

# Lab Updates

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Sept/Oct 2009

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*Laboratories*

# Proteinuria

- I. Definition** Proteinuria is defined as an **increase in protein excretion**.
- II. Overview** Albumin is the most abundant protein in normal urine, and it is the only protein that can be detected by urine dipstick test used in common medical laboratories. Under normal circumstances, < 200 mg of protein are excreted in the urine each day, below the level at which albumin can be detected by dipstick test. There is a certain degree of imprecision in dipstick measurement of albuminuria.

### III. Differential Diagnosis

#### A. Clinical conditions

- 1. Renal disease:** Proteinuria can occur in virtually any form of renal disease.
- 2. Glomerular lesion:** When albumin excretion is > 2 g/day, a glomerular lesion is likely.

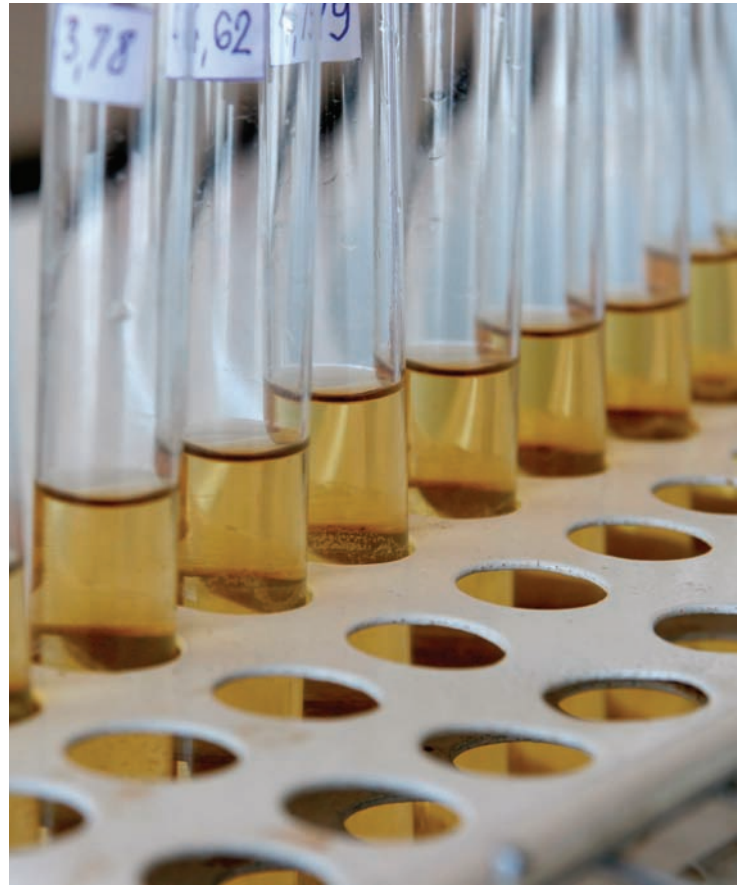


Photo: Kevin Vance

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**3. Nephrotic syndrome:** When albumin excretion is  $> 3$  g/day, the patient is said to have a nephrotic syndrome (the terms “nephrosis” and “nephrotic range proteinuria” are also used). Patients with nephrotic syndrome often “spill” other forms of protein [e.g., peptide hormones, immunoglobulins (Ig)] besides albumin. Common complications of nephrotic syndrome include edema, hyperlipidemia, and hypercoagulability.

## B. Types

- 1. Tubular proteinuria** refers to excretion of protein molecules small enough to be filtered, but that, under normal circumstances, do not appear in the urine since they are readily reabsorbed from the filtrate by tubular cells. When protein is present in the urine, therefore, a tubular lesion may be present. Nephrotic syndrome may trigger secondary tubular proteinuria since the reabsorption of filtered albumin and lipid by tubular cells may damage them through overload.  $\beta_2$ -microglobulin is the paradigm example of a tubular protein.
- 2. Overflow proteinuria** refers to the excretion of proteins, which while filterable, are normally not found in large amounts in the urine since they are not overly abundant in plasma. In certain pathologic conditions, however, they may be overproduced and presented in abnormally large quantities to the glomerulus. Examples include the **pigment proteins** [hemoglobin (Hg) and myoglobin] and **Ig fragments**. Most familiar of these are the light chains, which are often detected in the urine in plasma cell dyscrasias and amyloidosis (**Bence Jones proteins**).
- 3. Tissue proteinuria** arises from inflammation and infection in the urinary tract causing exudation or bleeding directly into the urine. It is usually of low grade.
- 4. Glomerular proteinuria** is attributable to damage to the glomerulus. The hallmark of glomerular proteinuria is **albuminuria**; massive albumin excretion cannot occur in the absence of significant damage to the glomerular basement membrane. In most glomerulopathies, however, nonalbumin proteins are also being lost in urine.

**IV. Diagnostic Evaluation** Detection and quantitation of urinary protein entails the following:

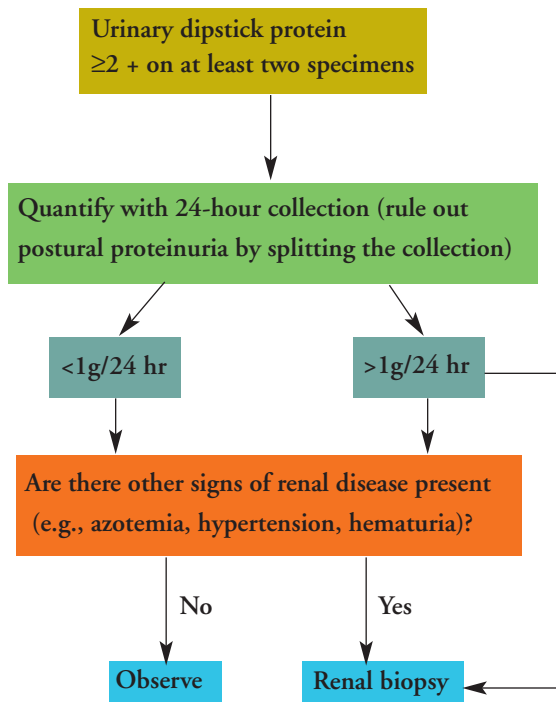
**A. Urine dipstick test.** This is actually an indirect test for albumin. The reagent is a pH indicator responding to the ability of albumin to buffer hydrogen ions in the urine. Three notes of caution include:

1. A high urinary pH will give a false-positive result.
2. The familiar 0 to 4+ grading system is an imprecise tool for quantifying proteinuria.
3. Proteins (e.g., Ig and light chains) that lack albumin's buffering properties will not be detected by dipstick.

**B. 24-hour protein determinations** employ direct chemical assay of protein in urine. They are, therefore, more accurate than the dipstick test in defining proteinuria.



### Diagnostic approach to proteinuria



Patients with systemic disorders or taking medications known to induce secondary proteinuria may not necessitate biopsy for diagnosis. Children presenting with nephrotic range proteinuria and normal renal functions are often empirically treated with steroids based on the likelihood of diagnosis of minimal change disease. Biopsy may later be entertained if therapeutic response is inadequate.

The main concern is to make certain that a 24-hour collection is complete. For this purpose, the volume of the collection is of little use; measuring the creatinine content of the specimen is better (expect  $\geq 12$  mg/kg/day in women,  $\geq 14$  mg/kg/day in men). Many clinicians favor the use of the urinary **protein-to-creatinine ratio**. A ratio of  $\leq 0.15$  mg protein/mg creatinine is normal; a ratio  $> 3$  mg protein/mg creatinine suggests the presence of nephrotic syndrome.

**C. Urine protein electrophoresis** enhances ability to detect and quantify different urinary protein species.

**D. Microalbuminuria** refers to a tendency in the early stages of progressive glomerulopathies, particularly diabetic renal disease, to excrete small amounts of protein on a regular basis. This finding may be critical for prognostic or screening purposes, but is too subtle to define by urine dipstick test or standard 24-hour assay methods. Albumin excretion rates of 15-30  $\mu\text{g}/\text{min}$  can be detected using radioimmunoassay techniques.

**V. Diagnosis of Albuminuria** This entry will consider only the patient with glomerular proteinuria (i.e., the patient found to have albuminuria).

**A. Confirm the presence of glomerular proteinuria.**

Vigorous exercise and fever can produce transient albuminuria in normal glomeruli. The persistent presence of > 1 + protein by dipstick test should be verified on sequential samples collected on different days.

**B. Establish excretion rate.** Using a 24-hour urine collection, the actual excretion rate of protein should be established. It is often helpful to have the patient divide the 24-hour specimen into separate daytime and nighttime collections to rule out the possibility of orthostatic proteinuria, a benign condition.



### Drugs and Disorders That May Cause Secondary Albuminuria

Drugs	Disorders
Ampicillin	Allergic reactions
Nonsteroidal antiinflammatory agents	Infections <ul style="list-style-type: none"> <li>• Bacterial (e.g., endocarditis, Streptococcus viridans, leprosy, tuberculosis, syphilis)</li> </ul>
Bismuth	<ul style="list-style-type: none"> <li>• Protozoal (e.g., malaria, toxoplasmosis)</li> <li>• Helminthic (e.g., filariasis, schistosomiasis)</li> </ul>
Penicillamine	<ul style="list-style-type: none"> <li>• Viral (e.g., cytomegalovirus, Epstein-Barr virus, hepatitis B, HIV)</li> </ul>
Captopril	Neoplasia (e.g., adenocarcinoma, lymphoma, Hodgkin's disease)
Probenecid	Amyloidosis
Gold salts	Collagen vascular diseases including
Tolbutamide	<ul style="list-style-type: none"> <li>• Dermatomyositis</li> </ul>
Lithium carbonate	<ul style="list-style-type: none"> <li>• Sjogren's syndrome</li> <li>• Systemic lupus erythematosus</li> <li>• Rheumatoid arthritis</li> <li>• Vasculitis (e.g., cryoglobulinemia, Henoch-Schonlein purpura, polyarteritis nodosa, Takayasu's arteritis, Wegener's granulomatosis)</li> </ul>
	Diabetes mellitus
	Goodpasture's syndrome
	Massive obesity
	Pre-eclampsia

## Primary Glomerular Diseases That Can Cause Proteinuria

Mainly Nephritic	Mainly Nephrotic
Poststreptococcal glomerulonephritis	Focal segmental glomerulosclerosis
Immunoglobulin A (IgA) nephropathy	Minimal change disease
Idiopathic crescentic glomerulonephritis	Membranous nephropathy
	Membranoproliferative glomerulonephritis

**C. Consider the patient’s medical background.** Having determined that the patient has truly pathologic proteinuria, the clinician should consider the patient’s overall medical background. There are several questions to answer:

1. **How serious is the proteinuria?** Most physicians will aggressively follow proteinuria > 1-2 g/24 hours in magnitude. Lesser amounts may be followed conservatively, unless the patient has other signs of renal dysfunction, such as hypertension, azotemia, or an active microscopic urinary sediment.
2. Is the proteinuria **transient** [fever, exercise, congestive heart failure CHF)], **intermittent** (prolonged standing), or **persistent** (most cases of glomerular proteinuria)?
3. Is the proteinuria likely due to a **primary or secondary renal condition**?
  - a. For example, if the patient has known long-standing diabetes mellitus (DM) and a history of retinopathy, the appearance of proteinuria is overwhelmingly likely to represent diabetic nephropathy.
  - b. Many medical conditions and even medications can induce proteinuria.
  - c. In the absence of systemic diseases or medications that can evoke proteinuric states, a primary glomerulopathy must be considered. Primary glomerulopathies generally require renal biopsy for precise diagnosis.



**Reference:** David Clive, *Guide to Diagnostic Testing*, pp 430–434

**If you have questions, comments or suggestions, please contact:**  
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# Evaluation of Pleural Effusions

## I. Overview

**A. Definition** Pleural effusion is defined as an increased amount of fluid in the pleural cavity. It is a common problem in clinical medicine.

**B. Dual challenge** The challenge with evaluating pleural effusions is attempting to identify the underlying cause of the effusion as well as minimize fluid accumulation.

## II. Pathophysiology

**A. Fluid accumulation** The pleural space normally contains a small amount of fluid, generally less than 20 ml. Fluid accumulates in this space when the rate of fluid production exceeds the rate of removal. There are two primary mechanisms through which this occurs:

**1. Transudate:** The pressure gradient favors secretion of fluid from capillary beds (via hydrostatic and oncotic pressure mechanisms). Fluid that accumulates in this fashion is generally referred to as transudate.

**2. Exudate:** There is excessive capillary leak of the pleural vessels, generally as a result of inflammation of the pleura. Fluid that accumulates in this fashion is generally referred to as exudate.

**B. Additional causes.** There are additional ways by which fluid may accumulate, such as fluid in the peritoneal cavity crossing through the diaphragm or through thoracic duct injury, where rupture or obstruction may occur, leading to accumulation of lymph (chylothorax).

## III. Differential Diagnosis

The most common causes of Pleural effusion are, in order, congestive heart failure (CHF)/fluid overload, pneumonia, and malignancy (i.e., direct infiltration of pleura).

## IV. Notes on the Differential Diagnosis

**A. Tuberculous pleural effusion.** The most common site for extrapulmonary tuberculosis is the pleura. Patients with tuberculous pleural effusion may have no other signs of lung disease on chest radiography. Hallmarks of tuberculous effusions include exudative, pH usually 7.3-7.4, and low glucose (may be < 30 mg/dl). It is rare to recover acid-fast bacilli from thoracentesis.

**B. Empyema** is a pleural effusion that is grossly purulent and frequently form loculations. Empyema requires immediate surgical drainage.

**C. Parapneumonic effusion.** When a patient develops a pleural effusion associated with pneumonia, it is referred to as a parapneumonic effusion.

**1. Types:** Simple parapneumonic effusion may resolve with resolution of the pneumonia. Complicated parapneumonic effusions have the potential to become an empyema.



**2. Thoracentesis:** While somewhat controversial, it is generally recommended that all patients with parapneumonic effusions undergo thoracentesis. It is difficult to predict which parapneumonic effusions will become complicated.

- a. Free-flowing parapneumonic effusions in which the pH > 7.30, glucose > 60, and lactate dehydrogenase (LDH) < 1000 are unlikely to organize and, therefore, require surgical drainage.
- b. If the pleural pH is < 7.10, glucose < 40, and LDH > 1000, there is a higher likelihood that the effusion will require surgical debridement, and many physicians recommend early chest tube replacement.

**D. Pulmonary embolism** and **sarcoidosis** are the most common conditions that can present with either a transudate or exudate.

**V. Clinical Approach** The history and physical examination are directed toward assessing symptoms resultant from and causative of the effusion. Given the broad range of causes, the history and examination should be comprehensive.

**A. History.** Assess for dyspnea, chest pain (pleuritic, anginal), cough, fever, sputum production, weight loss, tobacco abuse, risk factors for deep venous thrombosis, trauma, travel, medications, invasive procedures, and dermatologic and rheumatologic symptoms.

**B. Physical examination.** Assess for reduced breath sounds, wheezing, bronchial breath sounds, a third heart sound (S3)' displaced point of apical impulse, elevated jugular venous pressure, auscultatory evidence of significant valvular disease, peripheral swelling, ascites or stigmata of chronic liver disease, and lymphadenopathy. Perform a breast, pelvic, and rectal examination.



### Differential Diagnosis of Pleural Effusion

Transudate	Exudate
Congestive heart failure (CHF)	Malignancy (e.g., of the lung, breast, ovary, gastric, lymphoma most common)
Cirrhosis	Infectious: Parapneumonic effusion Tuberculosis
Nephrotic syndrome	Pancreatitis (usually left-sided effusion)
Peritoneal dialysis	Esophageal rupture
Atelectasis	Collagen vascular diseases: Systemic lupus erythematosus Rheumatoid arthritis
Pulmonary embolism	Drug-induced effusion
Hypoalbuminemia	Chylothorax
Superior vena cava obstruction	Hemothorax
Sarcoidosis	Postsurgical effusion
Myxedema	Trauma

## VI. Diagnostic Evaluation

### A. Radiologic guidance

1. **Plain radiography** will contribute information toward identifying the cause of effusion, such as heart size, presence of infiltrate, nodules, or lymphadenopathy.
2. **Chest radiography:** Pleural effusion is most frequently diagnosed on chest radiography. Findings suggestive of pleural effusion include blunting of the costophrenic angle and the presence of a meniscus posteriorly on a lateral chest view. This generally occurs with approximately 150 ml of fluid. However, the chest radiograph does not reach 100% sensitivity for diagnosis of pleural effusion until there is greater than 500 ml of pleural fluid.
3. **Lateral decubitus films** are used to define whether or not a pleural effusion is loculated, and can provide an additional estimate of the volume of fluid. It is better than plain films at detecting small effusions.

**B. Thoracentesis.** It is generally safe to perform thoracentesis without radiologic guidance if the pleural fluid layer is > 10 mm.

1. **Indications:** Thoracentesis is indicated primarily for:
  - a. **Diagnostic purposes**, when the pleural effusion cannot be easily explained by the clinical presentation
  - b. **Therapeutic purposes** to relieve dyspnea, drain infection, and prevent complications
2. **Contraindications:** There are no absolute contraindications to thoracentesis, but relative contraindications include anticoagulation, bleeding diathesis, small volume of fluid ( $\leq 10$  mm by imaging study), mechanical ventilation, an uncooperative patient, tapping a postpneumectomy space, and an overlying skin disease.

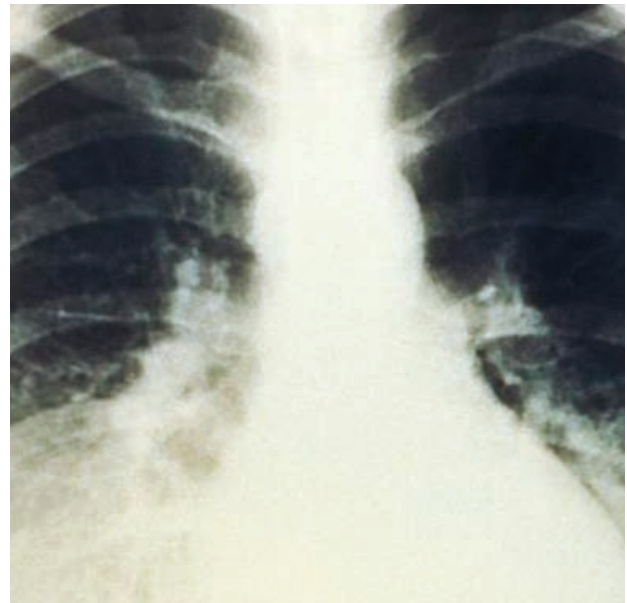


Image courtesy of Department of Health and Human Services  
Public Health Image Library (PHIL)

**C. Pleural fluid analysis.** Various studies may be performed on pleural fluid to help determine the underlying cause. There are few conditions for which there is a single pleural test that clinches the diagnosis. Initial studies are directed at determining whether the fluid is transudate or exudate.

#### 1. Chemistries

**a. Exudate versus transudate:** Fluid is considered exudative if it meets one of the following criteria:

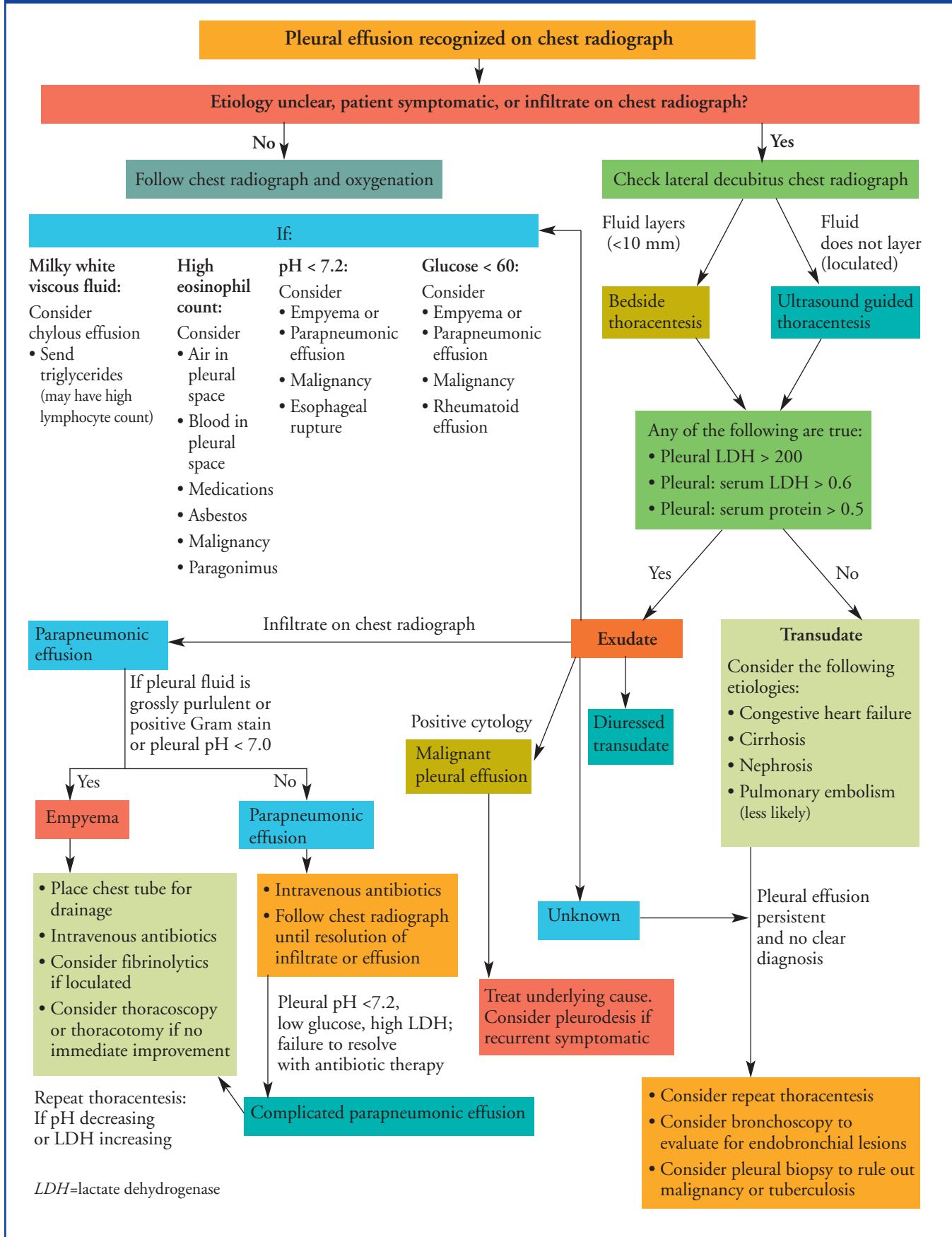
- (1) Pleural fluid: LDH  $\geq 200$
- (2) Pleural:serum LDH ratio  $\geq 0.6$
- (3) Pleural:serum protein  $\geq 0.5$

**b. New criteria:** Recent meta-analyses have shown that the following criteria are as accurate in identifying an exudate:

- (1) Pleural LDH above 0.45 of upper limits of normal serum values
- (2) Pleural cholesterol > 45 mg/dl
- (3) Pleural protein > 2.9 g/dl

**c. LDH criteria:** If exudate is determined by LDH criteria alone, cancer and parapneumonic effusion should be strongly considered.

# Algorithm for the Workup of Patients with Pleural Effusion



2. **Fluid appearance:** The appearance of pleural fluid may be informative.

a. A **milky, viscous pleural fluid** suggests chylothorax or pseudochylothorax. Triglyceride level and lymphocyte count should be obtained.

b. If the fluid is **grossly bloody**, a finding of  $> 100,000/\text{mm}^3$  red blood cells (RBCs) is suggestive of trauma, malignancy, and pulmonary embolism. If the fluid hematocrit approaches the blood hematocrit (ratio  $> 50\%$ ), the effusion is a hemothorax.

c. If the fluid is **grossly purulent**, it is an empyema.

d. **Straw-colored fluid** is not helpful in classifying the effusion.

### 3. Cell count

a. **RBCs**  $> 100,000/\text{mm}^3$  are frequently seen in malignancy, trauma, and pulmonary embolism.

b. **White blood cells (WBCs):** The differential of WBCs is more important than the absolute number of cells.

(1) **Neutrophils**  $> 50\%$  are seen in any acute inflammatory or infectious process, such as parapneumonic effusion or empyema.

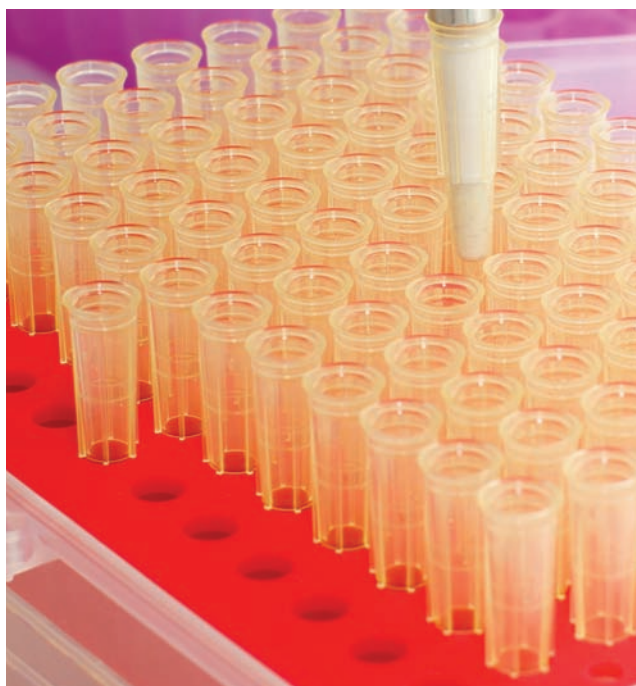
(2) **Lymphocytes**  $> 50\%$  are seen in lymphoma or malignancy, tuberculosis, fungal infections, sarcoid, and postpericardiotomy syndrome.

(3) **Elevated eosinophils** are seen in patients with air or blood in the pleural space, malignancy, drugs, parasitic infection, asbestos related conditions, and Churg-Strauss syndrome. High eosinophils contraindicate tuberculosis.

4. **Cytology studies** are positive in 66% of samples ultimately found to have malignant pleural effusions. Repeated thoracentesis will increase the yield.

5. **Culture and Gram stain:** If the Gram stain is positive for organisms, it is an empyema.

6. A **pH**  $< 7.2$  is seen in empyema, complicated parapneumonic effusion, rheumatoid disease, esophageal rupture, tuberculosis, and sometimes malignancy.



7. **Glucose**  $< 60 \text{ mg/dl}$  is seen in empyema, complicated parapneumonic effusion, rheumatoid disease, malignancy, and tuberculosis.

8. **Specialized studies** on pleural fluid can be used in the appropriate clinical scenario:

a. **Amylase**  $> 200$  is seen in acute pancreatitis and esophageal rupture.

b. **Rheumatoid factor**  $> 1:320$  is very supportive of rheumatoid effusion.

c. **Antinuclear antibody**  $> 1:160$  is seen in lupus pleuritis.

d. **Carcinoembryonic antigen (CEA)**  $> 10$  indicates malignancy.

e. **Adenosine deaminase**  $> 43 \text{ U/l}$  indicates tuberculous pleuritis.

f. **Pleural biopsy** (via thoracoscopy) is indicated for evaluation of exudative pleural effusion of unclear etiology. The most common indication is to evaluate for potential pleural tuberculosis, and it may improve the yield for malignancy as well.

**Reference:** Eric Alper, *Guide to Diagnostic Testing*, pp 375–380

If you have questions, comments or suggestions, please contact:  
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