cell Count and Differential	See next slide
Glucose Level	< 60 indicates infection, malignancy, or rheumatoid effusion
pH	< 7.2 indicates complicated infection, malignancy, rheumatoid effusion, esophageal leak

Exudate: Cell Count

General Characteristic	Possible Differential
Macrophage-predominant (~ 75%)	Normal
Neutrophil-predominant: Acute inflammation	Pneumonia Pulmonary Embolism Subdiaphragmatic Abscess Acute TB Connective Tissue Disease (Acute)
Lymphocyte-predominant: Chronic inflammation	Malignancy Connective Tissue Disease (Chronic) Chronic TB
Eosinophilia (>10% Eos): Non-specific	Drug-induced Pneumothorax Malignancy Infection Parasitic Disease

Undifferentiated exudate: Routine Studies: Our patient

Study	Indication
Appearance	Orange-yellow, viscous
Culture and Gram Stain	Negative
Cytology	Pending
Cell Count and Differential	See next slide
Glucose Level	79 (< 60 indicates infection, malignancy, or rheumatoid effusion)
pH	Not obtained (< 7.2 indicates complicated infection, malignancy, rheumatoid effusion, esophageal leak)

Exudate: Cell Count – Our Patient

WBC Count = 400; 76% L, 14% M, 8% N, 1% E

General Characteristic	Possible Differential
Macrophage-predominant (~ 75%)	Normal
Neutrophil-predominant: Acute inflammation	Pneumonia Pulmonary Embolism Subdiaphragmatic Abscess Acute TB Connective Tissue Disease (Acute)
Lymphocyte-predominant: Chronic inflammation	Malignancy Connective Tissue Disease (Chronic) Chronic TB
Eosinophilia (>10% Eos): Non-specific	Drug-induced Pneumothorax Malignancy Infection Parasitic Disease

Exudates: Extensive Differential

Common

- Parapneumonic
- Malignancy
- Pulmonary Embolism
- Post-cardiac injury

Less Common

- Tuberculosis
- Collagen Vascular Disease
- Pancreatic Disease
abdominal abscess,
esophageal perforation
- Chylothorax
- Hemothorax
- Drug-induced
- Benign Asbestos Effusion
- And others ...

Case 3: 82 yo male with dyspnea

- What further studies would you obtain?
 - A. Amylase
 - B. Total bilirubin
 - C. Rheumatoid factor
 - D. Adenosine deaminase
 - E. CT angiogram
 - F. All of these?
 - G. None of these, I'm saving health care dollars

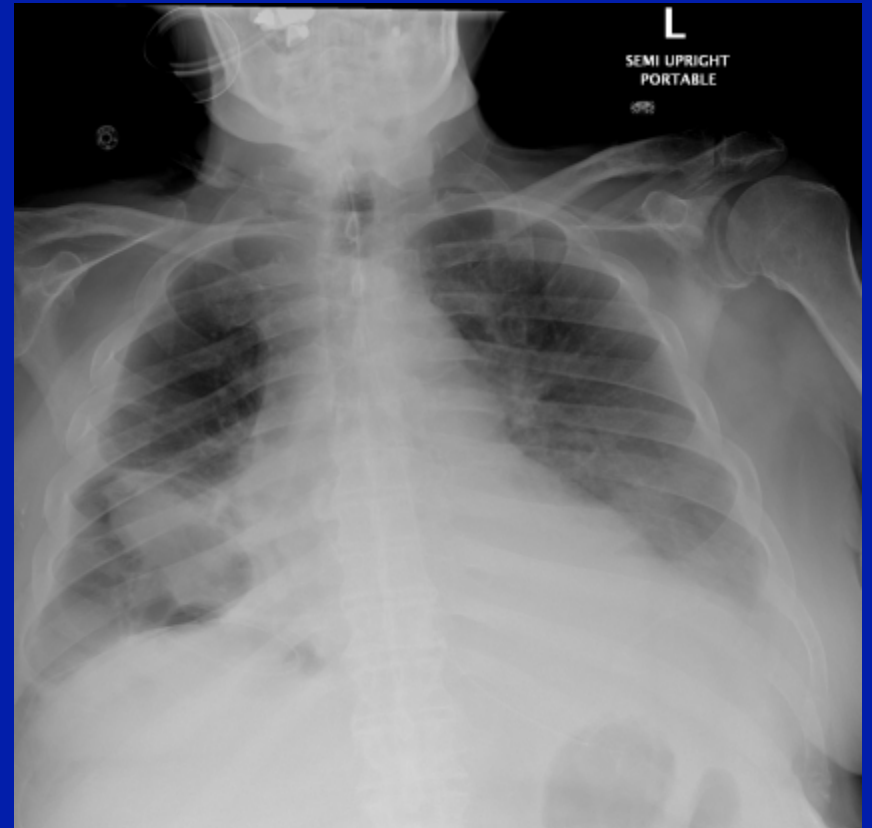
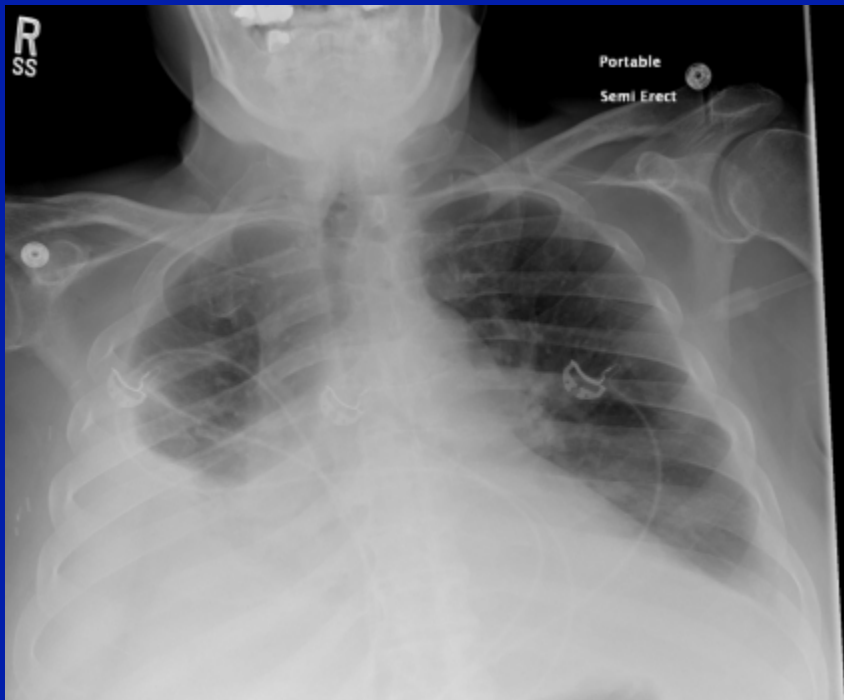
Ancillary Pleural Fluid Studies

Test	Indication
Adenosine deaminase (ADA)	Tuberculosis
Interferon-gamma	Tuberculosis
Amylase	Pancreatic disease, esophageal rupture
Hematocrit	> 50% of serum Hct: hemothorax
Rheumatoid Factor	Rheumatoid effusion
Triglyceride Level, Chylomicrons	Trig > 110 & pleural:serum cholesterol < 1.0: chylothorax Chylomicrons +ive: chylothorax
Creatinine	Urinothorax (transudate)
β_2 -transferrin	Cerebrospinal fluid leak; suspect if patient has a ventriculoperitoneal (VP) shunt or recent thoracic spine surgery (transudate)
Total Bilirubin	Biliary-pleural fistula

Treatment of Non-Infectious Exudate

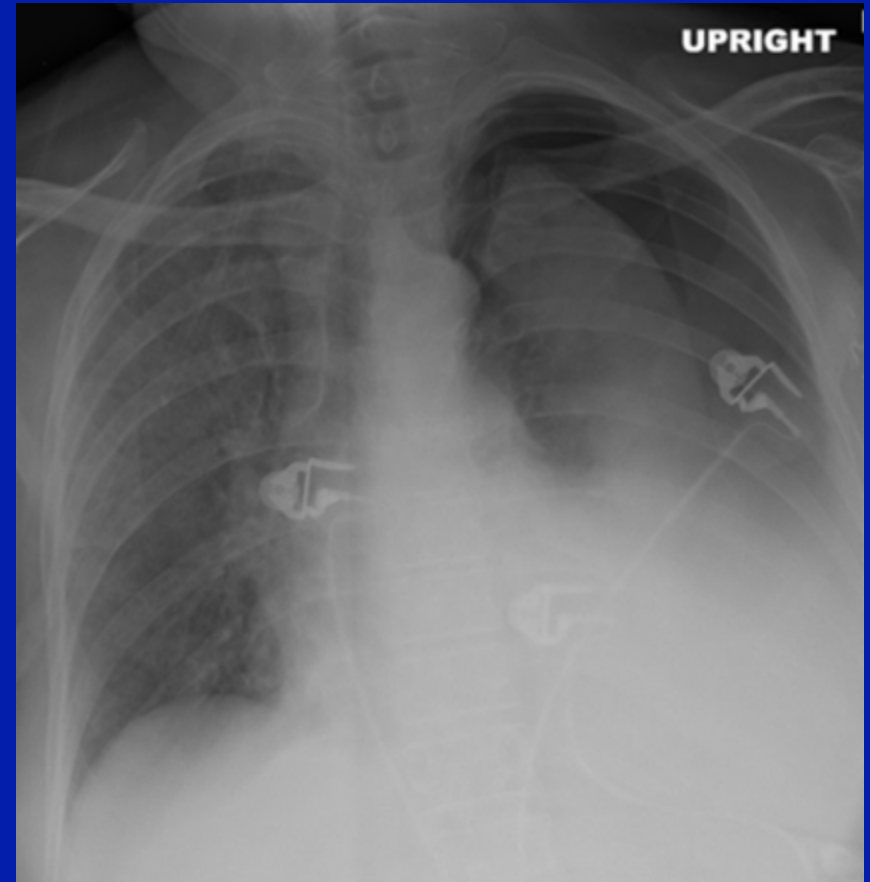
- Treat underlying cause
- Local treatment depends on symptoms; unlike complicated parapneumonic effusion or empyema, drainage is not required
- Simple drainage, indwelling pleural catheter, or pleurodesis may be used to treat a symptomatic effusion, depending on underlying cause

Case 3: 82 yo male with dyspnea



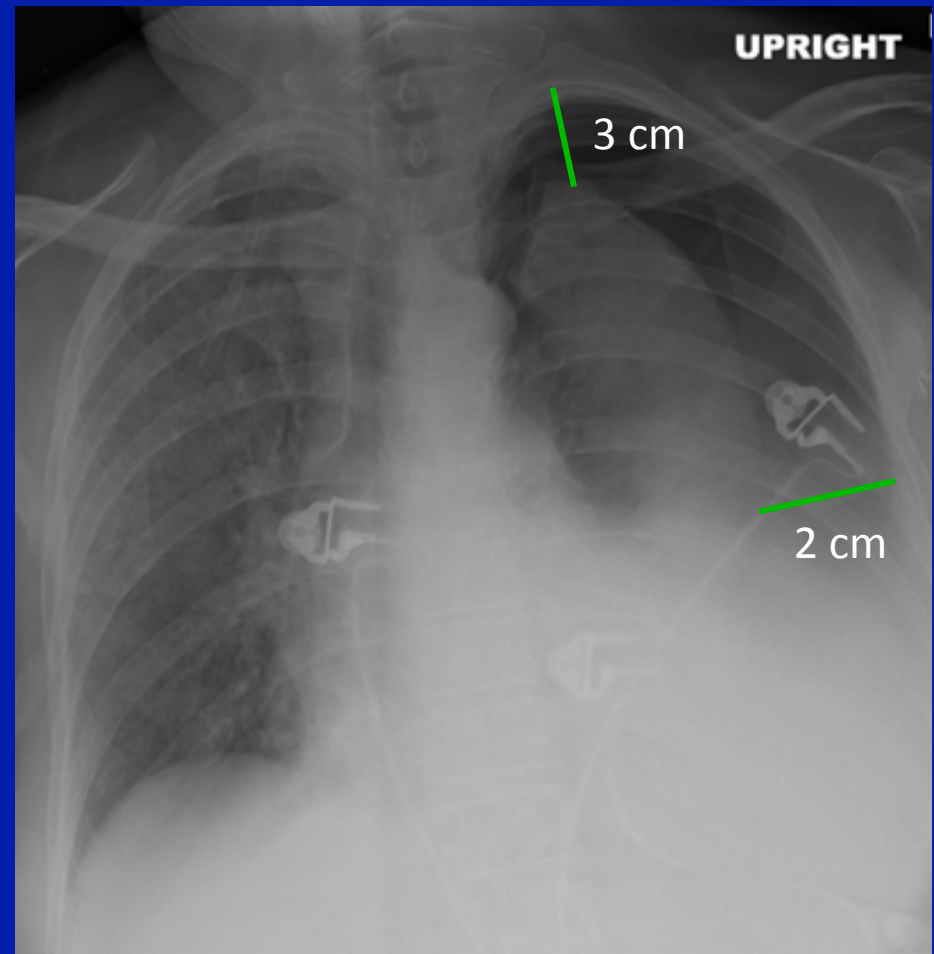
Pneumothorax

- Air in the pleural space (enters via breach of chest wall or lung)
- Presenting features: chest pain & dyspnea
- Exam findings: no fremitus, diminished breath sounds, hyper-resonant percussion note



Pneumothorax

- Measurement: “Large” if:
 - > 2 cm chest wall to ptx at hilum
 - > 3 cm apex to cupola
- Classification:
 - Primary spontaneous: develops in patient with normal lungs
 - Secondary spontaneous: develops in patient with lung disease
 - Traumatic: not spontaneous (penetrating trauma, blunt trauma +/- rib fracture, positive pressure ventilation)



Pneumothorax: Primary Spontaneous

- Spontaneous ptx in patient with normal lungs
- Risk factors:
 - Cigarette smoking
 - Male sex
 - Tall thin habitus
 - Genetic predisposition (Marfan's, Ehlers-Danlos, A1AT)

Pneumothorax: Primary Spontaneous

- Pathogenesis: Possibly rupture of subpleural blebs
- Treatment: depends on size and symptoms
 - Observation (very small ptx, minimal sx)
 - Supplemental oxygen
 - Simple aspiration +/- indwelling tube placement
 - Sclerotherapy or surgical management

Pneumothorax: Secondary Spontaneous

- Spontaneous ptx in patient with underlying lung disease (COPD, lung cancer, fibrosis, bronchiectasis, etc)
- Poorly tolerated due to lack of reserve for gas exchange; associated with >10% mortality
- Pathogenesis: abnormal parenchyma
- Treatment:
 - Indwelling catheter placement
 - Surgical management or sclerotherapy, usually offered with initial event to prevent recurrence

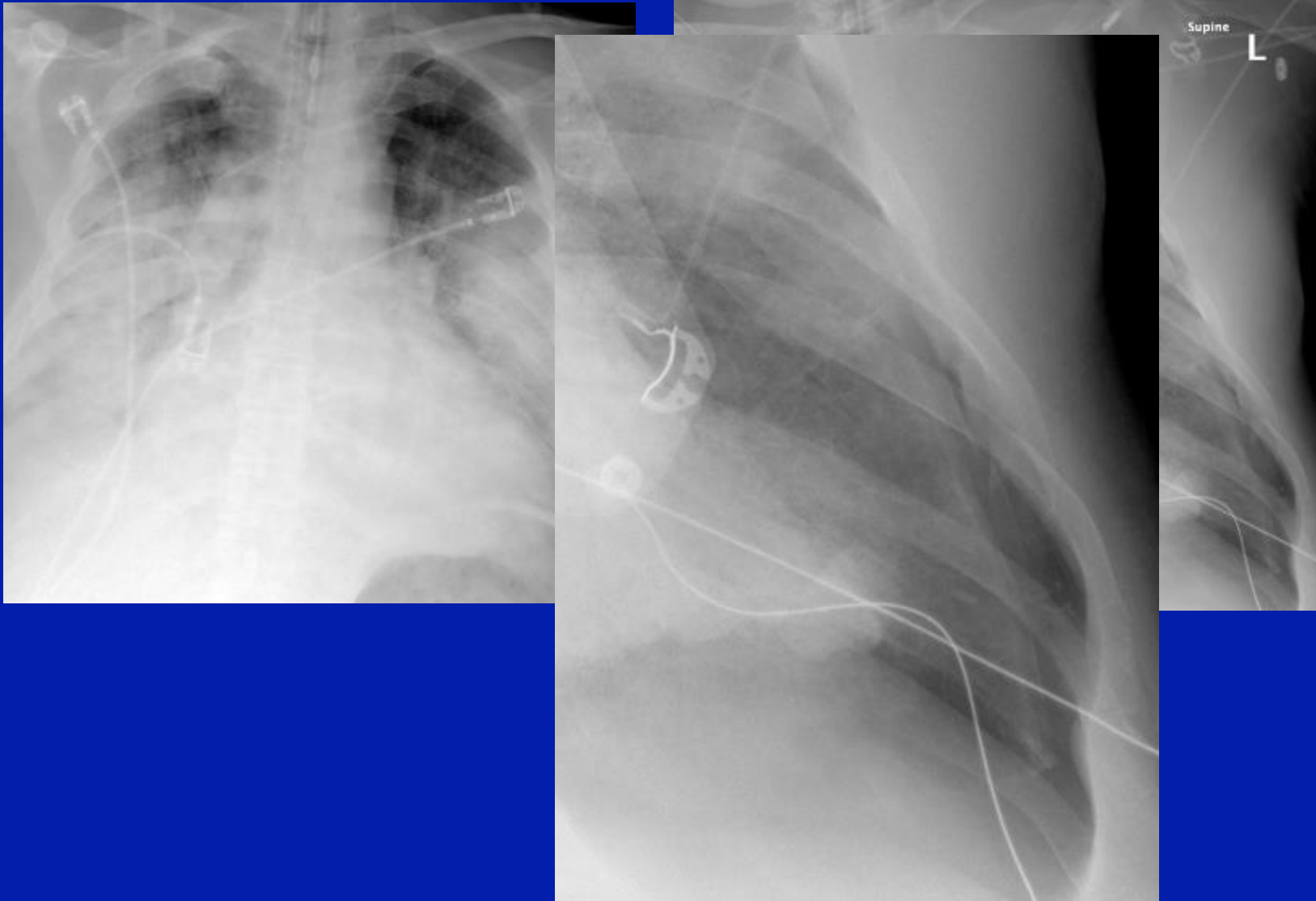
Recurrent Pneumothorax

- Recurrence rates range from 30-55% and are higher in secondary pneumothorax
- Risk Factors: Smoking, tall/thin habitus
- Sclerotherapy or surgical management usually pursued at time of first secondary pneumothorax d/t high risk of recurrence
- Similar interventions pursued for primary pneumothorax at time of first recurrence

Iatrogenic Pneumothorax: Mechanical Ventilation

- MV delivers positive pressure ventilation to the respiratory system, usually in setting of underlying parenchymal disease
- Risk factors: decreased pulmonary compliance, increased peak or mean airway pressures (ex: ARDS) -> leading to rupture of distended alveoli

Deep Sulcus in Supine CXR

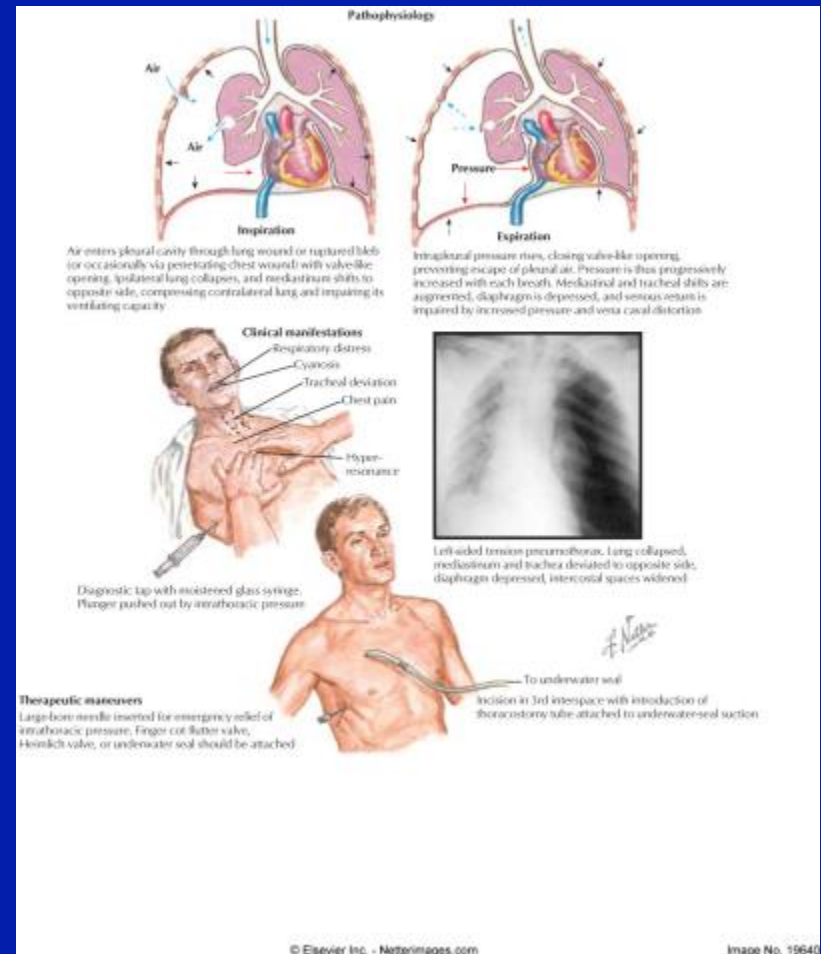


Tension Pneumothorax

- Life-threatening emergency
- Risk factors: positive-pressure ventilation
- Pathophysiology: “One-way valve”
phenomenon: air enters pleural space and
can't exit

Tension Pneumothorax

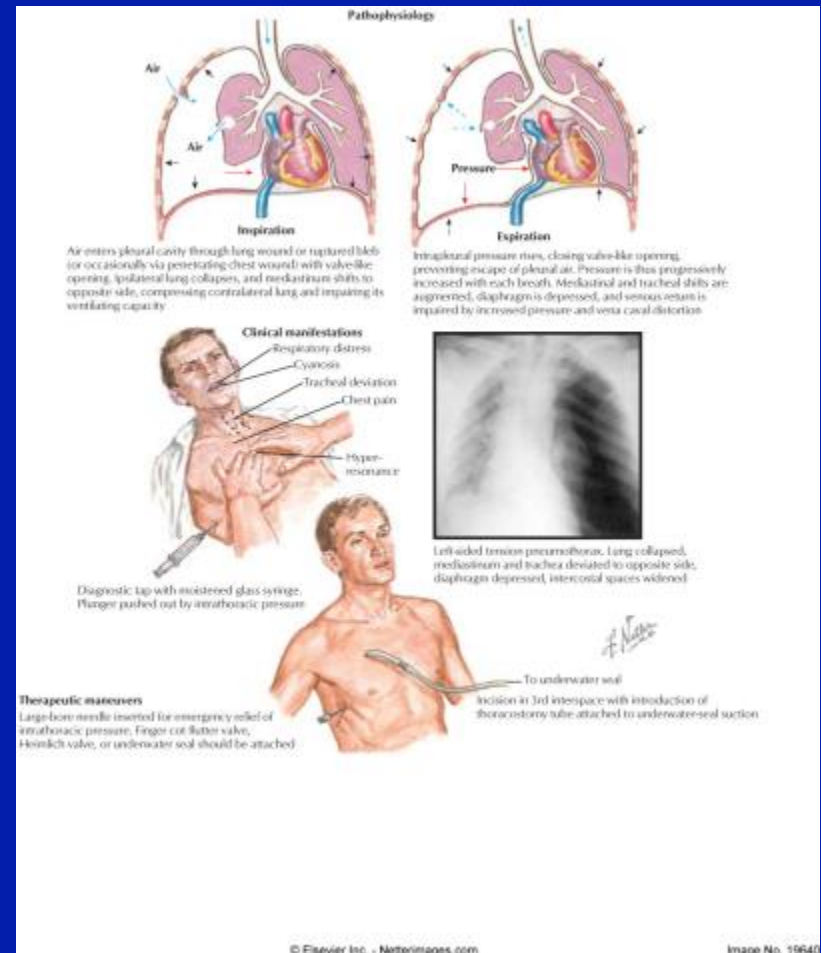
- Results in progressively positive pleural pressure maintained throughout the respiratory cycle
- Positive pleural pressure compromises venous return and decreases cardiac output; ultimately progresses to obstructive shock and cardiac arrest



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Tension Pneumothorax

- Classic exam findings: elevated JVP, absent breath sounds on affected side, tracheal shift away from affected side. Need not all be present
- Treatment: must allow positive pleural pressure to escape to lower pressure environment (atmospheric pressure) -> “decompression” of the pleural space
 - needle thoracostomy
 - tube thoracotomy



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Pleural Tumors

- Metastatic or primary
- Frequently associated with effusion
- Metastatic involvement most commonly from 3 primaries:
 - Lung Cancer
 - Breast Cancer
 - Hematologic Malignancy (Lymphoma, Leukemia)

Primary Pleural Tumors

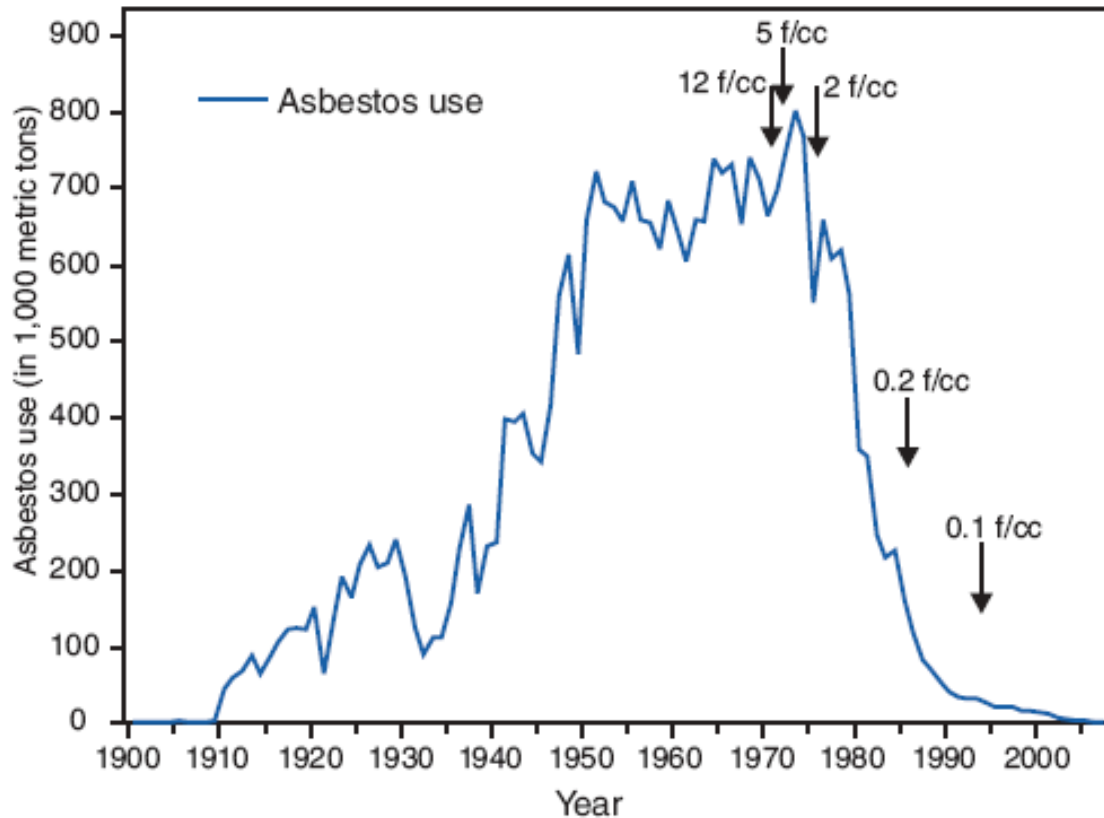
- Rare: Solitary fibrous tumor of the pleura (mesenchymal origin), usually benign
- More common: **Malignant Pleural Mesothelioma**

Malignant Pleural Mesothelioma

- Epidemiology: U.S. incidence ~10 per million, with ~ 2500 U.S. deaths/year, declining due to decrease in asbestos exposure
- Risk Factors: Asbestos fiber exposure (carpentry, plumbing, ship-building, pipe-fitting, brake work, insulation). Prolonged latency period – 20-40 years from time of exposure.
 - 80% of mesothelioma cases are related to asbestos
 - Develops in ~10% of persons with exposure history

Malignant Pleural Mesothelioma

FIGURE 1. Asbestos use and permissible exposure limits* --- United States, 1900--2007



www.cdc.gov. MMWR Weekly Reports 2009: 58(15); 393-396. Accessed October 2015.

f/cc: fibers/cubic centimeter; averaged over an 8-hour shift, limits per OSHA

Malignant Pleural Mesothelioma

- Clinical findings: chest pain, dyspnea, pleural thickening on chest imaging, +/- pleural plaques, frequently effusion
- Diagnosis: Requires pleural biopsy
- Histology: May be epithelioid, sarcomatoid, or mixed



<http://radiopaedia.org/encyclopaedia/cases/all>
Credit: Dr Ahmed Abd Rabou

Malignant Pleural Mesothelioma

- Staging:
 - T1: ipsilateral pleura (parietal only: T1a; visceral: T1b) without deep extension
 - T2: involves entire ipsilateral pleura and extends to diaphragm or lung
 - T3: locally advanced (may involve fascia, mediastinal fat, chest wall, partial pericardium) but “potentially resectable”
 - T4: unresectable: contralateral pleura, transmural pericardium, mediastinal organs, peritoneum, diffuse extension through chest wall

 - N0: No nodes
 - N1: ipsilateral hilar/bronchopulmonary nodes
 - N2: subcarinal, ipsilateral mediastinal, nodes
 - N3: contralateral nodes

 - M0: no mets
 - M1: mets

Malignant Pleural Mesothelioma

- Treatment: Primary focus is palliation of dyspnea and chest wall pain
 - Pleurodesis
 - Surgical (radical pleurectomy and decortication, extrapleural pneumonectomy) – selected cases, not considered standard of care
 - Chemotherapy (pemetrexed and cisplatin)
 - +/- Radiation
- Prognosis: poor, median survival 8-12 months from diagnosis.
 - Worse prognostic factors: older age, worse performance status, non-epithelioid histology, male gender, leukocytosis
- Survival benefits of treatment are unconvincing in most patients