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A photograph of a hospital room. A patient is lying in a hospital bed, covered with white linens. The room has a window with blinds, an exit sign above the door, and a desk with a vase of flowers in the foreground.

Diagnostic Approach to Pleural Effusion

Pleural Fluid Analysis and other Modalities

Learning Objectives:

- Review the causes and various forms of pleural effusion
- Analyze the clinical criteria for drainage of parapneumonic effusion
- Discuss the role and utility in measuring pleural fluid pH to aid in the diagnosis of pleural effusion

Leading Causes of Pleural Effusion in the United States

ding to

Approximately 1.5 million pleural effusions are diagnosed in the United States each year

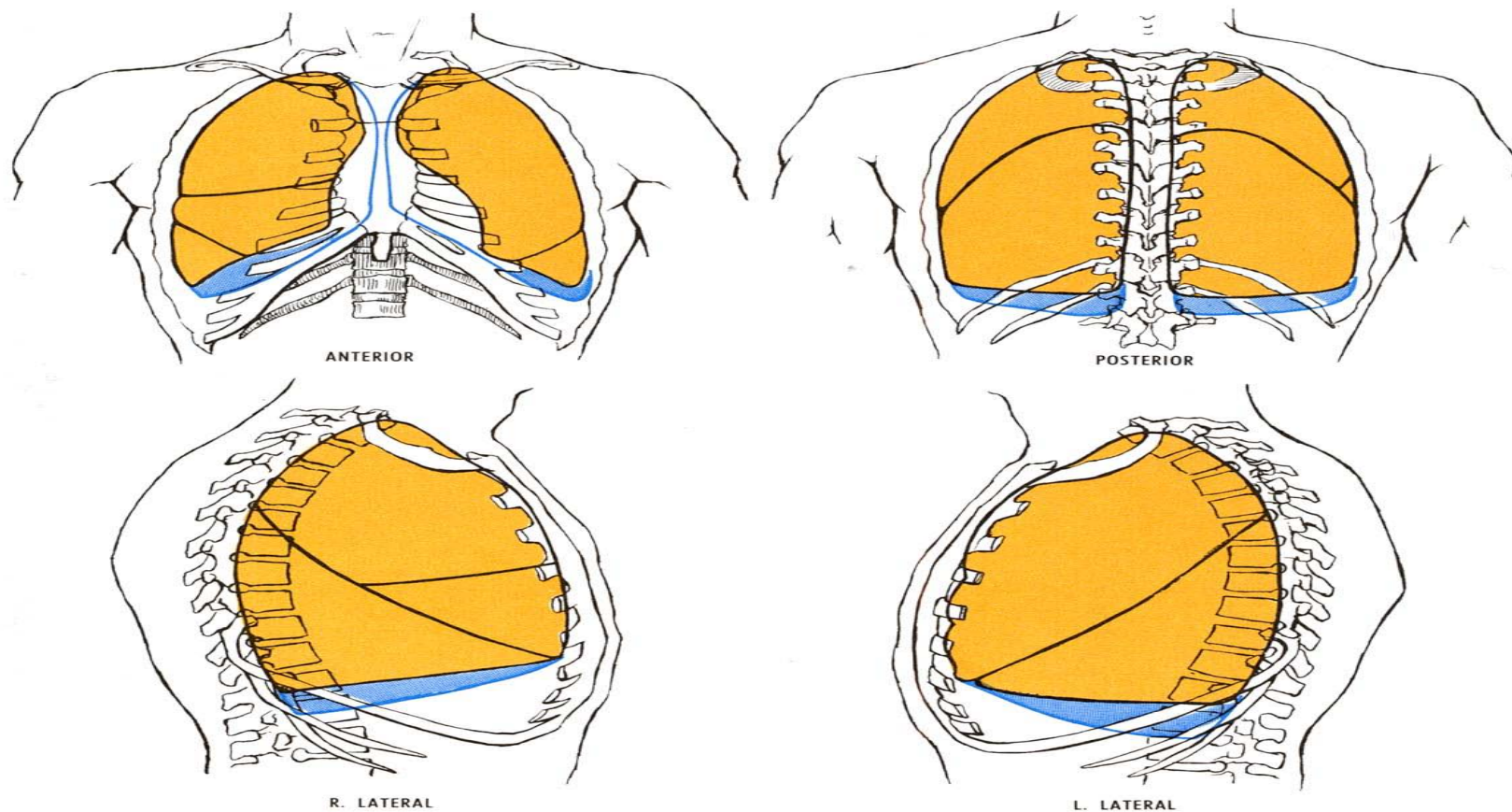
CAUSE	ANNUAL INCIDENCE	TRANSUDATE	EXUDATE
Congestive heart failure	500,000	Yes	No
Pneumonia	300,000	No	Yes
Cancer	200,000	No	Yes
Pulmonary embolus	150,000	Sometimes	Sometimes
Viral disease	100,000	No	Yes
Coronary-artery bypass surgery	60,000	No	Yes
Cirrhosis with ascites	50,000	Yes	No

*Adapted from Light.¹

N ENGL J MED 2002; 346:1971-1977

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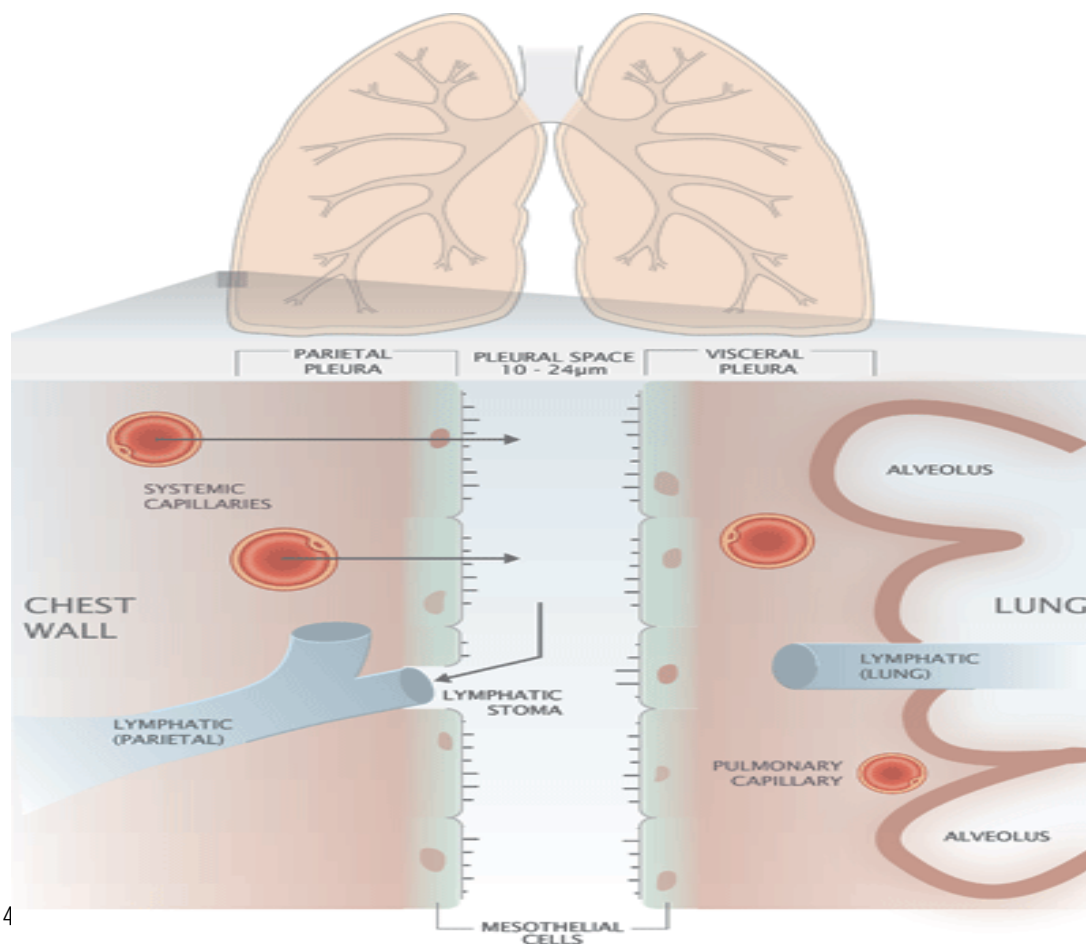
Anatomy



Curr Opin Pulm Med. Jul 2001;7(4):180-2.

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Diagrammatic representation of the pleura

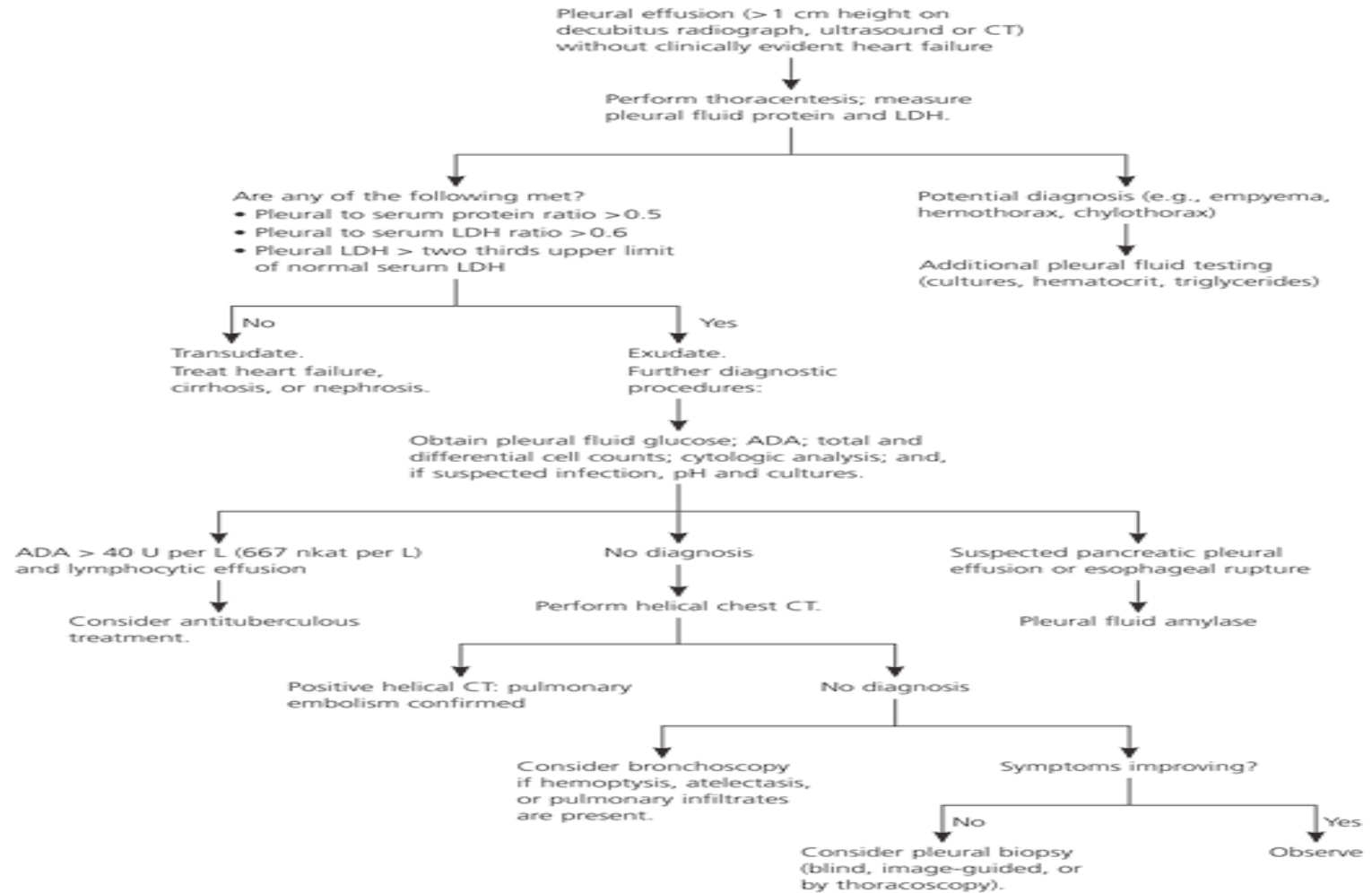


Critical Care & Pain 2007; 7: 10-14

Am J Respir Crit Care Med 2000; 162: 1023-26

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Algorithm for the evaluation of patients with pleural effusion



Initial Evaluation of Pleural Effusion



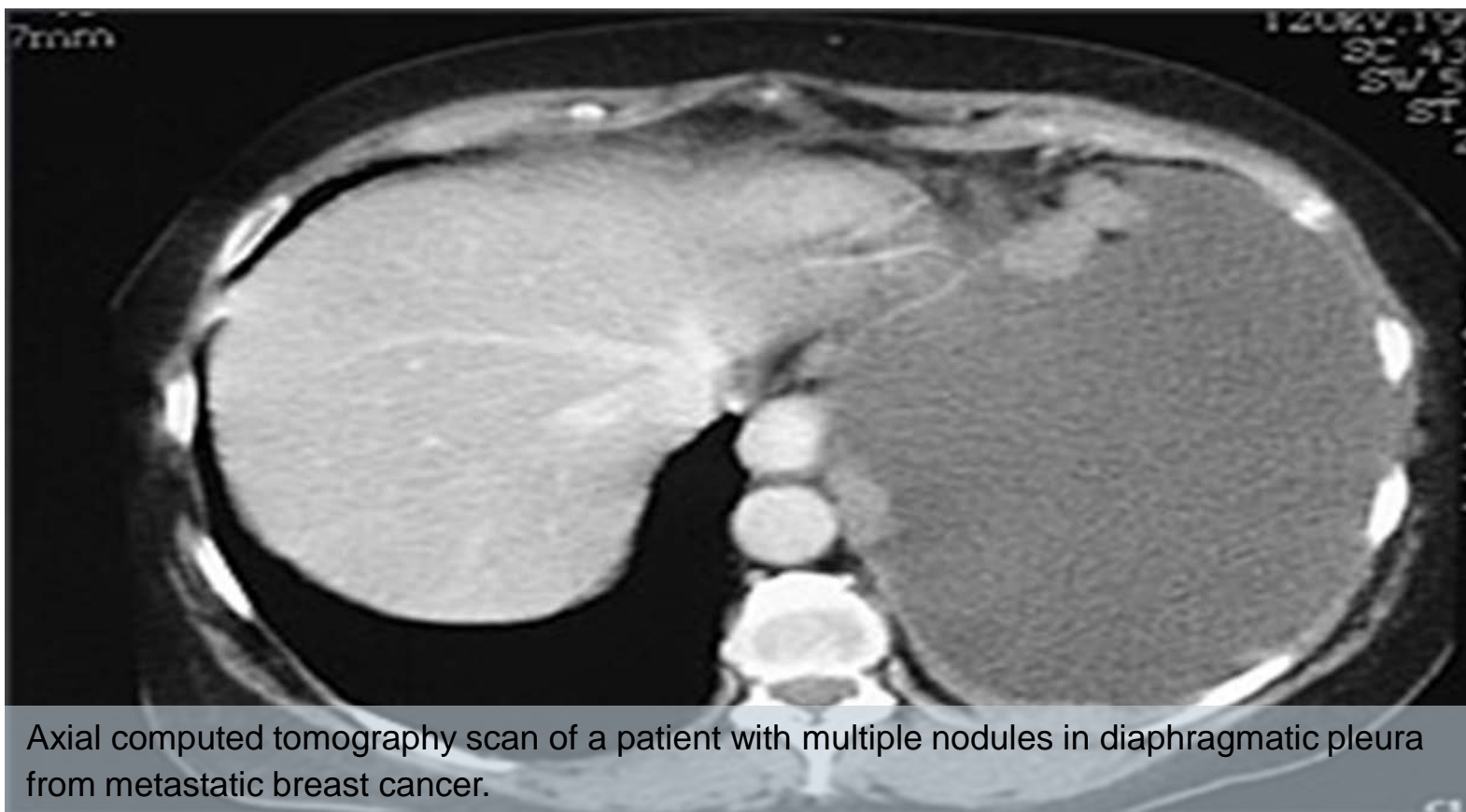
Left lateral decubitus of the same patient demonstrating a large amount of free pleural fluid.



PA radiograph demonstrating blunting of the left costophrenic angle

LIGHT RW. PLEURAL DISEASES. 4TH ED. PHILADELPHIA: LIPPINCOTT WILLIAMS & WILKINS, 2001

Other diagnostic procedures

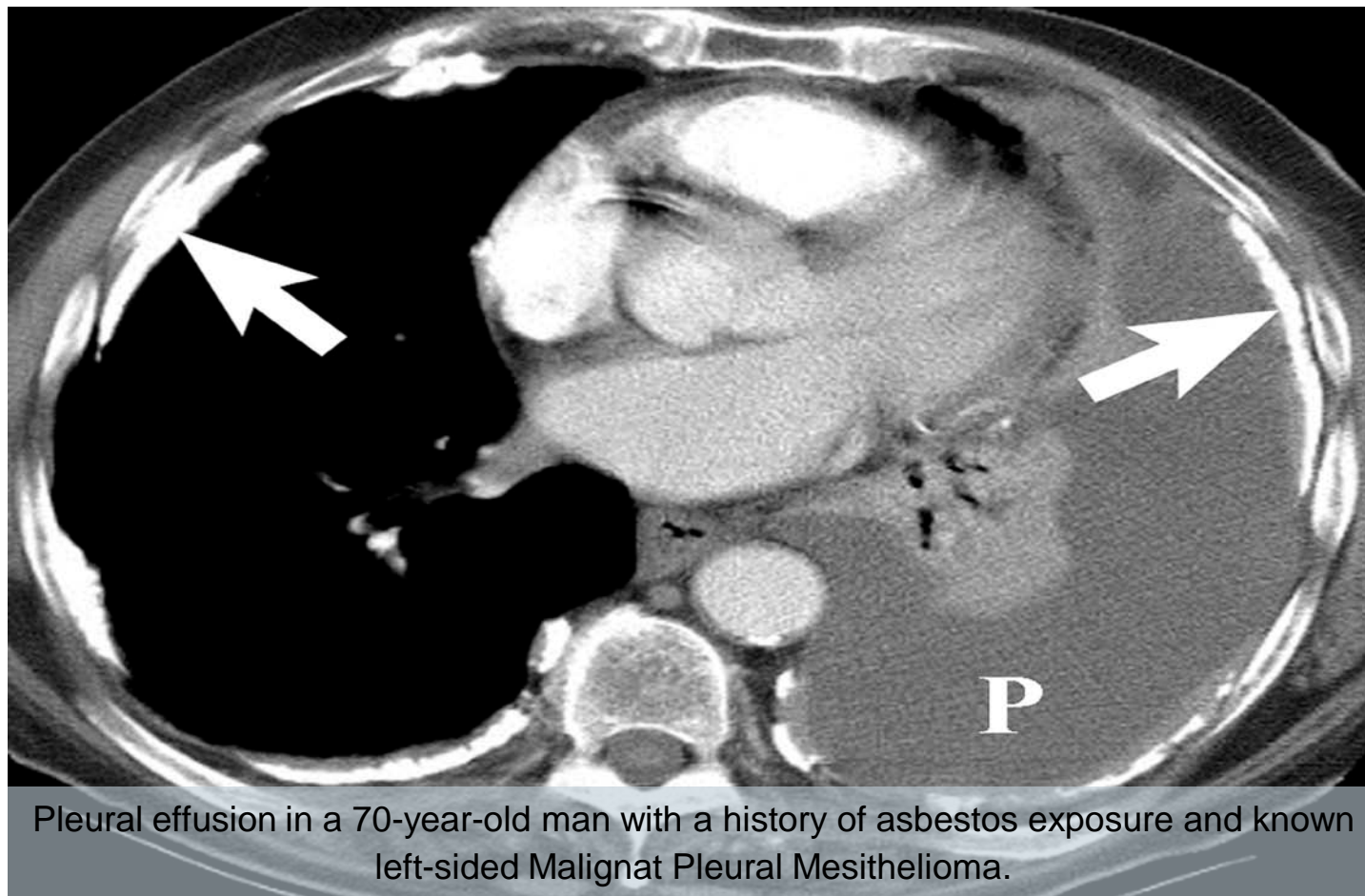


Axial computed tomography scan of a patient with multiple nodules in diaphragmatic pleura from metastatic breast cancer.

EUR RADIOL. 2000;10:681–90.

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Other diagnostic procedures

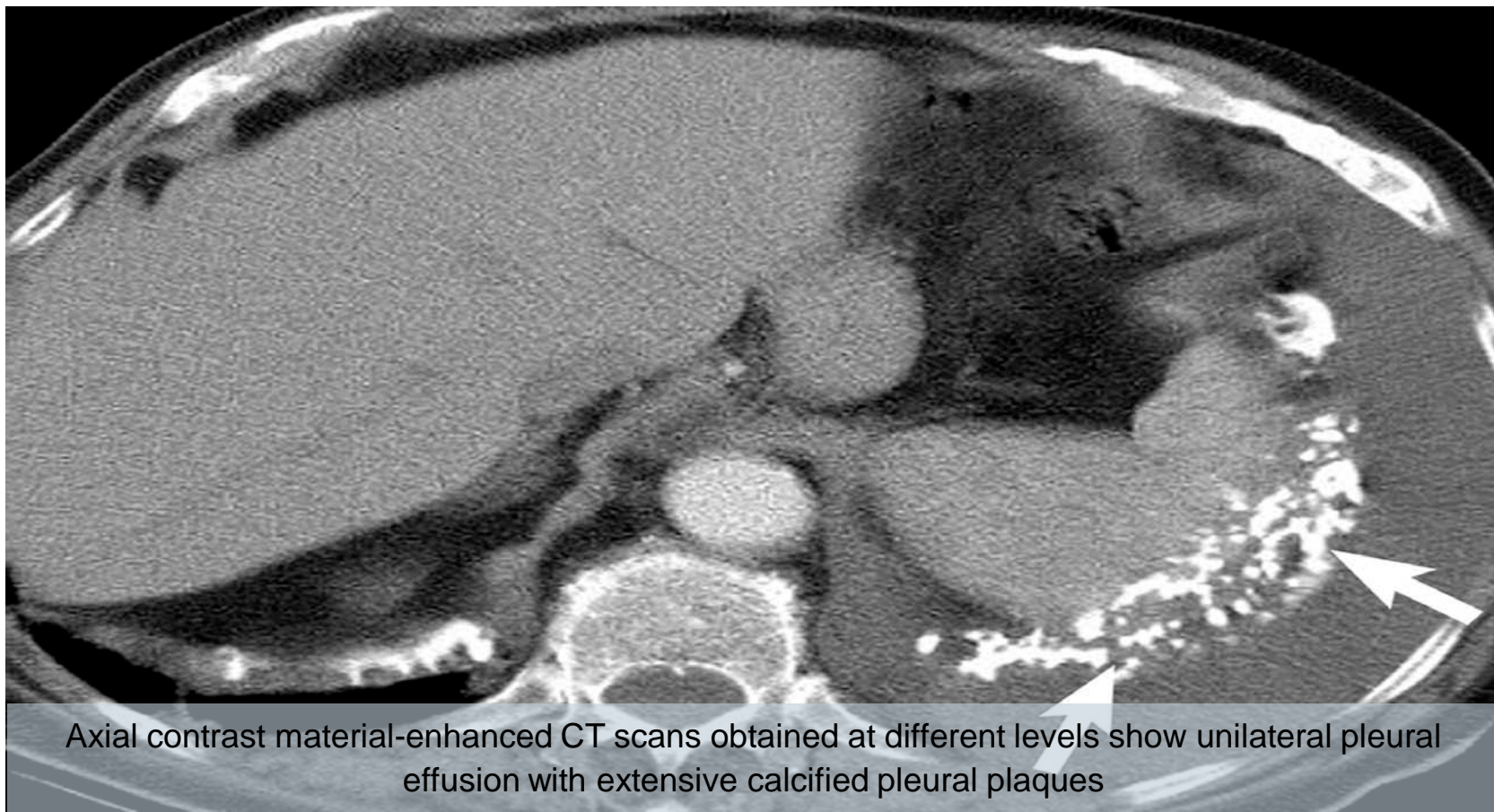


Pleural effusion in a 70-year-old man with a history of asbestos exposure and known left-sided Malignant Pleural Mesothelioma.

Radiographics 2004;24:105-119

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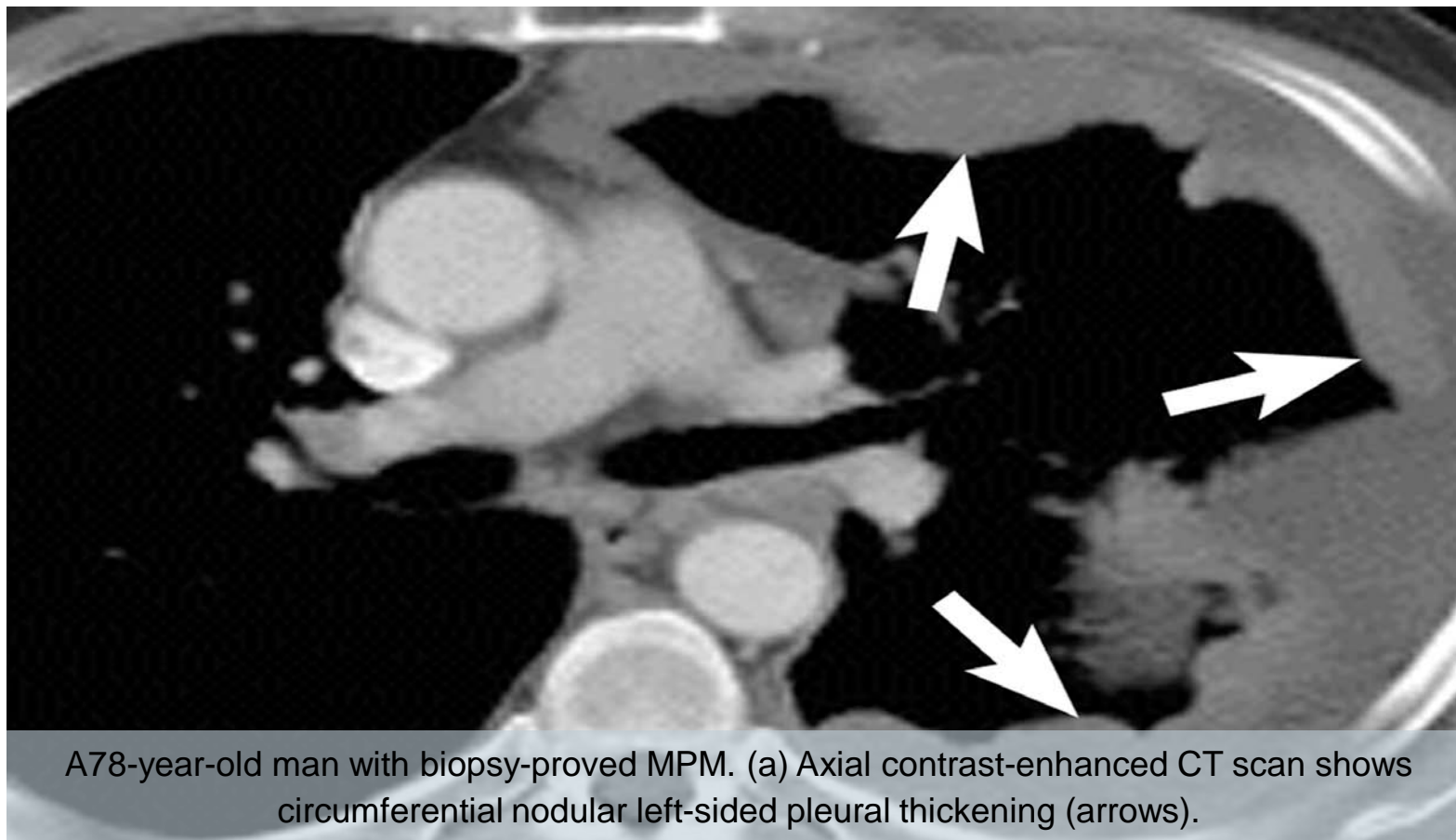
Other diagnostic procedures



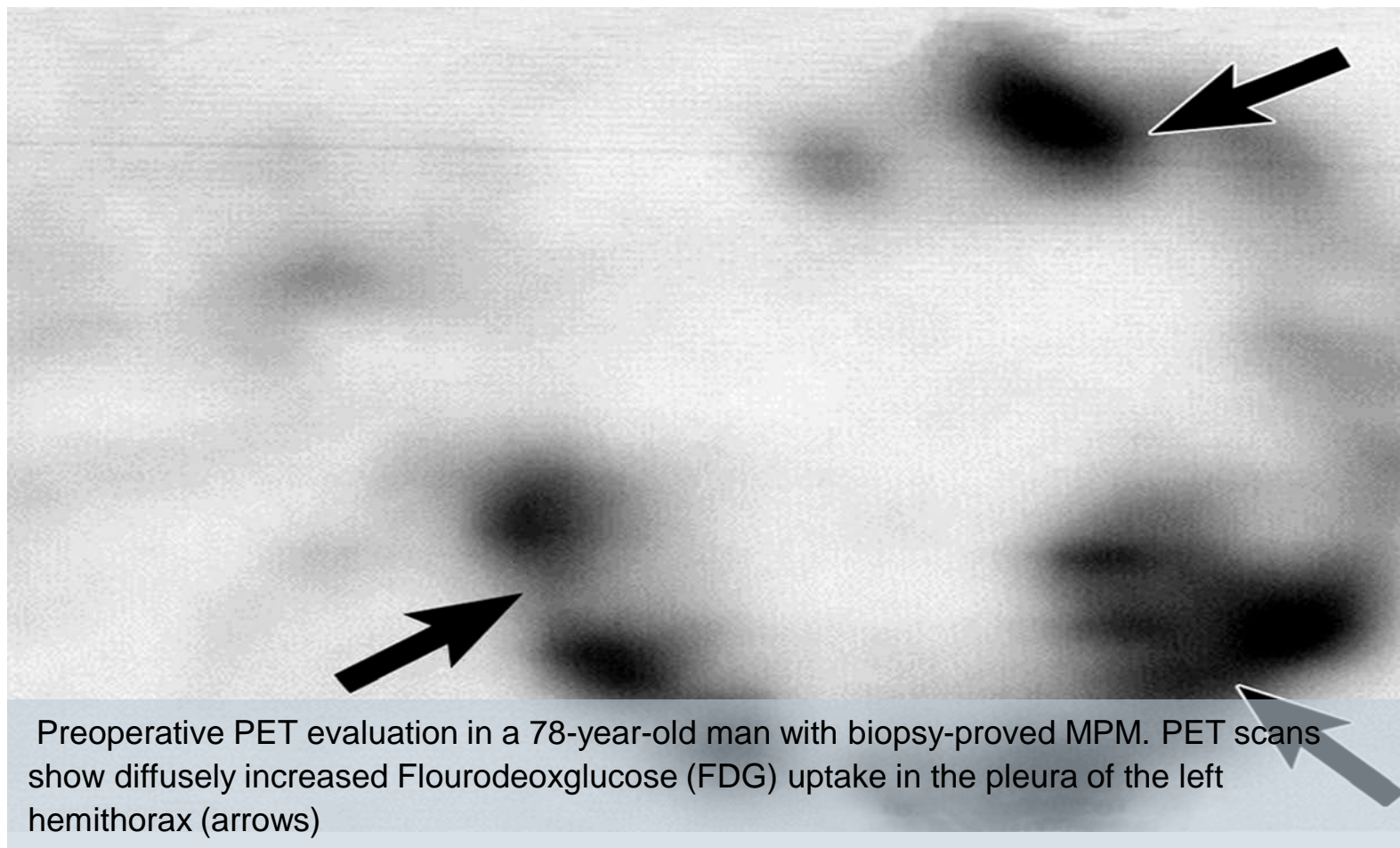
Radiographics 2004;24:105-119

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Other diagnostic procedures



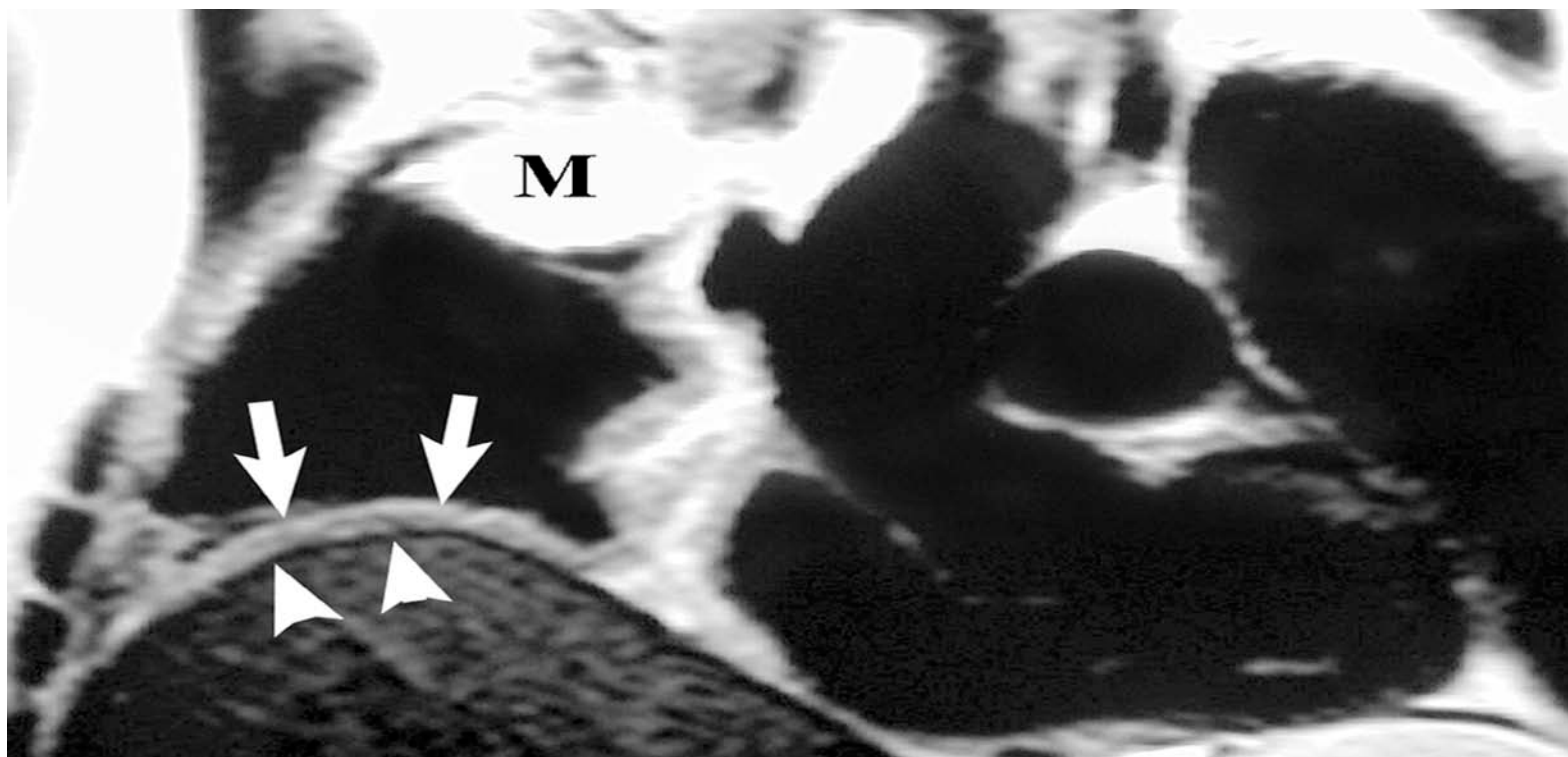
Other diagnostic procedures



Radiographics 2004;24:105-119

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Other diagnostic procedures



MR imaging evaluation of MPM in a 63-year-old man. MR images show the mass (M) with involvement of the diaphragmatic pleura (arrows). No invasion of the diaphragmatic muscle, visualized with intact black line above liver (arrowheads)

Pleural Effusion Definition

An abnormal collection of fluid in the pleural space resulting from excess fluid production or decreased absorption requiring urgent evaluation and treatment

Transudative Effusion

- Heart failure
- Cirrhosis
- Nephrotic Syndrome
- Hypoalbuminemia
- Hypothyroidism

Exudative effusion

- Infection
- Pulmonary Embolism
- Malignant diseases
- Autoimmune disease
- Pancreatitis
- Esophageal rupture
- Post CABAG
- Post MI
- Drug induced

Compr Ther. Winter 2007;33(4):237-46.

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History and physical examination evaluation of pleural effusion

The history and physical examination are critical in guiding the evaluation of pleural effusion

Signs and symptoms of an effusion vary depending on the underlying disease, but dyspnea, cough, and pleuritic chest pain are common.



Respiration. 2008;75(1):4-13.

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Causes of Pleural Effusions: History, Signs, and Symptoms

Condition	Potential Causes
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

N ENGL J MED. 2002;346:1971–7. *PEDIATR REV.* 2002;23:417–26.

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Approach Considerations

Thoracentesis should be performed for new and unexplained pleural effusions when sufficient fluid is present to allow a safe procedure

A second thoracentesis should be considered in the following situations:

- Suspected **malignant effusion** and the initial pleural fluid cytological examination is negative
- A **parapneumonic** effusion with borderline biochemical characteristics of the pleural fluid for indicating chest tube drainage
- Suspected **acute tuberculosis** pleurisy with initial non-diagnostic pleural adenosine deaminase (ADA) levels. (>100 IU/L is highly sensitive to tubercular pleural effusion but less specific)

Approach Considerations

Observation of benign etiologies are likely, as in the setting of overt congestive heart failure, viral pleurisy, or recent thoracic or abdominal surgery:

- Frankly **purulent fluid** indicates an empyema
- A **putrid odor** suggests an anaerobic empyema
- A **milky, opalescent fluid** suggests a chylothorax, resulting most often from lymphatic obstruction by malignancy or thoracic duct injury by trauma or surgical procedure
- **Grossly bloody fluid** may result from trauma, malignancy, postpericardiotomy syndrome, or asbestos-related effusion and indicates the need for a spun hematocrit test of the sample; a pleural fluid hematocrit level of more than 50% of the peripheral hematocrit level defines a hemothorax, which often requires tube thoracostomy

Distinguish exudate from transudate using Light's Criteria

Measured Parameters

Serum Total Protein (g/l)
Serum LDH (u/l)
Pleural Fluid Total Protein (g/l)
Pleural fluid LDH (u/l)

Calculated Parameters

Pleural Fluid Total Protein: Serum
Total Protein Ratio (TPR)
Pleural Fluid LDH: Serum LDH Ratio
(LDHR)

Criteria for Exudate

**TPR > 0.5 or
LDHR > 0.6 or
Pleural Fluid LDH > 200 u/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.

Approach Considerations

A **meta-analysis of 1448 patients** suggested that the following combined pleural fluid measurements might have sensitivity and specificity comparable to the criteria from Light et al for distinguishing transudates from exudates:

- Pleural fluid LDH value greater than 0.45 of the upper limit of normal serum values
- Pleural fluid cholesterol level greater than 45 mg/dL
- Pleural fluid protein level greater than 2.9 g/dL
- Clinical judgment is required when pleural fluid test results fall near the cutoff points

The criteria from ***Light et al*** and these alternative criteria identify nearly all exudates correctly, but they **misclassify approximately 20-25% of transudates as exudates**, usually in patients on long-term diuretic therapy for congestive heart failure (because of the concentration of protein and LDH within the pleural space due to diuresis)

Approach Considerations

- Use **serum minus pleural protein concentration** level of less than 3.1 g/dL, rather than a serum/pleural fluid ratio >0.5 , more correctly identifies exudates in these patients
- Although pleural fluid albumin is **not typically** measured, a gradient of serum albumin to pleural fluid albumin less than 1.2 g/dL also identifies exudate in these patients
- **Pleural fluid LDH** >1000 IU/L suggest empyema, malignant effusion, rheumatoid effusion, or pleural paragonimiasis
- **Pleural fluid glucose** should be measured during the initial thoracentesis in most situations.
- **Low pleural glucose** concentration (30-50 mg/dL) suggests malignant effusion, tuberculous pleuritis, esophageal rupture, or lupus pleuritis
- **Very low pleural glucose** concentration (ie, < 30 mg/dL) further restricts diagnostic possibilities, to rheumatoid pleurisy or empyema.

Approach Considerations

- **Transudative fluid** results from imbalances in hydrostatic and oncotic forces and are caused by a limited number of recognized clinical conditions such as heart failure and cirrhosis.
- **Less common causes** include nephrotic syndrome, atelectasis, peritoneal dialysis, constrictive pericarditis, superior vena caval obstruction, and urinothorax.
- Transudative effusions usually respond to treatment of the underlying condition (e.g., diuretic therapy)

Chest. Apr 1997;111(4):970-80 and *Chest.* Sep 2009;136(3):656-8

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Approach Considerations

- Studies suggest pleural fluid levels of N-terminal pro-brain natriuretic peptide (**NT-proBNP**) are elevated in effusions due to congestive heart failure
- Elevated pleural **NT-proBNP** was shown to **out-perform** pleural fluid **BNP** as a marker of heart failure–related effusion
- High pleural levels of NT-proBNP (defined in different studies as >1300-4000 ng/L) may help to **confirm heart failure** as the cause of an otherwise idiopathic chronic effusion

Chest. Apr 1997;111(4):970-80 and *Chest.* Sep 2009;136(3):656-8

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Pleural fluid pH – General Consideration

- The only study in which the **pH of normal human pleural fluid** has been measured determined a value of **7.64**
- Is in broad agreement with more recent animal studies that suggest that pleural fluid **pH normally lies within the range of 7.60-7.66, slightly alkaline compared with blood pH (7.35-7.45)**
- The relatively high bicarbonate concentration of pleural fluid accounts for this difference in pH
- The pH of pleural effusions is lower than that of normal pleural fluid and approximates much closer to the pH of blood, with transudative effusions generally having a higher pH (7.45-7.55) than **exudative effusions, which with some important exceptions, have a pH in the approximate range of 7.30-7.45**

Pleural fluid pH – General Consideration

- **Highest pleural fluid pH is seen in transudative effusions** resulting from heart failure
- Light et al measured pleural fluid pH in 178 patients, including 39 with heart failure. In all but four of these 39, pleural fluid pH was >7.4 and ranged from 7.40 to 7.58 (median 7.49). The four patients with pleural fluid pH <7.4 had an accompanying metabolic or respiratory acidosis, highlighting the fact that acidemia can itself cause a lowering of pleural fluid pH, which may complicate the interpretation of pleural fluid pH results.

Pleural fluid pH – General Consideration

- All transudative and most exudative effusions have a pH >7.30. Pleural fluid pH <7.30 (termed pleural acidosis) associated with a limited number of conditions.
 - **Esophageal rupture-** lowest pleural pH (5.0-6.5)
 - **Tuberculosis**
 - **Rheumatoid disease**
 - **Pneumonia**
 - **Malignant disease**
- A review of 475 patients with pleural effusion revealed 59 patients with pleural fluid pH <6.0.
- In all 59 cases the cause of pleural effusion was esophageal rupture. Pleural fluid pH of <6.0 virtually diagnostic of esophageal rupture

Parapneumonic effusion and pleural fluid pH

- **Pneumonia** is the second most common cause of pleural effusion after heart failure
- **Parapneumonic effusions (PPE):** (20-40 %) of patients hospitalized with pneumonia develop an exudative pleural effusion.
- PPE also arise from lung abscess, or bronchiectasis

Three Types of PPE (Parapneumonic Effusion)

Uncomplicated

- pH is >7.3 (7.33-7.47)
- Generally respond well to antibiotic treatment

Complicated

- Loculated pH is 6.70-7.21
- Presence of pus or gram stain-positive pleural fluid or pH <7.0
- Management includes chest tube drainage (tube thoracostomy) and antibiotics

Empyema

- Collection of pus in existing anatomical cavity, i.e. lung pleura
- pH 6.29-7.28
- Treatment includes antibiotics, drainage, re-expansion of lung, decortication

- pH of 7.2 as a cut-off value is based on a large meta-analysis study of pleural fluid pH in PPE
- Study demonstrated pleural fluid pH better able to predict the need for tube drainage than either pleural fluid LDH activity or glucose.

Parapneumonic effusion and Pleural Fluid pH

- A **low** pleural fluid pH value has prognostic and therapeutic implications for patients with parapneumonic and malignant pleural effusions
- Pleural fluid **pH** is **highly correlated** with pleural fluid **glucose** levels
- **Low** pleural fluid **pH** levels in **parapneumonic effusions** is more predictive of complicated effusions than **low** pleural fluid **glucose** levels
- A pH value **<7.20** in a patient with a parapneumonic effusion indicates the need for urgent drainage of the effusion, while a pleural fluid pH of **>7.30** suggests that the effusion may be managed with systemic antibiotics alone.
- **In malignant effusions**, a pleural fluid pH of **<7.3** has been associated in some reports with more extensive pleural involvement, higher yield on cytology, decreased success of chemical pleurodesis, and shorter survival times.

Ann Intern Med. Oct 1972;77(4):507-13

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Parapneumonic effusion and pleural fluid pH

- Pleural fluid pH of **<7.30** with a **normal arterial blood pH** level is caused by malignant effusion, tuberculosis pleuritis, esophageal rupture, or lupus pleuritis
- When a pleural fluid pH value is **not available**, a pleural fluid **glucose** concentration **<60 mg/dL** can be used to identify complicated parapneumonic effusions

Exceptions in Parapneumonic effusion and pleural fluid pH

- An exception to the rule that pleural fluids are increasingly acidotic in cases of PPE occurs when the causative bacteria is of the **Proteus species**.
- Only rarely a cause of PPE, these bacteria elaborate the enzyme urease that converts urea to ammonium, rendering pleural fluid markedly alkaline.
- In such cases pleural fluid pH is >7.45 and may be as high as 8.0.
- In these rare cases pleural fluid pH is diagnostically useful as few, if any, conditions are associated with pH greater than that of normal pleural fluid.
- However, it would clearly be inappropriate to use the 7.2 pH cut-off to guide the use of drainage therapy in such cases.
- Another problem that confuses interpretation of pleural fluid pH in cases of PPE demonstrated that the pH of pleural fluid can vary **between locules** in some patients with complicated "loculated" PPE.

Chest 1983; 84: 109-11

Chest 2004; 126: 2022-24

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Malignant Disease and Pleural Fluid pH

- Cancers of the lung, breast and ovary along with lymphoma account for most **(75 %) cases** of malignant pleural effusion (MPE)
- **Except** in the rare case of Mesothelioma (primary tumor of the pleural mesothelium).
- **Median survival** following diagnosis of MPE is just **5 months** although there is variation between cancer type; **breast cancer**, for example, is associated with much longer survival (**13 months**) than lung cancers (**2 months**)
- **Palliative treatment** for cancer patients with MPE includes therapeutic thoracentesis, but recurring MPE is treated by **pleurodesis**, a more invasive procedure in which the pleural space is first drained of fluid, then obliterated by inducing an inflammatory reaction that fuses parietal and visceral pleura.
- **Successful pleurodesis** prevents the formation of pleural fluid, thereby providing permanent relief from the debilitating breathlessness associated with MPE.

Malignant Disease and Pleural Fluid pH

- Pleural fluid pH has **prognostic significance** in cases of MPE
- **Good et al** determined pH of pleural fluid recovered from 44 patients with MPE ranged from **7.04 to 7.55 (median 7.40)**.
- Studies have demonstrated that low pleural fluid **pH (<7.3)** is associated with **reduced survival**, more extensive pleural involvement, higher yield on cytology, decreased success of chemical pleurodesis, and shorter survival times
- Relative acidosis is assumed to be result of the metabolic activity of an ever-growing tumor mass
- Retrospective study of 226 patients with MPE, pleural fluid pH ranged from 6.70 to 7.65. For 181 of these patients, whose pleural fluid pH was **>7.32**, median survival was **6.8 months** (range 4.6-9 months), this compared with median survival of just **2.4 months** (range 1.1-3.7) for the remaining 45 patients whose pleural fluid pH was **<7.32**.

Chest 1980; 78: 55-59 ,Eur J Int Med 2008; 19: 334-36, Respiration 2006; 73: 334-39 , Ann Intern Med 1988; 108: 345-49

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Malignant Disease and Pleural Fluid pH

- **Sahn et al** examined pleural fluid pH in 60 patients with malignant disease. **Median survival** of 40 patients with pleural fluid **pH >7.3** was **9.8 months** compared with just **2.1 months** for the remaining 20 patients whose pleural fluid pH was **<7.3**.
- **The decision to recommend pleurodesis** to patients suffering MPE must take account of predicted survival
- The risk and discomfort of this invasive technique, which is by no means always successful, is not justified for patients who have a very **short life expectancy**; thoracentesis might be the more appropriate treatment.
- The **observed correlation** between **pleural fluid pH and survival** outlined above has led to the recommendation that pleural fluid pH measurement be used in selecting patients for **pleurodesis**

Chest 1980; 78: 55-59 ,Eur J Int Med 2008; 19: 334-36, Respiration 2006; 73: 334-39 , Ann Intern Med 1988; 108: 345-49

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Malignant Disease and Pleural Fluid pH

- Studies that have demonstrated that **low pleural fluid pH** is associated with **increased risk of pleurodesis failure**.
- Some authorities have suggested that pleurodesis should not be considered in those with a pleural fluid pH <7.2.
- More recent guidelines from the **American Thoracic Society/European Respiratory Society** suggest pleural fluid pH **should not be the sole criterion** in deciding whether pleurodesis is indicated; rather, pleural fluid pH should be considered adjunctive information, one of several factors that need to be considered in selecting patients. This reflects current expert opinion .

Additional laboratory Testing

- If an exudate is suspected **clinically** or is **confirmed** by **chemistry test** results, send the pleural fluid for total, differential cell counts, gram stain, culture, cytology, total amylase, amylase isoenzymes, triglyceride, cholesterol, antinuclear antibody rheumatoid factor and adenosine deaminase (ADA),
- Further detail is **beyond the scope** of this lecture

Preanalytical /Analytical Considerations when measuring Pleural Fluid pH

- Despite widespread recommendation that pleural fluid pH should only be determined using a blood gas analyzer, two other methods, pH meter and pH indicator stick (or litmus paper) are commonly used
- A recent survey conducted in North Carolina revealed that of 11 hospital laboratories measuring pleural fluid pH, just two reported using blood gas analyzers; the rest used either pH indicator stick or more rarely pH meter.
- Most **(75 %)** chest physicians ordering the test in these hospitals **wrongly assumed a blood gas analyzer** was being used. The results of this survey are broadly consistent with two previous studies that suggest that only a **third of laboratories** use blood gas analyzers.
- The evidence that pH meters, pH indicator sticks and litmus paper are insufficiently accurate for measuring pleural fluid pH is contained in a number of studies

CHEST. 2000;118:1158–71, Thorax 2003; 58 (Suppl ii): 18-28, NC Med J 2009; 70: 9-13 South Med J 1999; 92: 214-17 Chest 1998; 144: 1368-72

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Preanalytical /Analytical Considerations when measuring Pleural Fluid pH

- Reluctance to use blood gas analyzers is attributed in part to the fear that pleural fluids may block or damage electrodes
- No clinical indication for measuring the pH of pleural fluids that contain visible pus because all such effusions require draining, irrespective of the pH.
- Collecting pleural fluid into heparin-containing syringes prevents clot formation
- No clearly defined standard method for the collection of pleural fluid for pH measurement.
- A recent study suggests that pleural fluid should be collected anaerobically into a heparinized blood gas syringe, ensuring that all air is expelled.
- Care should be taken that the sample is not contaminated with even a trace of local anesthetic (lidocaine) used to prepare the patient for thoracentesis.
- Analyze samples within 1 hour of collection.

Am J Respir Crit Care Med 2008; 178: 483-90

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Take Home Message

- Pleural effusion, defined as excess fluid in the pleural space, has many possible causes, the most common are:
 - **heart failure**
 - **pneumonia**
 - **malignant disease**
- Pleural effusions are classified as either transudates or exudates
- Normal pleural fluid has a pH of 7.60-7.66 , pH of pleural effusions almost invariably <7.
- pH of transudates generally higher (7.45-7.55) than exudates (7.30-7.40)
- Pleural acidosis (pH <7.3) occurs when pleural effusion results from:
 - **esophageal rupture**
 - **tuberculosis**
 - **rheumatoid disease**
 - **malignant disease (in most cases pH >7.3)**
 - **pneumonia (in most cases pH >7.3)**

Take Home Message

- The most important clinical utility of pleural fluid pH measurement is assessment of patients with **parapneumonic and malignant pleural effusions**
- In patients with parapneumonic effusion, **pleural fluid pH <7.2** indicates advanced disease and need for urgent tube drainage in addition to antibiotic therapy
- In patients with parapneumonic effusion, **pleural fluid pH >7.2** indicates that antibiotic therapy alone is probably sufficient therapy
- In patients with **malignant effusion**, **pleural fluid pH <7.3** indicates reduced survival and is a contraindication for pleurodesis
- **Blood gas analyzers** should be used to measure pleural fluid pH - pH indicator sticks and pH meters are not suitable.
- Pleural fluid for pH measurement should be collected anaerobically to a preheparinized syringe and analyzed within 1 hour of collection.

Thank you for your attention!

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