Diagnosis and management parapneumonic effusions

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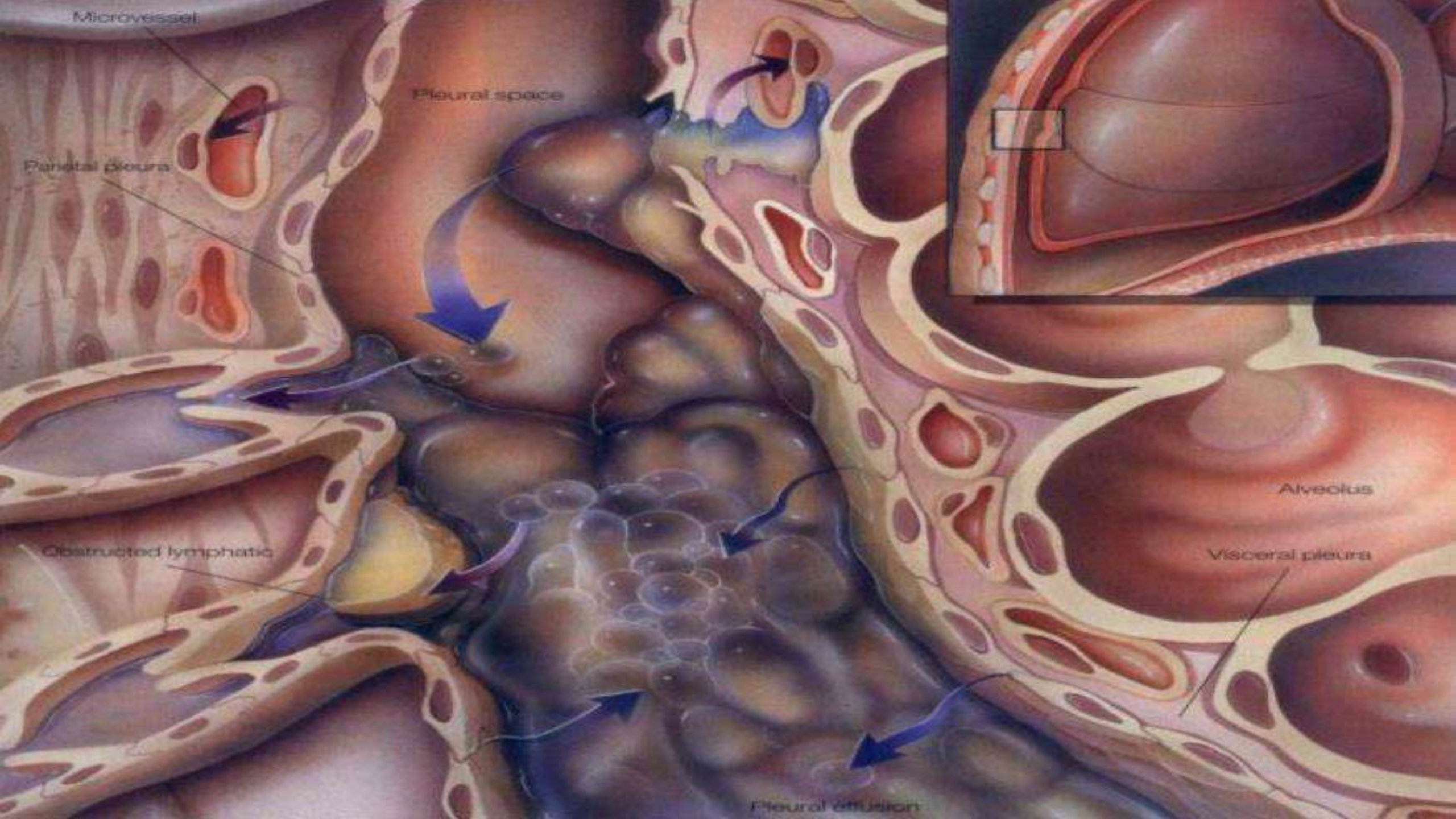
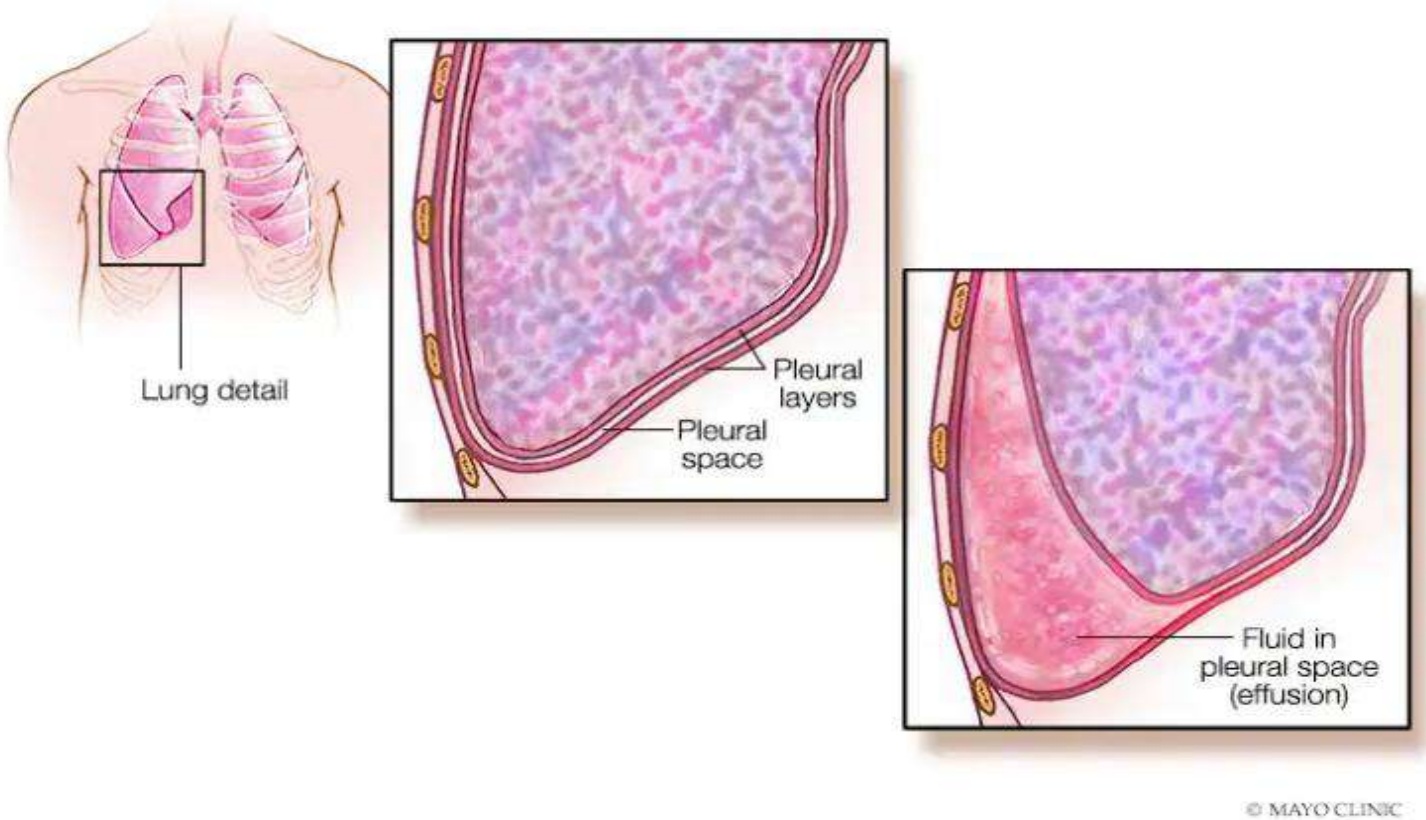

Microvessel
Pleural space
Parietal pleura
Alveolus
Obstructed lymphatic
Visceral pleura
Pleural effusion



Pleural diseases remain a common and challenging clinical problem. With an estimated 1.5 million new pleural effusions diagnosed annually in the United States

Development of Pleural Effusion

- ↑ PULMONARY CAPILLARY PRESSURE (CHF)
- ↑ CAPILLARY PERMEABILITY (Pneumonia)
- ↓ INTRAPLEURAL PRESSURE (atelectasis)
- ↓ PLASMA ONCOTIC PRESSURE (hypoalbuminemia)
- ↑ PLEURAL MEMBRANE PERMEABILITY (malignancy)
- LYMPHATIC OBSTRUCTION (malignancy)
- DIAPHRAGMATIC DEFECT (hepatic hydrothorax)
- THORACIC DUCT RUPTURE (chylothorax)

Pleural Effusion

- **Pleural effusion** is an abnormal accumulation of fluid in the pleural space. The 5 major types of pleural effusion are:
  - Transudate,
  - Exudate,
  - Empyema,
  - Hemorrhagic pleural effusion or hemothorax and
  - Chylous or chyliform effusion.

TABLE 1. LEADING CAUSES OF PLEURAL EFFUSION IN THE UNITED STATES, ACCORDING TO ANALYSIS OF PATIENTS SUBJECTED TO THORACENTESIS.*

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]

Table 1 Frequency and causes of transudate effusions

Cause of transudate	Frequency
Congestive Heart Failure	Very Common
Cirrhosis (with ascites)	Common
Hypoalbuminaemia	Common
Peritoneal Dialysis	Common
Hypothyroidism	Less Common
Nephrotic Syndrome	Less Common
Mitral Stenosis	Less Common
Pulmonary Embolism	Less Common
Constrictive Pericarditis	Rare
Urinothorax	Rare
SVC Obstruction	Rare
Ovarian Hyperstimulation	Rare
Meigs' Syndrome	Rare

Table 2 Frequency and causes of exudate effusions

Cause of exudate	Frequency
Pneumonia (para-pneumonic)	Common
Malignancy	Common
Viral disease	Less Common
CABG Surgery	Less Common
Pulmonary Infarction	Less Common
Rheumatoid Arthritis	Less Common
Autoimmune Disease	Less Common
Benign Asbestos Effusion	Less Common
Pancreatitis	Less Common
Post MI (Dressler's Syndrome)	Less Common
Yellow Nail Syndrome	Rare
Drugs	Rare
Fungal Infection	Rare

TABLE 4] Characteristics of 30-Day All-Cause Readmissions for Initial Pleural Disease Hospitalizations in the United States, 2016[a]

Characteristic	Malignant Mesothelioma	Malignant Pleural Effusion	Nonmalignant Pleural Effusion	Empyema	Primary Spontaneous Pneumothorax	Secondary Spontaneous Pneumothorax	Iatrogenic Pneumothorax	Pleural TB
No.[b]	343 (260-427)	14,721 (13,894-15,549)	42,562 (40,632-44,493)	2,735 (2,481-2,988)	595 (515-676)	363 (298-428)	4,464 (4,136-4,792)	27 (12-42)
Overall cohort	64,174 (95% CI, 61,303-67,045)[c]							
Incidence/100 pleural disease index hospitalization[d]	28 (17.7-38.7)	37 (34.9-38.3)	25 (24.3-25.7)	15 (13.8-16.1)	13 (11.3-15.1)	16 (12.1-19.5)	18 (16.2-18.9)	14 (6.8-21.9)
Proportion attributed to a pleural disease cause[e]	49 (38.1-59.5)	45 (43.8-46.5)	31 (29.8-31.3)	27 (24.9-29.8)	27 (20.7-33.2)	27 (18.7-36.2)	20 (18.0-21.7)	[f]
Age, y[d]	68.8 (66.7-70.9)	66.0 (65.5-66.4)	69.2 (68.8-69.6)	59.7 (58.7-60.7)	50.4 (47.6-53.2)	63.7 (61.1-66.3)	67.5 (66.6-68.3)	57.8 (48.8-66.9)
Age group, y[d]								
18-44	5.0 (0.36-9.5)	6.6 (5.8-7.3)	7.0 (6.5-7.5)	18.4 (16.3-20.6)	41.2 (34.2-48.2)	12.7 (7.4-18.1)	6.9 (5.6-8.2)	[f]
45-64	21.7 (15.1-28.3)	35.5 (34.1-36.9)	27.1 (26.1-28.1)	40.9 (37.9-43.9)	27.1 (21.3-33.0)	28.1 (21.0-35.1)	29.1 (26.8-31.5)	[f]
≥ 65	73.4 (66.3-80.4)	57.9 (56.3-59.6)	65.9 (64.6-67.1)	40.7 (37.7-43.7)	31.6 (25.2-38.1)	59.2 (51.4-67.0)	63.9 (61.2-66.7)	[f]
Female sex, %[d]	35 (28.0, 42.7)	56 (54.5, 56.9)	49 (48.6, 50.1)	37 (34.6, 39.8)	30 (24.3, 35.9)	31 (22.2, 40.6)	49 (46.7-51.8)	[f]
Time to readmission, d[c,f]	13.6 (12.4, 14.9)	12.0 (11.8, 12.2)	12.4 (12.3, 12.5)	11.7 (11.2, 12.2)	11.4 (10.4, 12.4)	10.3 (8.8, 11.8)	13.0 (12.5-13.5)	12.4 (8.5, 16.2)
Length of stay, d[c,f]	6.9 (5.7, 8.1)	6.5 (6.3, 6.7)	7.8 (7.6, 7.9)	7.8 (7.3, 8.3)	6.5 (5.7, 7.3)	8.1 (6.6, 9.5)	7.1 (6.7-7.6)	10.4 (4.7, 16.2)
Cost per case, $[c,f]	18,606 (12,451.8-24,759.5)	16,281 (15,550.4-17,011.0)	18,920 (18,366.1-19,474.4)	19,349 (17,637.8-21,059.5)	16,736 (13,267.0-20,204.8)	23,454 (14,225.8-32,682.5)	18,750 (17,278.8-20,221.0)	20,392 (11,274.4-29,508.8)
Total national costs, $ million[c,g]	6.3 (3.2- 9.4)	236.3 (218.5-254.2)	793.9 (749.2-838.5)	51.8 (45.4-58.2)	9.7 (7.3-12.1)	8.4 (4.9-11.9)	82.4 (73.8-90.9)	0.6 (0.1-1.0)

[a]Age, sex, and comorbidity index adjusted.
[b]Expressed as weighted No. (95% CI).
[c]Expressed as μ (95% CI).
[d]Expressed as % (95% CI).
[e]Unweighted numbers are: malignant mesothelioma, n = 187; malignant pleural effusion, n = 8,000; nonmalignant pleural effusion, n = 22,641; empyema, n = 1,431; primary spontaneous pneumothorax, n = 302; secondary spontaneous pneumothorax, n = 180; iatrogenic pneumothorax, n = 2,303; and pleural tuberculosis, n = 16.
[f]Estimated based on unweighted n ≤ 10 and their complements are omitted following Healthcare Utilization Project guidelines.
[g]For the first instance of readmission within 30 d of index hospitalization.

Evaluation

- History:
  - Dyspnea
  - Pleuritic chest pain
  - Cough
  - Fever
  - Hemoptysis
  - Wt. loss
  - Trauma
  - Hx. of cancer
  - Cardiac surgery

- Physical:
  - Dullness to percussion
  - Decreased breath sounds
  - Absent tactile fremitus
  - Other findings: ascites, JVP, peripheral edema, friction rub, unilateral leg swelling

ANATOMY AND PHYSIOLOGY IN A HEALTHY LUNG

The Right Lung

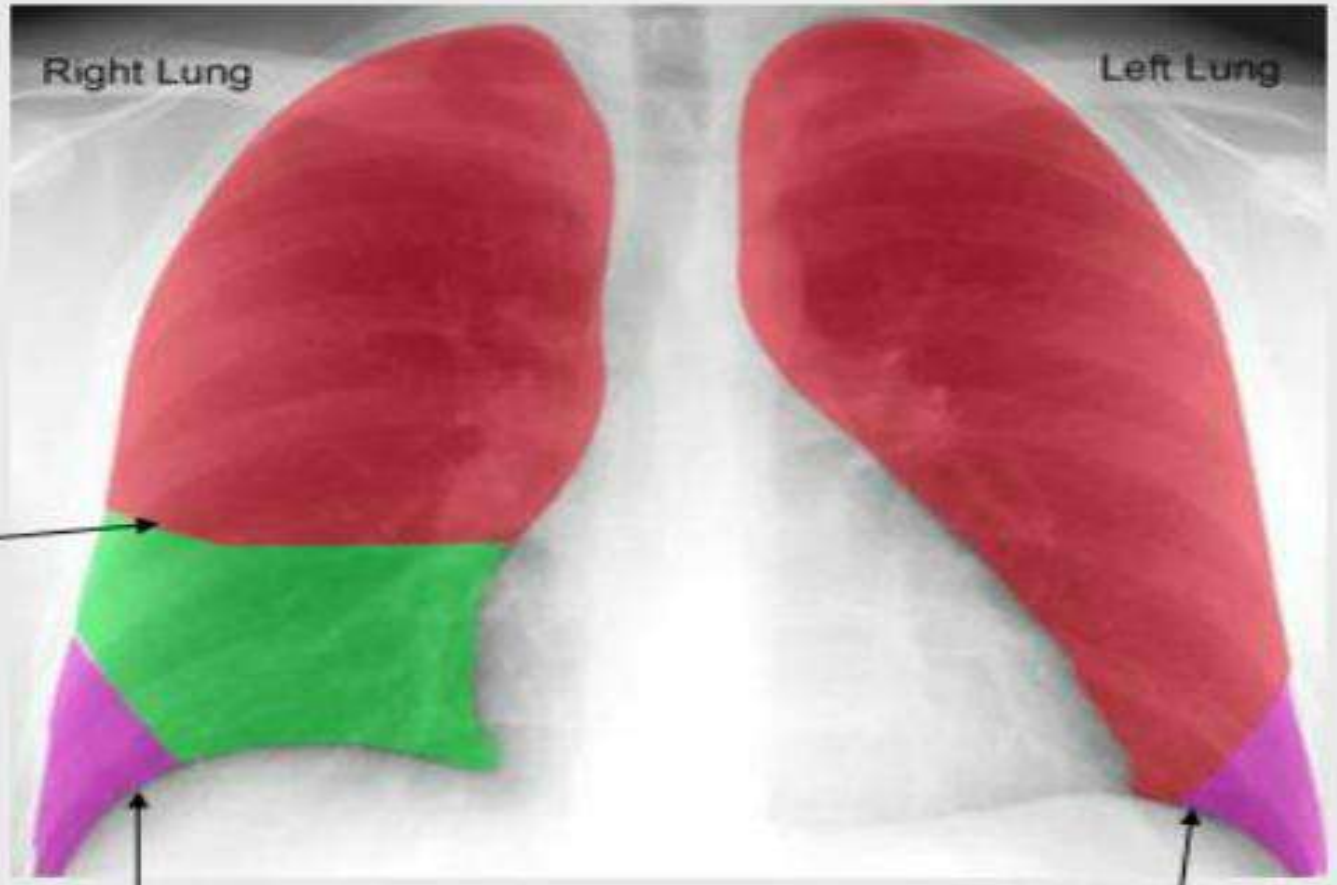
-Makes up 56% of the total lung volume

-Three lobes-the superior, middle and inferior, which are separated by the horizontal fissure and the oblique fissure.

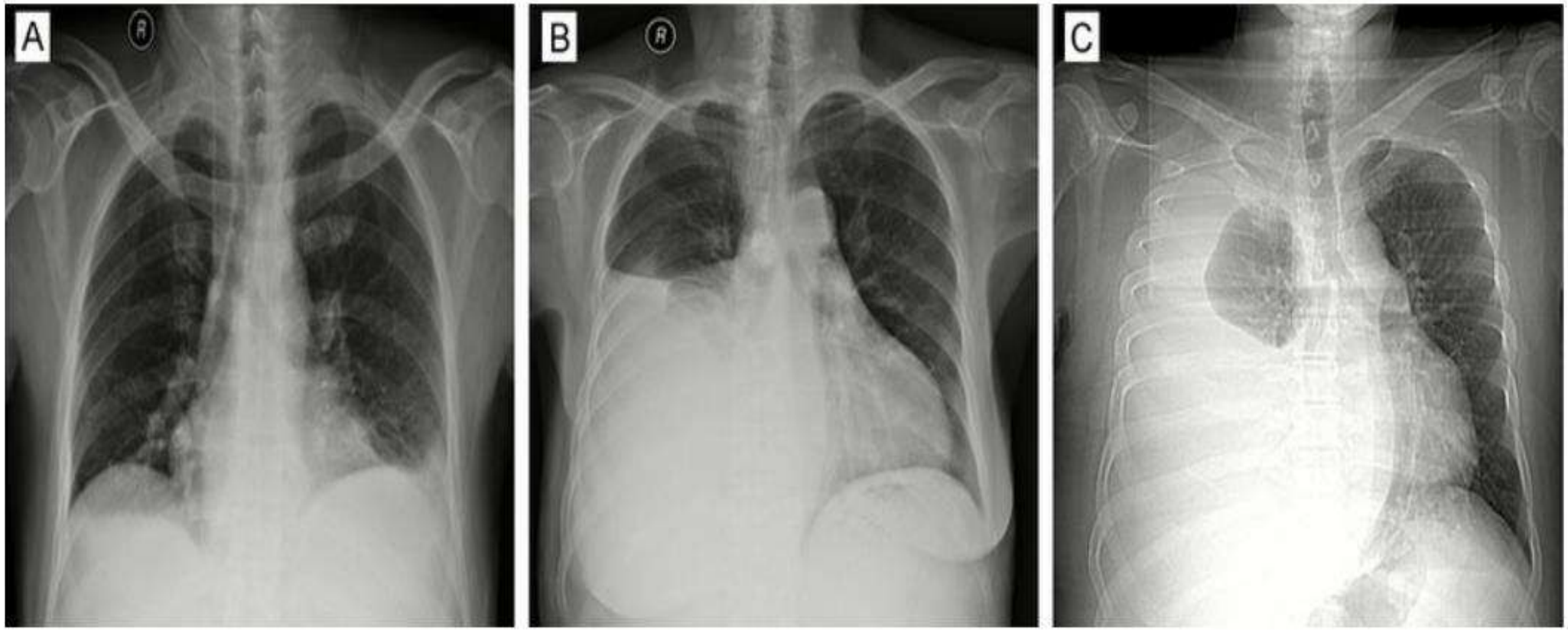
The Left Lung

-Makes up 44% of the total lung volume

-Two lobes which are separated by the oblique fissure.



http://fitsweb.uchc.edu/ctanatomy/chest/review/segments-posterior.html



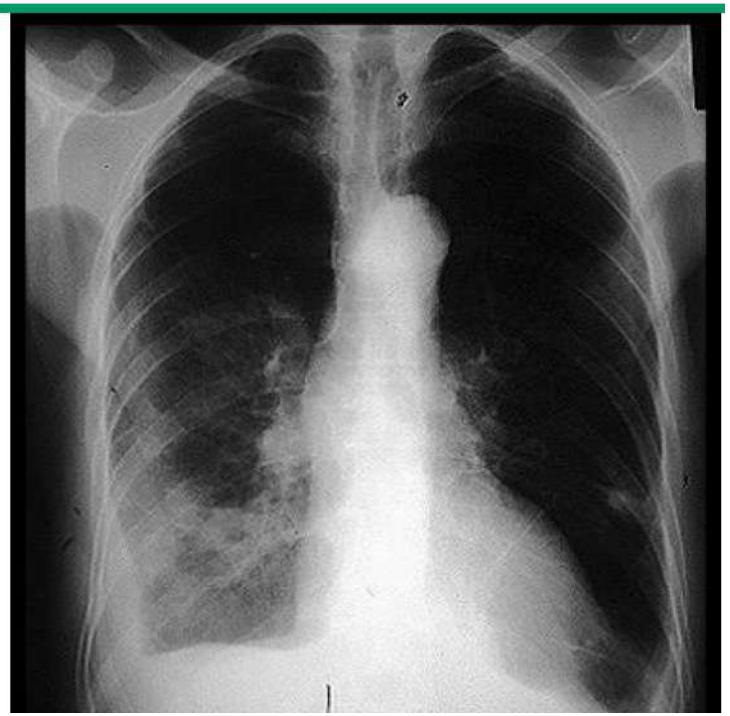
Grade of pleural effusion. A. Mild pleural effusion. B. Moderate pleural effusion. C. Severe pleural effusion.

Grading	Description	Landmarks	Intercostal spaces
Grade 1: minimum	Limited to costophrenic sinus	Diaphragmatic dome partially evident	Limited to costophrenic sinus
Grade 2: small	Lower lung lobe partially involved	Diaphragmatic dome completely evident	1 intercostal space
Grade 3: small to medium	Lower lung lobe partially collapsed	Lower lung lobe partially atelectasic Pulmonary hilum not visible	2–3 intercostal spaces
Grade 4: medium	Lower lung lobe completely collapsed	Atelectasis of the lower lung lobe Pulmonary hilum visible	3–4 intercostal spaces
Grade 5: large	Upper lung lobe partially involved	Atelectasis of the lower lung lobe Upper lung lobe partially atelectasic	4 intercostal spaces or more
Grade 6: massive	Lung fully collapsed	Atelectasis of the whole lung Hilum completely visible	

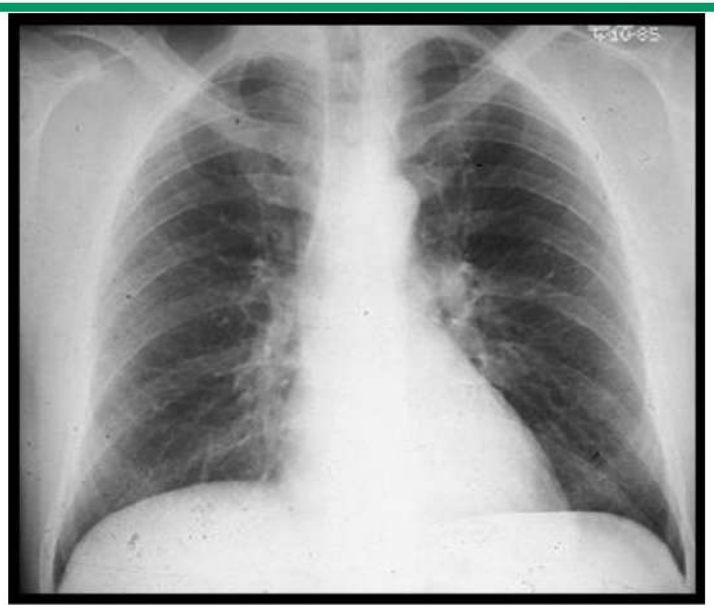
Standardized grading method proposed for pleural effusions

- In an upright patient, some free-flowing effusions are subtle lying in a subpulmonic location (<75 mL)
- Pleural effusions can be appreciated on lateral chest radiography as blunting of the posterior Costophrenic angle (>75 mL)
- Anteroposterior chest radiography as blunting of the lateral costophrenic angle (>175 mL)
- Large effusions may obscure the diaphragm (>500 mL) and demonstrate a meniscus sign
- The entire hemithorax may be occupied by an effusion with associated underlying lung collapse

Parapneumonic effusion chest radiograph



Normal chest radiograph



Ultrasonography

- Bedside
- Evaluate the size
- Characteristics of the effusions
- Ultrasonography is best utilized for selecting and guiding needle or
- Catheter placement for thoracentesis
- Provides important prognostic and therapeutic information

Chest computed tomography

- Loculations, often lenticular in shape, may be appreciated by tapered borders and obtuse angles between the fluid and the chest wall with an absence of the meniscus sign.

- Parietal pleural thickening is seen in 86 percent and pleural enhancement in 96 percent of patients with empyema Thickening of the visceral and parietal pleura is suggestive of empyema when associated with significant (usually >30 mm) separation of the pleural surfaces (split pleura sign), which can be appreciated in up to 68 percent of patients
- Pleural infection is also associated with increased attenuation of extracostal fat
- Air within the pleural fluid may suggest associated pneumothorax, bronchopleural fistula, air introduced during thoracentesis, a nonexpandable lung after pleural drainage or rarely gas-producing anaerobic organisms.

- Older empyemas that have spontaneously organized and remained undetected over years may exhibit minor or major calcification (eg, tuberculous empyema).

- Distinguishing pleural fluid from pleural masses and distinguishing empyema from a lung abscess

Thoracentesis and pleural fluid analysis

- In the past, it was considered safe to sample pleural fluid when a free-flowing effusion was demonstrated on chest radiography with at least 1 cm depth to the chest wall on a lateral decubitus film
- However, most pleural effusions are now sampled under ultrasound guidance; since there is no definition of what is considered a "safe" amount for sampling by ultrasonography, much of this decision is at the discretion of the ultrasonographer, although most experts would consider a pleural space of >1 cm (between parietal and visceral pleural) safe.
- A pleural fluid thickness cutoff of 2 to 2.5 cm has been suggested to guide thoracentesis by chest CT, because smaller effusions on CT are likely to resolve with antibiotics alone

Observations of pleural fluid helpful in diagnosis

	Suggested diagnosis
Color of fluid	
Pale yellow (straw)	Transudate, some exudates
Red (bloody)	Malignancy, benign asbestos pleural effusion, postcardiac injury syndrome, or pulmonary infarction in absence of trauma
White (milky)	Chylothorax or cholesterol effusion
Brown	Long-standing bloody effusion; rupture of amebic liver abscess
Black[1-4]	Aspergillus niger, Rhizomes oryzae, metastatic melanoma, pancreaticopleural fistula, crack cocaine use, bronchogenic adenocarcinoma, esophageal perforation during treatment with activated charcoal, chronic hemothorax
Yellow-green	Rheumatoid pleurisy
Dark green	Biliothorax
Color of:	
Enteral tube feeding	Feeding tube has entered pleural space
Central venous catheter infusate	Extravascular catheter migration
Character of fluid	
Pus	Empyema
Viscous	Mesothelioma
Debris	Rheumatoid pleurisy
Turbid	Inflammatory exudate or lipid effusion
Anchovy paste	Amebic liver abscess
Odor of fluid	
Putrid	Anaerobic empyema
Ammonia	Urinothorax

References:

1. *Chhabra A, Mukherjee V, Chowdhary M, et al. Black Pleural Effusion: A Unique Presentation of Metastatic Melanoma. Case Rep Oncol 2015; 8:222.*
2. *Huang TY, Tsai MJ. Education and imaging. Gastrointestinal: black pleural effusion induced by pancreaticopleural fistula. J Gastroenterol Hepatol 2013; 28:1798.*
3. *Jayakrishnan B, Dildar B, Rizavi DM, et al. Black pleural effusion. Lancet 2015; 386:e7.*
4. *Saraya T, Light RW, Takizawa H, Goto H. Black Pleural Effusion. Am J Med 2013; 126:641.e1.*

Graphic 74757 Version 2.0

PLEURAL FLUID ANALYSIS — Tests routinely performed on pleural fluid include the following:

- Cell count and cell differential
- pH
- Protein
- Lactate dehydrogenase (LDH)
- Glucose

Additional commonly performed tests :

- Amylase
- Cholesterol
- Triglycerides
- N-terminal pro-brain natriuretic peptide (NT-proBNP)
- Creatinine
- Adenosine deaminase (ADA)
- Gram and acid-fast bacillus (AFB) stain, bacterial and AFB culture
- Cytology

*According to the traditional **Light's Criteria Rule**, if at least one of the following three criteria (ie, component tests of the rule) is fulfilled, the fluid is defined as an exudate:*

- Pleural fluid protein/serum protein ratio greater than 0.5
- Pleural fluid LDH/serum LDH ratio greater than 0.6
- Pleural fluid LDH greater than two-thirds the upper limits of the laboratory's normal serum LDH

Calculator: Clinical criteria for exudative pleural effusion in adults (Light's criteria)

Input

Total serum protein		g/dL
Pleural fluid protein		g/dL
Serum LDH		units/L
Pleural fluid LDH		units/L
Upper limit of normal serum LDH		units/L

Results

Pleural fluid protein to serum protein ratio		ratio
Pleural fluid LDH to Serum LDH ratio		ratio
Pleural fluid LDH to Upper limit of normal serum LDH		ratio

Decimal precision 2

Reset form

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.

Causes of transudative pleural effusions

Causes of transudative effusions	Comment
Processes that *always* cause a transudative effusion	
Atelectasis	Caused by increased intrapleural negative pressure
Cerebrospinal fluid leak into pleural space	Thoracic spinal surgery or trauma and ventriculopleural shunts
Heart failure	Acute diuresis can result in borderline exudative features
Hepatic hydrothorax	Rare without clinical ascites
Hypoalbuminemia	Edema liquid rarely isolated to pleural space
Iatrogenic	Misplaced intravenous catheter into the pleural space; post Fontan procedure
Nephrotic syndrome	Usually subpulmonic and bilateral
Peritoneal dialysis	Acute massive effusion develops within 48 hours of initiating dialysis
Urinothorax	Caused by ipsilateral obstructive uropathy or by iatrogenic or traumatic GU injury
Processes that *may* cause a transudative effusion, but *usually* cause an exudative effusion	
Amyloidosis	Often exudative due to disruption of pleural surfaces
Chylothorax	Most are exudative effusions
Constrictive pericarditis	Bilateral effusions
Hypothyroid pleural effusion	From hypothyroid heart disease or hypothyroidism per se
Malignancy	Usually exudative, but 3 to 10 percent transudative possibly due to early lymphatic obstruction, obstructive atelectasis, or concomitant disease (eg, heart failure)
Pulmonary embolism	Most are exudative effusions
Sarcoidosis	Stage II and III disease
Superior vena caval obstruction	May be due to acute systemic venous hypertension or acute blockage of thoracic lymph flow
Coronavirus disease 2019 (COVID-19)	Limited data profile the nature of pleural fluid in COVID-19-related pleural effusions, although transudative effusions have been reported
Nonexpandable lung*	A result of remote or chronic inflammation

GU: genitourinary.

* Trapped and entrapped lung are examples of nonexpandable lung. While trapped lung typically causes a transudative pleural effusion, entrapped lung is typically associated with an exudative effusion.

Graphic 73530 Version 9.0

Causes of exudative pleural effusions

Infectious
Bacterial pneumonia
Tuberculous pleurisy
Parasites
Fungal disease
Viral pneumonias (eg, influenza, coronavirus disease 2019 [COVID-19])
Nocardia, Actinomyces
Subphrenic abscess
Hepatic abscess
Splenic abscess
Hepatitis
Spontaneous esophageal rupture
Cholecystitis
Iatrogenic or trauma
Central venous catheter misplacement/migration
Drug-induced (eg, nitrofurantoin, dantrolene, methysergide, dasatinib, amiodarone, interleukin-2, procarbazine, methotrexate, clozapine, phenytoin, beta blocker, ergot drugs)
Esophageal perforation
Esophageal sclerotherapy
Enteral feeding tube in pleural space
Radiofrequency ablation of pulmonary neoplasms
Hemothorax
Chylothorax
Malignancy-related
Carcinoma
Lymphoma
Mesothelioma
Leukemia
Chylothorax
Paraproteinemia (multiple myeloma, Waldenstrom's macroglobulinemia)
Paramalignant effusions
Other inflammatory disorders
Pancreatitis (acute, chronic)
Benign asbestos pleural effusion
Pulmonary embolism
Radiation therapy
Uremic pleurisy
Sarcoidosis
Postcardiac injury syndrome
Acute respiratory distress syndrome (ARDS)
Immunoglobulin G4-related disease (fibroinflammatory)

Increased negative intrapleural pressure with accompanying pleural malignancy or inflammation
Lung entrapment
Cholesterol effusion (eg, due to tuberculosis, rheumatoid arthritis)
Connective tissue disease
Lupus pleuritis
Rheumatoid pleurisy
Mixed connective tissue disease
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Granulomatosis with polyangiitis (Wegener's)
Familial Mediterranean fever
Endocrine dysfunction
Hypothyroidism
Ovarian hyperstimulation syndrome
Lymphatic abnormalities
Malignancy
Chylothorax (eg, yellow nail syndrome, lymphangioleiomyomatosis, lymphangiectasia)
Movement of liquid from abdomen to pleural space
Pancreatitis
Pancreatic pseudocyst
Meigs' syndrome
Chylous ascites
Malignant ascites
Subphrenic abscess
Hepatic abscess (bacterial, amebic)
Splenic abscess, infarction
Miscellaneous
Endometriosis
Drowning
Electrical burns
Capillary leak syndromes
Extramedullary hematopoiesis

Graphic 54055 Version 12.0

Protein

Most transudates have absolute total protein concentrations below 3.0 g/dL (30 g/L), although acute diuresis in heart failure can elevate protein levels into the exudative range . However, such patients have a serum to pleural fluid albumin gradient (the difference between the serum and pleural values) greater than 1.2 g/dL (12 g/L), or a protein gradient >3.1 g/dL, which correctly categorizes their effusions as transudates . Elevated blood NT-proBNP also supports the diagnosis of heart failure when Light's criteria yield results in the exudative range

Diagnoses established "definitively" by pleural fluid analysis

Disease	Diagnostic pleural fluid tests
Empyema	Observation (pus, putrid odor), positive culture
Malignancy	Positive cytology
Tuberculous pleurisy	Positive AFB stain, culture
Esophageal rupture	High salivary isoenzyme form of amylase, low pH (often as low as 6), ingested vegetable or meat fragments
Fungal-related effusions	Positive fungal stain, culture
Chylothorax	Triglycerides >110 mg/dL, chylomicrons by lipoprotein electrophoresis
Cholesterol effusion	Cholesterol >200 mg/dL with a cholesterol to triglyceride ratio >1, cholesterol crystals under polarizing light
Hemothorax	Ratio of pleural fluid to blood hematocrit >0.5
Urinothorax	Pleural fluid creatinine to serum ratio always >1 but diagnostic if >1.7
Peritoneal dialysis	Protein <0.5 mg/dL and pleural fluid to serum glucose ratio >1 in peritoneal dialysis patient
Extravascular migration or misplacement of a central venous catheter	Pleural fluid to serum glucose ratio >1, pleural fluid gross appearance mirrors infusate (eg, milky white if lipids infused)
Rheumatoid pleurisy	Cytologic evidence of elongated macrophages and distinctive multinucleated giant cells (tadpole cells) in a background of amorphous debris
Glycinothorax	Measurable glycine after bladder irrigation with glycine-containing solutions
Cerebrospinal fluid leakage into pleural space	Detection of beta-2 transferrin
Parasite-related effusions	Detection of parasites

Graphic 50027 Version 4.0

PLEURAL FLUID ANALYSIS
parapneumonic effusion

- Cell count with differential and chemistries
- A total protein, lactate dehydrogenase (LDH), and glucose should be obtained together with serum values for protein and LDH. A neutrophil predominance is more common in patients with bacterial pneumonia while a lymphocyte predominance may indicate tuberculous or fungal etiologies

Microbiologic analysis

- Microbiologic analysis of the pleural fluid with appropriate stains and cultures (eg, aerobic, anaerobic, mycobacterial, fungal) is critical. Although sampling should ideally occur before the administration of antibiotics, thoracentesis should not delay prompt antimicrobial therapy. Samples should be drawn directly from the pleural space because cultures from previously placed catheters or tubing can be colonized or contaminated with bacteria or fungi

- A putrid odor of fluid is considered diagnostic of anaerobic infection; the Gram stain will also help identify anaerobes because of the unique morphology of some anaerobic Gram-negative rods

Blood and pleural culture results yield a diagnosis in approximately 60 percent of cases . There are several reasons why bacteria may not be identified in culture for the remaining 40 percent:

- Anaerobic organisms may be difficult to culture
- Anaerobic cultures are not specifically requested
- Sampling is often performed after a patient has received antibiotics
- Sterile inflammatory fluid may be aspirated adjacent to an infected loculus of infection
- Current culture methods are insufficiently sensitive
- Bacteria may be located in the pleural membranes rather than in the fluid

pH

The most useful test when determining the therapeutic course

Cytology

Cytologic examination for appropriate stains (eg, mycobacteria, actinomyces, nocardia) can be sent when organisms requiring special stains are needed. In addition, malignancy can cause pleural fluid acidosis; thus, sending fluid for cytology for malignant cells is prudent

Other tests

Although blood cultures are frequently negative in patients with parapneumonic effusion and empyema, they should be obtained. Growth from cultures can help make the microbiologic diagnosis as well as identify concurrent bacteremia. The need for additional microbiologic testing should be determined on a **case-by-case** basis (eg, **sputum cultures, urine S. pneumoniae antigen testing, interferon-gamma release assays for tuberculosis, galactomannan, cryptococcal antigen).**

Procalcitonin's usefulness for distinguishing bacterial from nonbacterial parapneumonic effusions is not well studied but is not likely to be high. In one study, serum procalcitonin levels >0.18 ng/mL were associated with a sensitivity of 83 percent and specificity of 81 percent for the pleural effusion having a bacterial infectious etiology . However, this marker rises in the setting of invasive and systemic infections; thus the sensitivity for determining whether bacteria are present in a contained space infection is questionable. Neither high nor low procalcitonin levels are likely to change the need for drainage

parapneumonic effusion

The annual incidence of bacterial pneumonia is estimated to be 4 million, with approximately 25% of patients requiring hospitalization. Because as many as 40% of hospitalized patients with bacterial pneumonia have an accompanying pleural effusion . 5 to 10 percent of those progress to empyema

Risk factors

- Aspiration
- Poor dental hygiene
- Malnutrition
- Alcohol or intravenous drug abuse
- Immunosuppression
- Age (<18 years, >65 years)
- Partially-treated pneumonia
- Influenza
- Gastroesophageal reflux

Pleural Diseases .Richard W. Light.2013

Parapneumonic effusion and empyema terminology

Parapneumonic effusion and empyema terminology

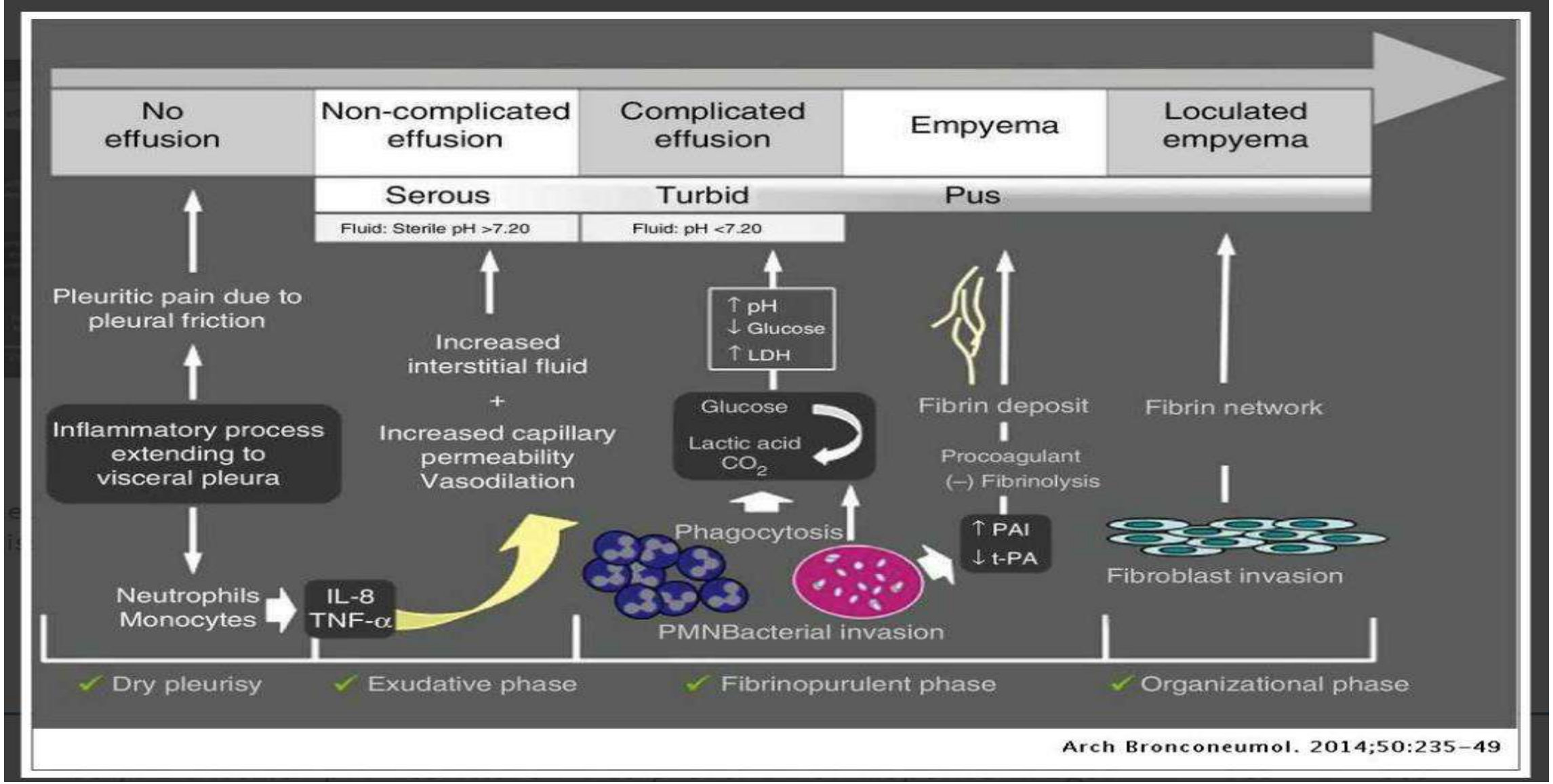
Term	Definition
Parapneumonic effusion	Fluid in the pleural space in the setting of an adjacent pneumonia
Uncomplicated (simple) parapneumonic effusion	Free-flowing effusion that is sterile
Complicated parapneumonic effusion	Effusion infected with bacteria or other micro-organisms or having biochemical properties suggestive of recent infection
Empyema	Pus in the pleural space (from pneumonia or other source)
Complex effusion	Effusion with internal loculations (septae)
Uniloculated effusion	Effusion that is without internal septae (free-flowing or fixed)

Graphic 121161 Version 1.0

Developmental stages of parapneumonic effusion and empyema: Diagnosis and management

Developmental stages of parapneumonic effusion and empyema: Diagnosis and management

Stage	Stage 1 (uncomplicated/simple)	Stage 2 (complicated/fibropurulent*)	Stage 3 (complicated/organizing*)
Timing	Early (days)	Late (days to weeks)	Late (weeks to months)
Pleural fluid characteristics	Exudative characteristics ¶ Low to moderately elevated WBC LDH level <1000 international units/L Normal pH and glucose levels No bacterial organisms	Exudative characteristics ¶ High WBC LDH >1000 international units/L pH <7.20 Glucose <40 mg/dL (2.2 mmol/L) **OR** Bacterial organisms present	Fluid may be difficult to obtain Bacterial organisms may or may not be present
Imaging characteristics	Generally small to moderate in size Free-flowing	Generally large and free-flowing, loculated, and/or with associated pleural thickening with contrast enhancement	May be large, loculated, and/or with pleural thickening (may be extensive and demonstrate a pleural rind) Pleural calcification may be evident Δ
Treatment	Typically resolves with antibiotic therapy alone Drain if symptomatic	Antibiotics PLUS drainage ◇ Fibrinolytics/DNase may be required §	Antibiotics PLUS drainage Fibrinolytics/mucolytics **or VATS** may be required § ¥



Outline of the pathogenesis of parapneumonic pleural effusion. IL-8, interleukin-8; TNFα, tumor necrosis factor; PAI, plasminogen activator inhibitor, t-PA, tissue plasminogen activato

Recommendations of Diagnosis and Treatment of Pleural Effusion pages 235-249 (June 2014)

Prevalence of pathogens causing parapneumonic effusions and empyema

Prevalence of pathogens causing parapneumonic effusions and empyema

Typical setting	Pathogen(s)	Overall prevalence range	Comments
Community-acquired	*Streptococcus pneumoniae*	10 to 20%	Common cause of community-acquired pneumonia; PPE caused by *S. pneumoniae* are often monomicrobial.
	Microaerophilic streptococci ▪ *S. intermedius* ▪ *S. anginosus* ▪ *S. constellatus*	4 to 24%	Common residents of oral flora; often associated with aspiration pneumonia and polymicrobial infection.
	Anaerobes, including*: ▪ *Fusobacterium nucleatum* ▪ *Prevotella* species ▪ *Peptostreptococcus* species ▪ *Bacteroides* species	6 to 20%	Common residents of oral flora; often associated with aspiration pneumonia and polymicrobial infection.
Hospital-acquired	*Staphylococcus aureus*	10 to 15%	Most common cause of hospital-acquired infections. Frequently monomicrobial and can be associated with necrotizing or cavitary pneumonia.
	Gram-negative anaerobes **and aerobes** including: ▪ *Escherichia coli* ▪ *Klebsiella pneumoniae* ▪ *Pseudomonas aeruginosa*	8 to 10%	Other common causes of hospital-acquired infections. May be monomicrobial or polymicrobial, with polymicrobial infection more likely if associated with aspiration pneumonia. Pseudomonas may be associated with necrotizing or cavitary pneumonia.

TABLE 12.3 • Percentage of Pleural Effusions and of Positive Pleural Fluid Cultures with Various Bacterial Pneumonias

Organism	Reference	Pleural Effusion (%)	Positive Pleural Fluid Culture (%)
Anaerobic	(53)	35	90
Gram-positive			
Streptococcus	(2,54)	40-60	1-5
pneumoniae			
Staphylococcus aureus			
Adults	(58,59)	50	20
Children	(54,57)	70 80	
Streptococcus pyogenes	(63,63)	55-95	30-40
Bacillus anthracis	(75,76)	90-100	20-100

TABLE 12.3 • Percentage of Pleural Effusions and of Positive Pleural Fluid Cultures with Various Bacterial Pneumonias

Organism	Reference	Pleural Effusion (%)	Positive Pleural Fluid Culture (%)
Aerobic gram-negative			
Escherichia coli	(65)	40	80
Pseudomonas	(66)	25-50	40-50
Klebsiella pneumoniae	(69)	50	50
Haemophilus influenza			
Adults	(64,72,73)	10-45	20
Children	(59,63,70,71)	75	80
Proteus species	(74)	20	50
Legionella species	(79,80,81,82)	25-60	?

The numbers in parentheses indicate the number of isolates that were recovered in pure culture.

[a]Data from Bartlett JG, Gorbach SL, Thadepalli H, et al. Bacteriology of empyema. *Lancet*. 1974;1:338-340, with permission.

[b]Data from Varkey B. Rose HD, Kutty CPK, et al. Empyema thoracis during a ten-year period. *Arch Intern Med*. 1981;141:1771-1776, with permission.

[c]Data from Brook I, Frazier EH. Aerobic and anaerobic microbiology of empyema. A retrospective review in two military hospitals. *Chest*. 1993;103:1502-1507, with permission.

Event or State Precipitating Empyema in 319 Patients

Event or State	Number	Percentage
Pulmonary infection	177	55
Surgical procedure	66	21
Trauma	18	6
Esophageal perforation	15	5
Spontaneous pneumothorax	7	2
Thoracentesis	6	2
Subdiaphragmatic infection	4	1
Septicemia	4	1
Miscellaneous or unknown	22	7
Total	319	100

Data from Yeh TJ, Hall DP, Ellison RG. Empyema thoracis: a review of 110 cases. *Am Rev Respir Dis*. 1963;88:785-790; Snider GL, Saieh SS. Empyema of the thorax in adults: review of 105 cases. *Chest*. 1968;54:12-17; and Smith JA, Mullerworth MH, Westlake GW, et al. Empyema thoracis: 14-years experience in a teaching center. *Ann Thorac Surg*. 1991;51:39-42, with permission.

TABLE 12.5 • A Classification and Treatment Scheme for Parapneumonic Effusions and Empyema

Event or State	Number
Class 1 Nonsignificant pleural effusion	Small <10 mm thick on decubitus x-ray study No thoracentesis indicated
Class 2 Typical parapneumonic pleural effusion	>10 mm thick Glucose >40 mg/dL, pH >7.2 LDH <3 × upper limit normal for serum Gram's stain and culture negative Antibiotics alone
Class 3 Borderline complicated pleural effusion	7.0 <pH <7.20 and/or LDH >3 × upper limit normal and glucose >40 mg/dL Gram's stain and culture negative Antibiotics plus serial thoracentesis
Class 4 Simple complicated pleural effusion	pH <7.0 or glucose <40 mg/dL or Gram's stain or culture positive Not loculated not frank pus Tube thoracostomy plus antibiotics
Class 5 Complex complicated pleural effusion	pH <7.0 and/or glucose <40 mg/dL or Gram's stain or culture positive Multiloculated Tube thoracostomy plus fibrinolytics (rarely require thoracoscopy or decortication)
Class 6 Simple empyema	Frank pus present Single locule or free flowing Tube thoracostomy ± decortication
Class 7 Complex empyema	Frank pus present Multiple locules Tube thoracostomy ± fibrinolytics Often require thoracoscopy or decortication

LDH, lactic dehydrogenase.

TABLE 12.4 • Bad Prognostic Factors for Parapneumonic Effusions and Empyema

Pus present in pleural space
Gram stain of pleural fluid positive
Pleural fluid glucose below 40 mg/dL
Pleural fluid culture positive
Pleural fluid pH <7.0
Pleural fluid LDH >3 × upper normal limit for serum
Pleural fluid loculated

Listed in order of decreasing importance.

LDH, lactic dehydrogenase.

TABLE 12.6 ▪ Categorizing Risk for Poor Outcome in Patients with Percentage of Pleural Effusions

	Pleural Space Anatomy			Pleural Fluid Bacteriology			Pleural Fluid Chemistry	Category	Risk of Poor Outcome	Drainage
A_0	Minimal, free-flowing effusion (<10 mm on lateral decubitus)	AND	B_X	Culture and Gram's stain results unknown	AND	C_X	pH unknown	1	Very low	No
A_1	Small-to-moderate free-flowing effusion (>10 mm and < ½ hemithorax)	AND	B_0	Negative culture and Gram's stain	AND	C_0	pH ≥7.20	2	Low	No
A_2	Large, free-flowing effusion (≥ ½ hemithorax) loculated effusion, or effusion with thickened parietal pleura	OR	B_1	Positive culture and Gram's stain	OR	C_1	pH <7.20	3	Moderate	YES
A_3			B_2	Pus				4	High	YES

From Colice GL, Curtis A, Deslauriers J, et al. Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. *Chest*. 2000;118:1158-1171, with permission.

ANTIBIOTIC THERAPY

Empiric therapy

- For most patients, empiric antibiotic therapy should be started as soon as the diagnosis of a parapneumonic effusion or empyema is known or suspected
- Nearly all antibiotics adequately penetrate the pleural space. Aminoglycosides (**eg, gentamicin, amikacin, tobramycin**) are exceptions. Because their pleural penetration is poor and because they may be inactivated in acidic environments (eg, empyemas), we generally avoid them when alternatives are available
- Initial antibiotic therapy should be given intravenously. Transition to oral therapy can be considered once the patient has demonstrated clear clinical improvement and adequate drainage has been achieved. There is no role for routine use of intrapleural antibiotics

Activity of antimicrobial agents against anaerobes

Agent	Comments
Nearly always active	
Metronidazole	Inactive versus microaerophilic streptococci (eg, *S. milleri*), *Cutibacterium* (formerly *Propionibacterium*), and *Actinomyces* species; bactericidal versus most gram-negative anaerobic strains
Carbapenems	Resistant to most *Bacteroides* beta-lactamases, although a novel beta-lactamase that cleaves carbapenems was found in rare *B. fragilis* strains[1]
Beta-lactam plus beta-lactamase inhibitors	The addition of a beta-lactamase inhibitor to a beta-lactam dramatically increases activity against anaerobes that produce a beta-lactamase
Usually active	
Clindamycin	*B. fragilis* group: 19 to 60 percent of strains resistant; some Clostridia other than *C. perfringens* are resistant[2]
Cefoxitin	*B. fragilis* group: 0 to 23 percent of strains resistant with considerable institutional variation at least partly reflecting use patterns; poor activity versus Clostridia[2]
Variable activity	
Penicillin	Inactive versus some or most penicillinase-producing anaerobes, including most of the *B. fragilis* group and many strains of *Prevotella melaninogenica*, *P. intermedia*, *P. bivia*, *P. disiens*, and some Clostridia
Cephalosporins	Less activity in vitro than penicillin G versus most anaerobes and limited published clinical experience to document efficacy other than cefamycins
Tetracycline	Inactive versus many anaerobes and most strains of *B. fragilis*; doxycycline and minocycline are somewhat more active than tetracycline
Vancomycin	Active against gram-positive anaerobes; inactive versus gram-negative anaerobes
Macrolides	Inactive versus many *Fusobacterium* spp and some *B. fragilis* spp
Fluoroquinolones	Moxifloxacin is the best in this class for anaerobic infections, but the *B. fragilis* group shows increasing resistance and moxifloxacin is no longer recommended in the IDSA guidelines for intra-abdominal sepsis
Tigecycline	Active against some anaerobes, including strains of *B. fragilis* that are resistant to beta-lactams, clindamycin, and quinolones[2]
Poor activity	
Aminoglycosides	
Trimethoprim-sulfamethoxazole	
Monobactams (aztreonam)	

Community-acquired

Local epidemiology should also be taken into account when selecting empiric antibiotics because the prevalence of pathogens that cause parapneumonic effusions vary with geography

- A third-generation cephalosporin (eg, ceftriaxone or cefotaxime) plus metronidazole
- A beta-lactam/beta-lactamase inhibitor combination (eg, ampicillin-sulbactam)

penicillin hypersensitivity who cannot tolerate cephalosporins

- Carbapenem (eg, imipenem, meropenem)
- Combination therapy with a respiratory fluoroquinolone (eg, levofloxacin, moxifloxacin)plus metronidazole
- Monobactam (eg, aztreonam) plus metronidazole
- Although clindamycin has been used historically for the treatment of anaerobic lung infections, resistance rates to clindamycin among anaerobes now consistently exceed 20 percent across treatment settings. For this reason, we no longer routinely use clindamycin for empiric treatment of anaerobic infections.

Hospital-acquired

- we select an empiric IV antibiotic regimen that targets MRSA, gram-negative bacteria (including Pseudomonas spp), and anaerobic bacteria .

vancomycin + metronidazole +cefepime or ceftazidime

- However, there is growing concern that the combination of vancomycin plus piperacillin-tazobactam is nephrotoxic . Thus, some clinicians use linezolid in place of vancomycin when piperacillin-tazobactam is used.
- For those who are penicillin-allergic, we suggest combining vancomycin with metronidazole and an antipseudomonal fluoroquinolone (eg, ciprofloxacin); alternatively, combining vancomycin with an antipseudomonal carbapenem (eg, imipenem or meropenem) is appropriate

Duration of therapy

The optimal duration of therapy is not known. We generally individualize the duration of therapy based upon the type of effusion, the adequacy of drainage, clinical and radiographic response to treatment, and the patient's immune status.

- Uncomplicated bacterial parapneumonic effusions, therapy may last one to two weeks
- Complicated parapneumonic effusions two to three weeks
- Empyema four to six weeks
- While we take radiographic response into account when determining the duration of therapy, complete radiographic resolution may take many weeks or months and residual pleural thickening can persist for longer periods. Thus, treating with the goal of complete radiographic resolution is not necessary.

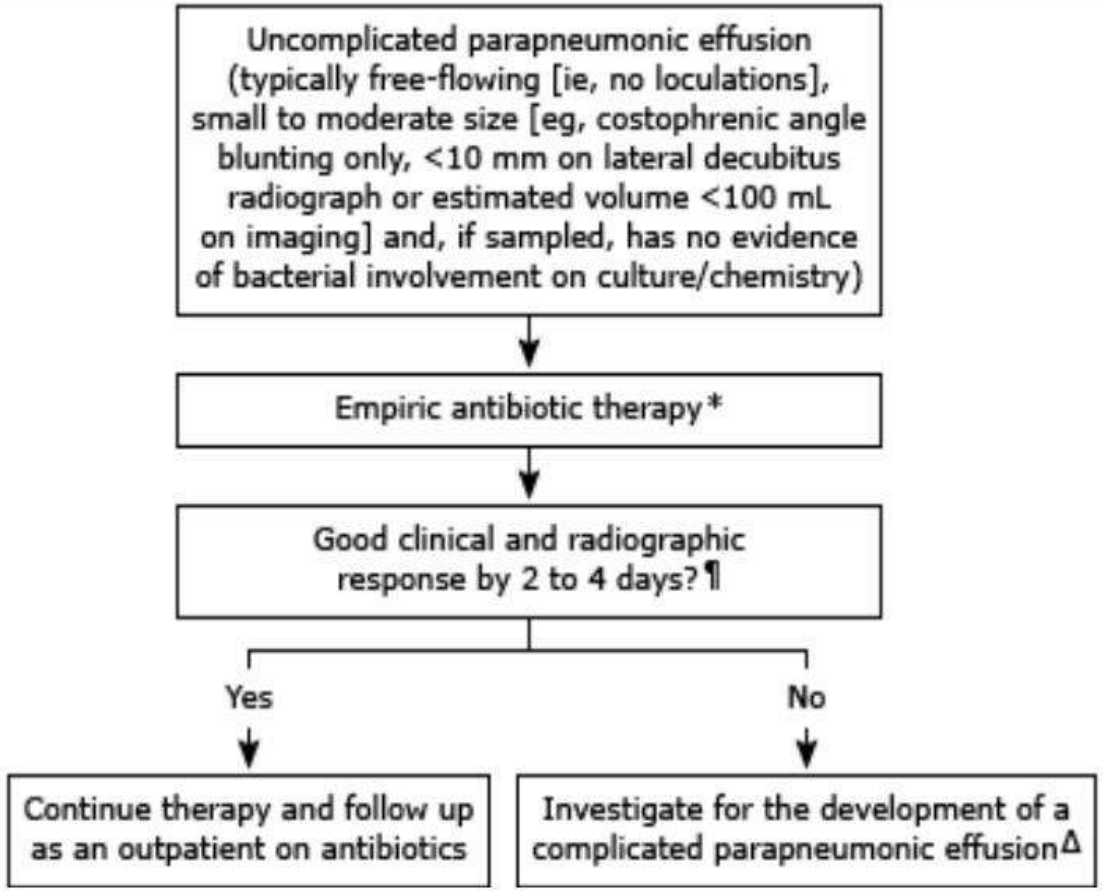
- The initial IV antibiotic regimen can be switched to an oral regimen with a similar treatment spectrum when clinical response is clear (eg, patient is afebrile, hemodynamically stable, clinically improving), no further drainage procedures are needed, and the patient is able to tolerate oral medications

Uncomplicated parapneumonic effusion (antibiotics alone)

Uncomplicated parapneumonic effusions are small to moderate-sized (ie, less than half the hemithorax) free-flowing effusions with no evidence of infection by culture or chemistry that generally resolve with antibiotics alone and generally do not need drainage. In such cases, the diagnosis and therapy with antibiotics alone are empiric

The treatment and prognosis of parapneumonic effusion and empyema

Treatment of uncomplicated parapneumonic effusion



Thoracentesis may be performed

- Underlying lung disease
- Symptomatic relief
- Severe clinical presentation
- The pleural space is the suspected source of infection. (eg, patient with septic shock)
- All patients with uncomplicated parapneumonic effusion should be followed clinically and with serial chest radiographs or ultrasound examinations to assess for improvement or deterioration. The optimal frequency of radiographic follow-up is unknown but it is appropriate that the first follow-up imaging be obtained within 48 hours if thoracentesis was not performed. If thoracentesis was performed and confirms an uncomplicated parapneumonic effusion, serial radiographs can be repeated within one week of the diagnosis and followed every one to two weeks until resolution since progression to empyema while appropriate antibiotics are being administered is rare.

Complicated pleural effusion and empyema (antibiotics plus drainage)

- Empyema (ie, overtly purulent pleural fluid)
- Positive pleural fluid Gram stain or culture
- Loculated pleural effusion
- Large free-flowing effusions (ie, ≥0.5 hemithorax)
- Effusions associated with thickened parietal pleura
- Sepsis from a pleural source

Initial drainage (tube or catheter thoracostomy)

Efficacy

All of the features that comprise a complicated effusion and empyema (loculations, large size, pleural fluid acidosis) are associated with an increased risk of progression and poor outcomes including the requirement for more than one procedure, eventual need for surgery, and longer hospitalization

One meta-analysis of seven observational studies reported that pleural pH <7.2 was the most useful predictor of a complicated clinical course. If pleural pH is not measured, a pleural fluid glucose value <40 mg/dL (2.2 mmol/L) and/or pleural fluid lactate dehydrogenase (LDH) value >1000 international units/L, or significant loculations also appear predictive of the need for tube thoracostomy.

Assessment of response

Immediately following drainage, patients typically undergo chest radiographic imaging for a rudimentary assessment of tube or catheter placement and response. Patients are then followed clinically (signs and symptoms, laboratory values, and drainage volume) for the next 24 to 48 hours. Chest CT imaging is typically performed within that time frame since CT provides accurate details regarding chest tube position and adequate drainage of the effusion or empyema , thereby helping to inform the clinician regarding the next-steps in decision-making.

- If imaging shows that the chest tube is not in a good position, then it can be manipulated or replaced (typically under image guidance), following which drainage volume should be monitored and a repeat chest CTobtained.

- If the drainage tube is in good position but the drainage is inadequate and/or the lung has not reexpanded adequately, then several options need to be explored

- If imaging reveals marked improvement, removing the drainage tube should be considered Bronchoscopy is rarely indicated unless there is suspicion for endobronchial obstruction or a bronchopleural fistula.

Discontinuing drainage

- Chest tubes can generally be removed when drainage volume falls below 50 to 100 mL/day (for two to three days assuming there is no blockage)
- Complete resolution of pleural thickening radiologically is not required as this may require months.
- The patient is typically discharged on antibiotics and evaluated as an outpatient with follow-up imaging (typically chest CT) in about two weeks
- A small fraction of patients may be discharged with a temporary catheter in place for clearance of residual fluid, provided adequate follow-up in outpatient clinic is assured.
- Antibiotics should be discontinued once clinical and radiologic improvement is observed and it is assured that the effusion has not worsened or reaccumulated.

Drainage options

Intrapleural tPA +/- additional drainage

Indications

- Intrapleural tPA/DNase is frequently administered to patients with complicated parapneumonic effusion or empyema who fail antibiotic therapy and initial drainage
- It is also a suitable option in patients who are not candidates for or do not want surgery
- Both tPA (10 mg) and DNase (5 mg) are administered via the chest tube or catheter twice daily for three days

Adverse effects

Side effects of intrapleural administration of fibrinolytic agents include chest pain, fever, allergic reactions (more frequent with streptokinase), and pleural hemorrhage

- These agents typically decrease the need for surgery (by approximately 30 to 80 percent) but a mortality benefit has not been proven

Drainage options

Additional drainage tubes

In some patients in whom drainage is inadequate with a single chest tube or catheter, particularly those with complex (ie, multiloculated) effusions and those who fail fibrinolytic therapy, the placement of additional chest tubes is appropriate

Video-assisted thoracic surgery (VATS)

VATS is often indicated in symptomatic patients with parapneumonic effusion or empyema that fails to resolve with antibiotics, tube thoracostomy, and a course of tPA/Dnase

VATS is preferred over open thoracotomy since outcomes are similar and morbidity and hospital length of stay is lower

REFRACTORY CASES

In rare patients who fail antibiotics, tube thoracostomy, and fibrinolytic/mucolytic therapy, who are not candidates for VATS, options are limited but may include persisting with conservative care (antibiotics and multiple drains) and in some cases, performing an open-window thoracostomy.

PROGNOSIS

The long-term survival of patients with parapneumonic effusion and empyema is good, provided therapy is adequate and prompt

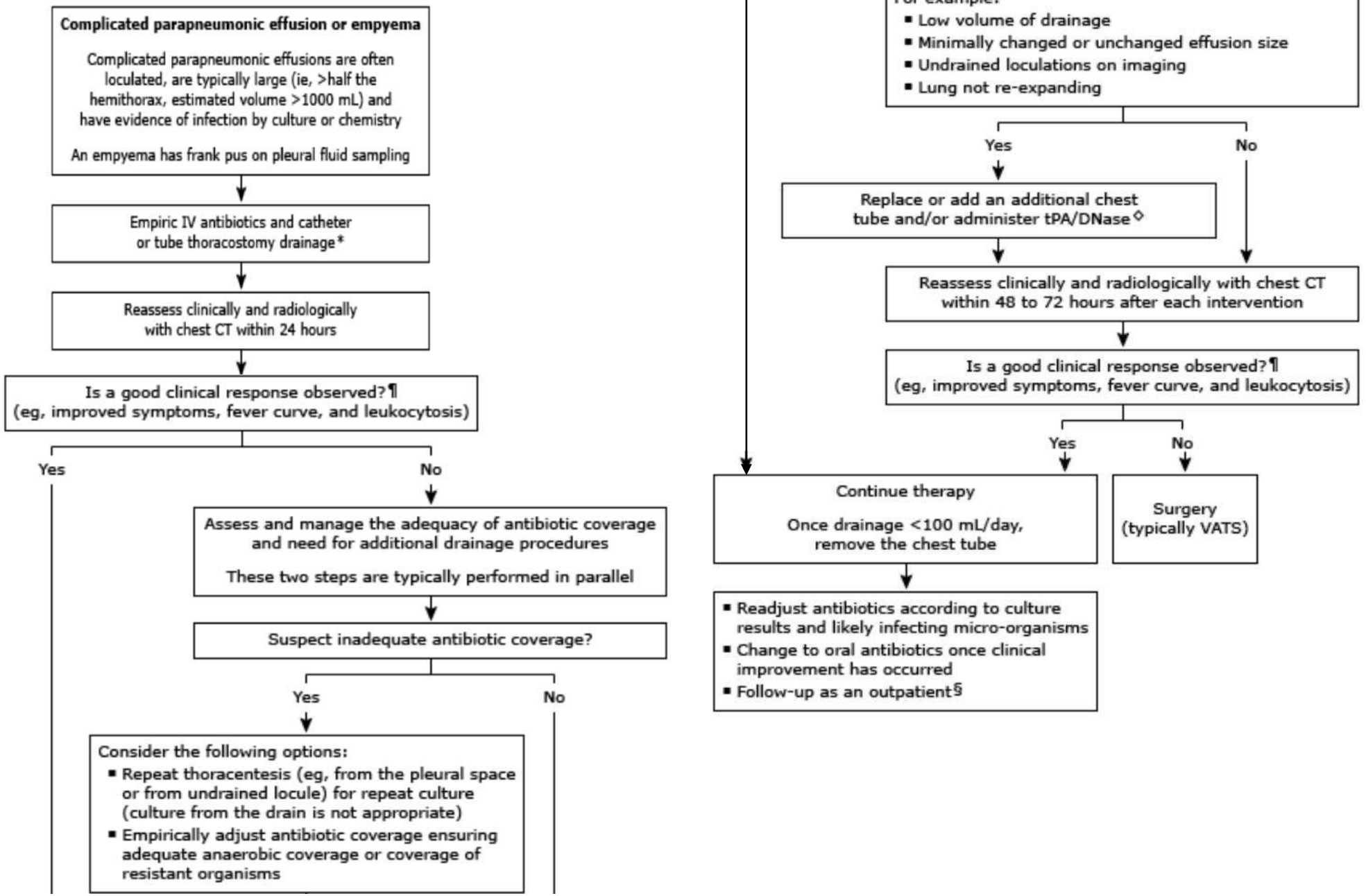
- Mortality is highest in those with empyema with retrospective series reporting a mortality of approximately 15 percent among empyema patients who are admitted to hospital . In another prospective series of 85 patients, the mortality at four years was 14 percent with most deaths occurring in the first 400 days after drainage but many deaths were due to comorbid conditions or surgical complications rather than due to the empyema itself .

- One series reported that mortality was highest among those who require open surgery or decortication and 30-day readmission rates were highest in those who were managed with chest thoracostomy tubes alone (21 percent) compared with those treated with video-assisted thoracic surgery (VATS; 11 percent) and open surgery (13 percent) .

- In contrast, another retrospective analysis of over 9000 patients with a discharge diagnosis of empyema reported that over a 20-year period, patients treated with chest tube drainage with or without fibrinolytics had a higher mortality than those treated with VATS decortication (17 versus 11 percent); in addition there were no differences in readmission rates at 90 days .

- In a database analysis of over 21,000 hospitalizations for empyema, older age, number of comorbidities, were associated with increased odds of death .

Treatment of complicated parapneumonic effusion and empyema



با تشکر از شما