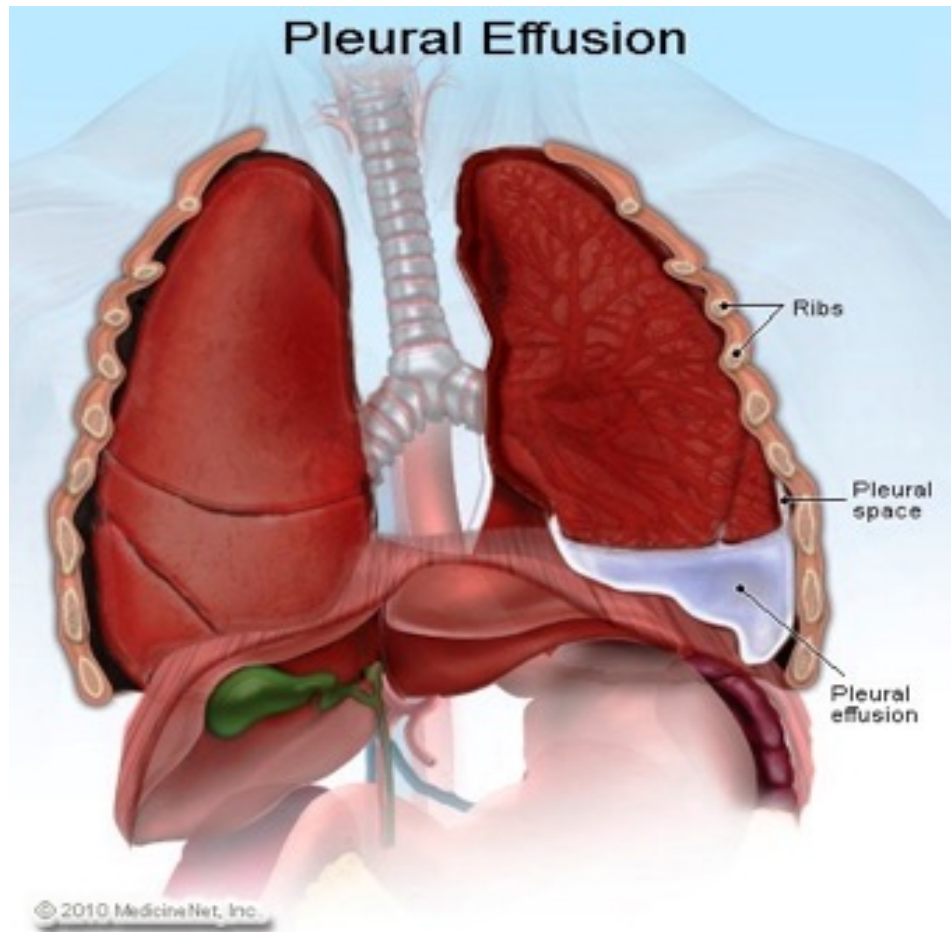
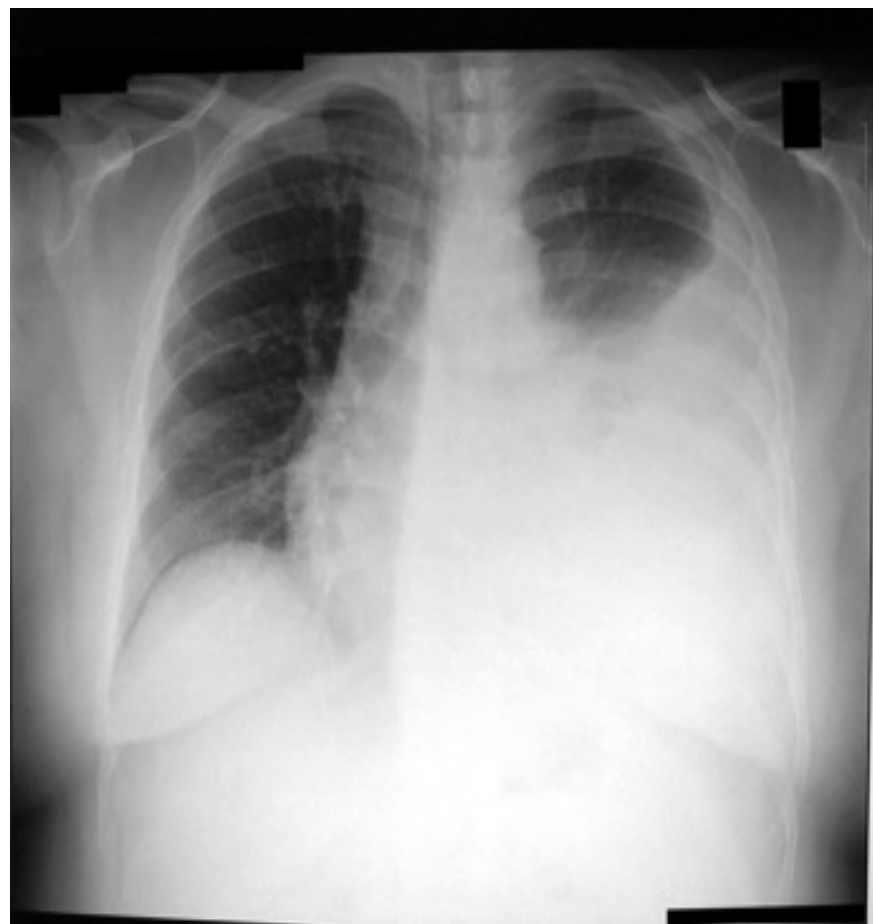


DIAGNOSTIC APPROACH TO A PATIENT WITH PLEURAL EFFUSION



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Clinical Update series



OUTLINE

- Definition
- Anatomy & physiology
- Pathophysiology
- Case illustration
- Pleural fluid (PF) assessment
- Diagnostic algorithm
- Conclusion

PLEURAL EFFUSION

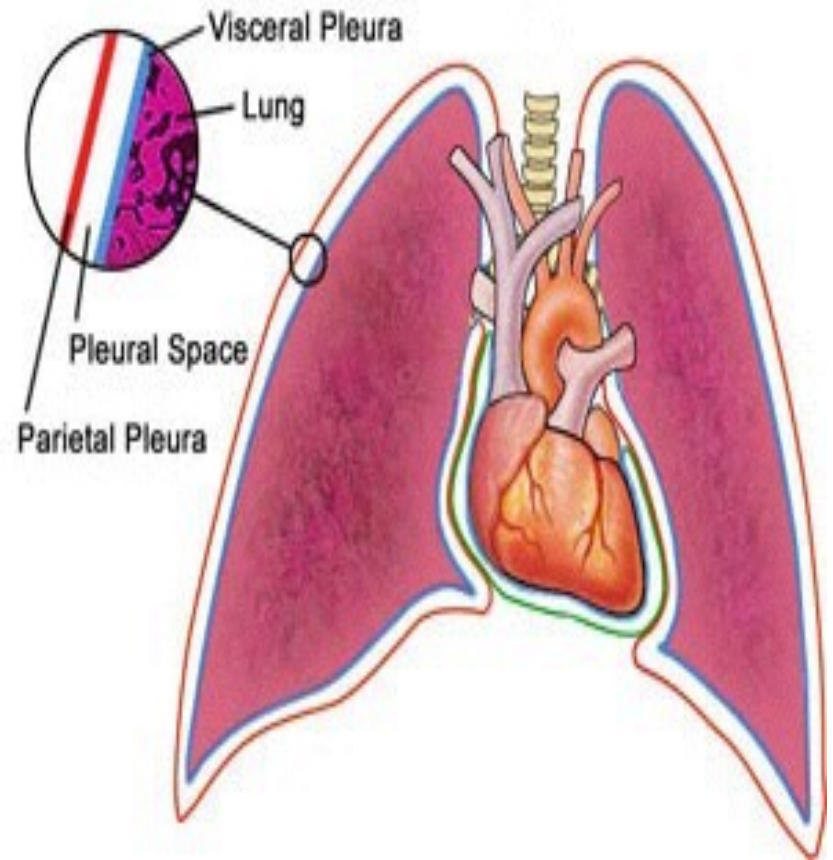
- Accumulation of excess fluid in the pleural cavity
- Types
 - Hydrothorax
 - Haemothorax
 - Urinothorax
 - Chylothorax
 - Pyothorax

ANATOMICAL CONSIDERATIONS

- The visceral and parietal pleural layers and the lubricating liquid in the interposed pleural space have a combined thickness of **0.2 to 0.4 mm**
- The width of the pleural space is **10 to 20 micrometers**
- Lubricating fluid to allows the lung surface to glide within the thorax during the respiratory cycle.

Anatomy (2)

- **Visceral pleura:** covers lung & interlobar fissures
- **Parietal pleura:** covers chest wall, diaphragm & mediastinum
- Both surfaces
 - 1000cm²
 - Single layer of mesothelial cells
 - Nourished by systemic circulation
- Difference: Parietal pleura has **lymphatic stomata** that opens directly into the pleural space



Anatomy(3)

- The **stoma** is a gap in the mesothelial layer which is continuous with the endothelial layers of the lymphatics → join to form a lacuna → collecting ducts → intercostal trunk lymphatics → parasternal and periaortic lymph nodes

PHYSIOLOGY OF PLEURAL FLUID IN THE NORMAL STATE

- Normally approx **15 mL/day** of fluid enters & exits this potential space, primarily from the capillaries of the parietal pleura.
 - (0.25ml/kg of low protein liquid)
- The fluid originates from the **systemic vessels** of the pleural membranes
- This fluid is removed by the **lymphatics** in the parietal pleura.
- At any one time there is about **20 mL** of fluid in each hemithorax and the layer of fluid is 2 to 10 mm thick.

MECHANISMS OF PLEURAL LIQUID ACCUMULATION IN DISEASE

- This regulated fluid balance is disrupted when local or systemic derangements occur.
- When **local factors** are altered, the fluid is protein- and LDH-rich and is called an **exudate**.
- Local factors include leaky capillaries from inflammation due to infection, infarction, or tumour.
- When **systemic factors** are altered, producing a pleural effusion, the fluid has low protein and LDH levels and is called a **transudate**

Mechanisms (2)

- Fluid may enter the pleural space from the interstitial spaces of the lung via the visceral pleura
- From the peritoneal cavity via small holes in the diaphragm

Increased fluid entry

- Increase in permeability
- Increase in microvascular pressure
- Decrease in pleural pressure
- Decrease in plasma osmotic pressure

Mechanisms (3)

Decreased fluid exit

- **Intrinsic factors**

Interfere with or inhibit the ability of lymphatics to contract:

- **Cytokines** & products of inflammation
- **Endocrine abn** (eg, hypothyroidism)
- **Injury** due to radiation or drugs (eg, chemotherapeutic agents)
- **Infiltration** of lymphatics by cancer
- **Anatomic abnormalities** (eg, yellow nail syndrome)

Mechanisms (4)

- **Extrinsic factors**

Inhibit lymphatic function although the lymphatics themselves are normal. These include:

- **Limitation of respiratory motion** (eg, diaphragm paralysis, lung collapse, pneumothorax)
- **Extrinsic compression of lymphatics** (eg, pleural fibrosis, pleural granulomas)
- **Blockage of lymphatic stomata** (eg, fibrin deposition on pleural surface, pleural malignancy)

Mechanisms (5)

- **Decreased intrapleural pressure** (eg, trapped lung caused by a fibrous rind on the visceral pleura)
- **Increased systemic venous pressure** - Acutely, increases in venous pressure may decrease lymphatic flow because of the higher downstream pressures; chronically, the lymphatics may be able to adapt.
- **Decreased liquid availability** - After pneumothorax, for example, liquid will be in contact with fewer lymphatic stomata and may accumulate in the pleural space.

Case

- 63 yr-old man with a history of multiple MI's presents with increasing **dyspnea on exertion**.
- He has difficulty climbing stairs, orthopnea and difficulty getting his shoes on because his **feet and ankles are swollen**.
- A chest radiograph done shows cardiomegaly and a moderate-sized **right pleural effusion**.
- Lateral decubitus films confirm that the effusion is free-flowing, and a diagnostic thoracentesis is performed.

Case (contd)

- The pleural fluid studies show:
 - PF LDH **100**
 - Serum LDH **250** (ULN - 180),
 - Total protein 2.5 (serum value 7.5).
 - There are **200 white cells** and only **trace RBCs**.
 - The white blood cell differential includes
 - **70% macrophages**
 - **15% lymphocytes**
 - **5% PMNs.**
 - The gram's stain is negative.

Case (cont'd)

- **Is this effusion a transudate or an exudate?**
 - LDH is less than $2/3$ the upper limit of normal for serum
 - Protein ratio is 0.33
 - LDH ratio is 0.4.
- Therefore, this effusion should be classified as a transudate.
- **Differential diagnosis**
 - heart failure
 - hepatic hydrothorax
 - nephrotic syndrome
 - hypoalbuminemia
 - atelectasis with a trapped lung.

Case (cont'd)

- **What additional diagnostic studies should you order?**
 - B-type natriuretic peptide
 - Echocardiogram
 - urine protein-to-creatinine ratio
 - chemistry panel
 - albumin
 - liver function test
 - INR

CLINICAL FEATURES

- Pleural friction rub
- Asymmetric chest expansion
- Reduced vocal resonance – egophony superior to the effusion
- Reduced vocal fremitus
- Auscultatory percussion
- Diminished breath sounds
- Dullness to percussion
- Crackles

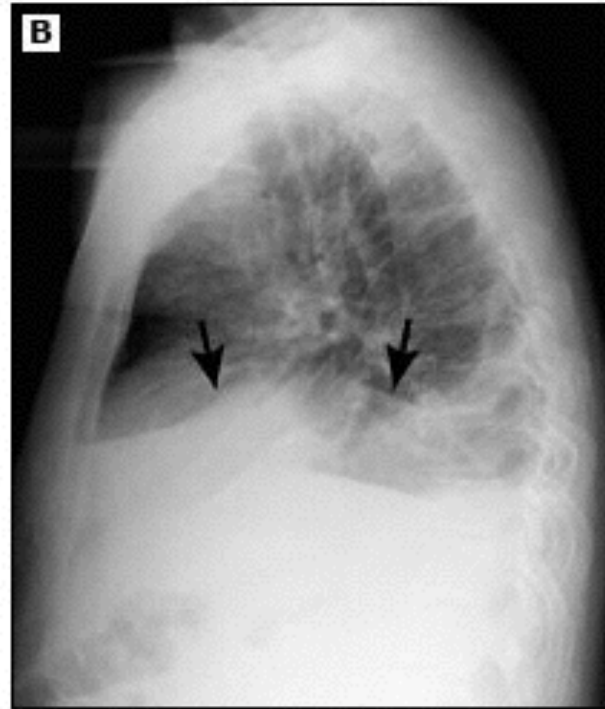
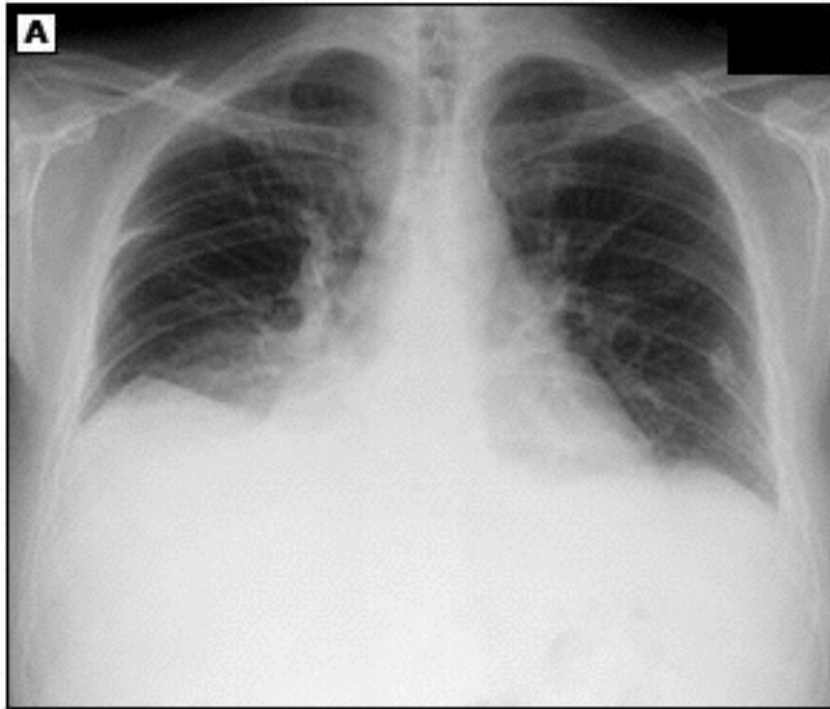
IMAGING OF PLEURAL EFFUSIONS

- Conventional chest radiograph - frontal, lateral, oblique, and decubitus radiographs
- CT scan
- Ultrasound
- MRI

Chest Radiographs

- PF accumulates in the **most dependent** part of the thoracic cavity - lung is less dense than liquid \therefore floats on the effusion.
- Initial accumulation - **subpulmonic location**
- Up to **75 mL** of effusion can occupy the subpulmonic space without spillover.
- As it accumulates, pleural liquid spills over into the costophrenic sulcus posteriorly, anteriorly, and laterally.
- It surrounds the lung and forms a cloak, or cylinder, which looks like a meniscoid arc in radiographic projections.

Subpulmonic effusions with Rock of Gibraltar sign



CXR

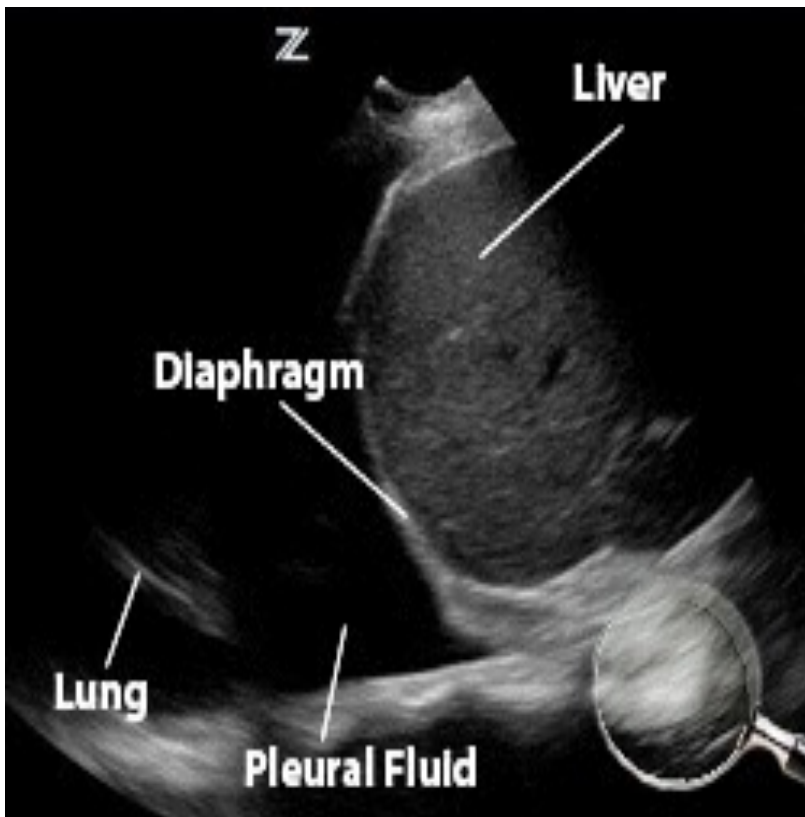
- The amount of pleural effusion can be estimated based on standard frontal and lateral radiographs.
- On an upright chest radiograph;
 - 75 mL - obliterate the posterior costophrenic sulcus
 - 175 mL - obscure the lateral costophrenic sulcus
 - 500 mL - obscure the diaphragmatic contour
 - 1000 mL - level of the fourth anterior rib

CXR(2)

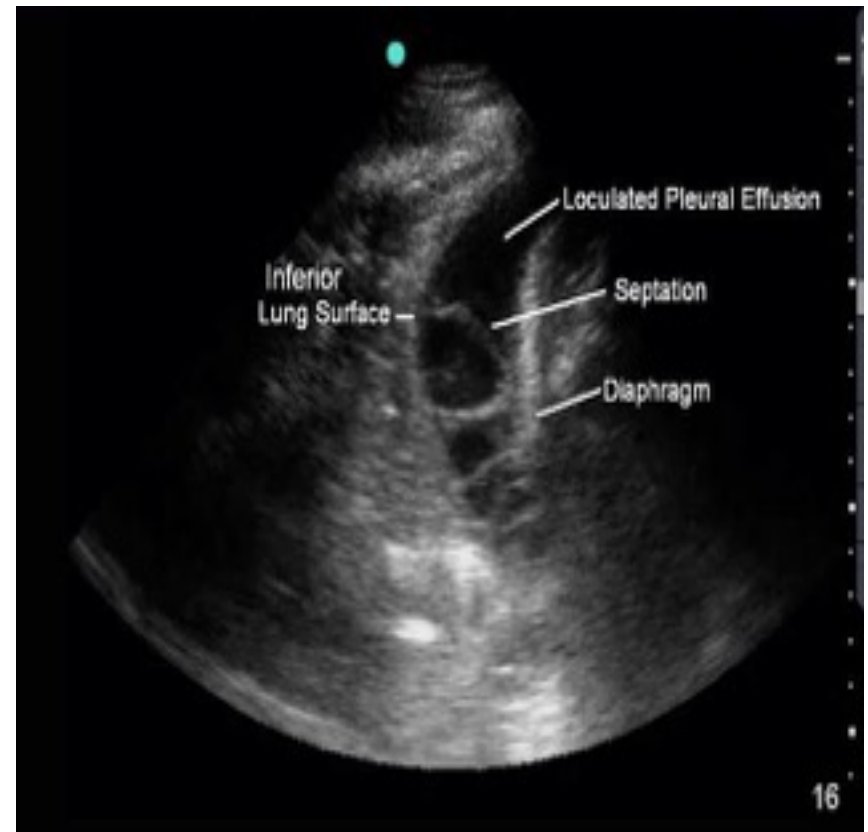
- On decubitus radiographs and CT scans, less than 10 mL, and possibly as little as 2 mL, can be identified
- For quantitation on decubitus views
 - small effusions are thinner than 1.5 cm
 - moderate effusions are 1.5 to 4.5 cm thick
 - large effusions exceed 4.5 cm.
- Effusions thicker than 1 cm are usually large enough for sampling by thoracentesis, since at least 200 mL of liquid are already present

THORACIC ULTRASOUND

Generalised effusion



Loculated effusion



CT SCAN CHEST



DIAGNOSTIC EVALUATION OF PLEURAL EFFUSION: INITIAL

- Gross appearance
- Characterisation : transudate/exudate
- Chemical analysis
- Tumour markers
- Nucleated cells

Gross Appearance

Gross appearance	Interpretation
<i>Pale yellow (straw)</i>	<i>Transudate, some exudates</i>
<i>Red (bloody)</i>	<i>Malignancy, post cardiac surgery syndrome, pulmonary infarction in absence of trauma</i>
<i>White (milky)</i>	<i>Chylothorax or cholesterol effusion</i>
<i>Brown</i>	<i>Longstanding bloody effusion or rupture of amoebic abscess</i>
<i>Black</i>	<i>Aspergillus</i>
<i>Yellow- green</i>	<i>Rheumatoid pleurisy</i>
<i>Dark green</i>	<i>Biliothorax</i>
<i>Colour of;</i>	
<i>Enteral tube feed</i>	<i>Feeding tube in pleural space</i>
<i>CVC infusate</i>	<i>Extravascular catheter migration</i>

Character & odour of fluid

Character	
<i>Pus</i>	<i>Empyema</i>
<i>Viscous</i>	<i>Mesothelioma</i>
<i>Debris</i>	<i>Rheumatoid pleurisy</i>
<i>Turbid</i>	<i>Inflammatory exudate or lipid effusion</i>
<i>Anchovy paste</i>	<i>Amoebic liver abcess</i>
<i>Odour of fluid</i>	
<i>Putrid</i>	<i>Anaerobic empyema</i>
<i>Ammonia</i>	<i>Urinothorax</i>

Transudative effusions

- Due to imbalance of the hydrostatic and oncotic pressures in the chest

Processes that	ALWAYS cause a transudative effusion
<i>Atelectasis</i>	<i>↑ intrapleural negative pressure</i>
<i>CSF leak into pleural space</i>	<i>Thoracic spinal surgery & ventriculoperitoneal shunts</i>
<i>Heart failure</i>	<i>Acute diuresis causing borderline exudative features</i>
<i>Hepatic hydrothorax</i>	<i>Rare without clinical ascitis</i>
<i>Hypoalbuminemia</i>	<i>Edema fluid rarely isolated to pleural space</i>
<i>Iatrogenic</i>	<i>Misplaced intravenous cath . In pleural space</i>
<i>Nephrotic syndrome</i>	<i>Usually subpulmonic & bilateral</i>
<i>Peritoneal dialysis</i>	<i>Acute massive effusion dvps within 48 hrs of initiation dialysis</i>
<i>Urinothorax</i>	<i>Ipsilateral obstructive uropathy</i>

Cont'd

- Processes that may cause a transudative effusion but **USUALLY** cause an exudative effusion
 - Amyloidosis
 - Chylothorax
 - Constrictive pericarditis
 - Hypothyroid pleural effusion
 - Malignancy
 - Pulmonary embolism
 - Sarcoidosis
 - Superior vena cava syndrome
 - Trapped lung

Exudative effusions

- Primarily result from
 - **Lung and pleural inflammation**, causing increased capillary and pleural membrane permeability
 - **Impaired lymphatic drainage** of the pleural space, Resulting in decreases removal of protein and other LMW constituents from pleural space
 - **Movement of fluid from the peritoneal space** ie acute or chronic pancreatitis, chylous ascites and peritoneal carcinomatosis

Cont'd

- Disease from any organ can result in exudative effusions
 - Infection
 - Malignancy
 - Immunologic response
 - Lymphatic abnormality
 - Non infectious inflammation
 - Iatrogenic causes
 - Movement of fluid from below the diaphragm

LIGHTS CRITERIA

- Traditional method
 - Transudates vs Exudates
 - serum and pleural fluid LDH and protein
- 1 or more of
 - **Pleural fluid protein/ Serum protein ratio > 0.5**
 - **Pleural fluid LDH/serum LDH RATIO > 0.6**
 - **Pleural fluid LDH greater than 2/3 the upper limits of the laboratory's normal serum LDH**

OTHER CRITERIA

- Require one criterion to be met to define an exudate
- **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 cholesterol 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

CHEMICAL ANALYSIS

- Pleural fluid protein
- LDH
- Glucose
- pH
- Cholesterol
- Triglycerides
- Amylase

LDH

- Upper normal limit– 200IU/L
- Pleural fluid LDH $> 1000\text{IU/L}$
 - **Empyema**
 - **Rheumatoid pleurisy**
 - **Pleural paragonimiasis**
 - **Malignancy**
- PCP – pleural fluid/serum LDH ratio > 1.0 & pleural fluid/serum protein < 0.5
- Urinothorax – Elevated pleural LDH with low pleural fluid protein

PROTEIN

- Most transudates have total protein below 3.0g/dL
 - NB in acute diuresis in heart failure – however the patient will have a serum to pleural fluid albumin gradient of 1.2 g/dL which categorises it as a transudate. The dx will be supported by an elevated NT- pro BNP
- Tuberculous Effusions >4.0 g/dL
- Waldenstroms macroglobulinemia & Multiple myeloma , total protein 7-8 g/ dL

CHOLESTEROL

- Derived from degenerating cells and vascular leakage from increased permeability
- Cholesterol effusion has elevated cholesterol > 250 mg/dL

TRIGLYCERIDES

- Chylothorax - \uparrow pleural fluid TG > 110 mg/ dL, a level less than 50mg/dL excludes it

GLUCOSE

- All transudates & some exudates have pleural fluid glucose concentration similar to that of blood
- Low pleural fluid glucose $< 60\text{mg/dl}$ (3.33 mmol/L)
Narrows the DDX to
 - Rheumatoid pleurisy *
 - Complicated parapneumonic effusion & empyema**
 - Malignant effusion* **
 - Tuberculous pleurisy**
 - Lupus pleuritis
 - Esophageal rupture

The listed also have low pleural Ph < 7.30 , with normal arterial ph

*Decreased transport of glucose from blood to pleural fluid

**Increased utilisation of glucose by neutrophils, bacteria(empyema) & malignant cells

pH

- Should be measured in a blood gas machine
- Ph of normal pleural fluid ~ 7.6 due to bicarb gradient between blood & pleural fluid
- Transudates 7.40-7.55
- Exudates 7.30-7.45
- Mechanisms for pleural acidosis include
 - **↑ acid production by pleural fluid cells & bacteria**
 - **↓ hydrogen ion efflux from pleural space due to pleuritis, tumour or pleural fibrosis –malignant, TB, RA**

pH(2)

- ↓ PF pH
 - Diagnostic
 - prognostic
 - therapeutic implications - pts with parapneumonic and malignant effusions.
- ↓ PF pH in malignancy - ↑ cytologic yield
 - shorter survival
 - poorer response to chemical pleurodesis

Amylase

- 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 1.0
- narrows the differential diagnosis of an exudative effusion to the following major possibilities:
 - **Acute pancreatitis**
 - **Chronic pancreatic pleural effusion**
 - **Esophageal rupture**
 - **Malignancy**

Amylase (2)

- Other rare causes of an amylase-rich pleural effusion include
 - Pneumonia
 - Ruptured ectopic pregnancy
 - Hydronephrosis
 - Cirrhosis.
- Pancreatic disease is associated with **pancreatic isoenzymes**
- Malignancy and oesophageal rupture are characterized by a predominance of **salivary isoenzymes**

Adenosine deaminase

- Helps differentiate **malignant vs tuberculous pleurisy** when an exudative effusion is lymphocytic, but initial cytology and smear and culture for tuberculosis are negative.
- Typically > 35 to 50 U/L in tuberculous pleural effusions
- Specificity is increased when the lymphocyte to neutrophil ratio is > 0.75 and the ADA is > 50 U/L .
- More valuable for ruling in the diagnosis of tuberculous pleurisy in geographic locations with high prevalence of tuberculosis

N-terminal pro-BNP

- Elevated in the PF of pts who have heart failure & a pleural effusion
- PF NT-proBNP, has no added value as compared with blood NT-proBNP levels.
- Blood NT-proBNP testing is useful for diagnosing a cardiogenic pleural effusion in patients whose pleural fluid appears exudative (eg, due to diuresis).

Tumor markers

- No single pleural fluid tumor marker is accurate enough for routine use in the diagnostic evaluation of pleural effusion

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:
 - < 5000/ microL – TB, Malignancy
 - >10,000/microL, exudative –bacterial pneumonia, acute pancreatitis, lupus pleuritis
 - >50,000/ microL - complicated parapneumonic effusions, including empyema

contd

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

Cont'd

- **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
 - Chylothorax
- Carcinomatous pleural effusions will be lymphocyte-predominant in over one-half of cases;
 - however, the percentage of lymphocytes is usually between 50 and 70 percent)

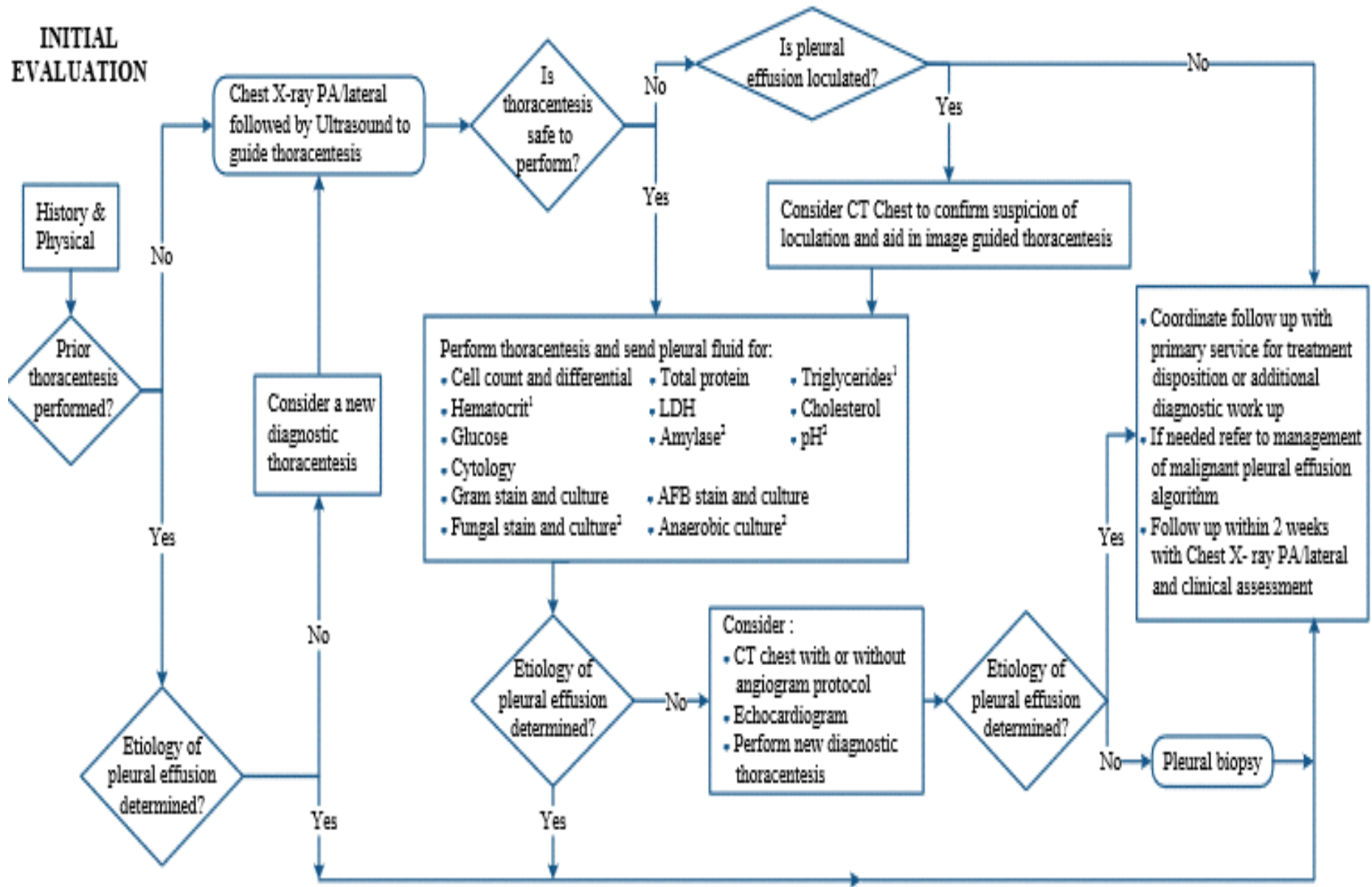
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- **PF Eosinophilia** — defined by pleural fluid eosinophils representing more than 10 percent of the total nucleated cells, usually suggests a benign, self-limited disease, and is commonly associated with air or blood in the pleural space
- **DDX:**
 - **Pneumothorax**
 - **Hemothorax**
 - **Pulmonary infarction**
 - **Benign asbestos pleural effusion**
 - **Parasitic disease**
 - **Fungal infection**
 - **Drugs**
 - **Malignancy (carcinoma, lymphoma)**
 - **Catamenial pneumothorax with pleural effusion**
- Pleural fluid eosinophilia appears to be rare with tuberculous pleurisy on the initial thoracentesis.

THORACOCENTESIS

- [..\Downloads\Pleural tap vid.m4v](#)

INITIAL EVALUATION



¹If pleural effusion is blood-tinged or serosanguinous add hematocrit and triglycerides
²If pleural fluid is milky or there is clinical suspicion of chylothorax, add triglycerides

²If clinically indicated

THE END

GOSH!
WHAT A MASSIVE
PLEURAL EFFUSION!!

