PAKISTAN CHEST SOCIETY

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STRIVING FOR PULMONARY CARE

Clinical Practice Guidelines

Pleural Effusion

PAKISTAN CHEST SOCIETY-2026

Guidelines on

Pleural Effusion

March 2026

PAKISTAN CHEST SOCIETY

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Preface

It is an honor to present the updated edition of the Pakistan National Guideline on Pleural Effusion on behalf of the Pakistan Chest Society (PCS). Pleural effusion is one of the most common medical issues we face, presenting a daily diagnostic and treatment challenge for doctors across the country. While global medical standards continue to advance, we urgently need a structured framework that fits our own hospitals. This document represents a unified effort to simplify and improve our clinical approach, ensuring that every patient receives safe, high-quality care no matter where they are treated.

Managing pleural effusion in Pakistan comes with unique challenges. Unlike Western countries where heart failure or cancer dominate, our daily practice is heavily shaped by an overwhelming burden of tuberculosis, alongside rising cases of complicated pneumonia and malignancies. Recognizing this, we focused on our own ground realities to create a resource-stratified pathway. This guide is designed to be highly practical and useful for a frontline doctor in a basic rural clinic, as well as a specialist in a major city hospital.

This guideline is the result of close collaboration and detailed discussions among leading Pakistani pulmonologists. We evaluated every recommendation for its real-world safety, efficacy, and cost-effectiveness for our patients. The document focuses on critical, everyday clinical decisions—such as making the best use of pleural fluid analysis, adopting ultrasound-guided procedures, and knowing exactly when to refer a patient for surgery or thoracoscopy. Our main goal is to provide a clear roadmap that reduces diagnostic delays and minimizes procedural complications.

As Chair of the committee, I am deeply grateful to my colleagues and the PCS leadership for their hard work and dedication. However, a guideline is only useful if it is practiced. I call upon medical colleges, postgraduate programs, and frontline physicians across Pakistan to actively adopt these protocols. It is our sincere hope that this document will make daily clinical decisions clearer, protect our patients, and inspire further localized research tailored to the needs of our population.

Dr Kamran Khan Sumalani
Chair, Pleural Effusion Guideline Committee
Pakistan Chest Society

Message by the President

Pakistan Chest Society

Exudative pleural effusion represents a common yet complex clinical challenge requiring a structured diagnostic approach. These guidelines provide evidence-based algorithms for evaluation, including pleural fluid analysis and advanced diagnostic procedures, as well as management strategies tailored to underlying etiology. PCS expects this document to facilitate timely diagnosis and effective patient care.

Prof. Shereen Khan
President
Pakistan Chest Society

Message by the Chairman

Guideline Committee, Pakistan Chest Society

It is my great pleasure to present the first edition of the Pakistan Chest Society Guidelines for the Management of Pleural Effusion. Pleural effusion is a common clinical problem encountered in respiratory practice and may arise from a wide range of benign and malignant conditions. Accurate diagnosis and timely management are essential for improving patient outcomes and reducing morbidity. While international recommendations from organizations such as the British Thoracic Society and the American Thoracic Society provide a strong evidence-based framework, it is crucial to adapt these recommendations to the local disease spectrum, healthcare resources, and clinical realities of Pakistan.

These guidelines have been carefully developed by a dedicated working group under the chairmanship of Dr. Kamran Khan Sumalani. I sincerely commend Dr. Sumalani and his team for their outstanding efforts in critically reviewing both international and local evidence and translating it into practical recommendations for clinicians across the country. I am confident that this document will help standardize the evaluation and management of pleural effusion and contribute significantly to improving the quality of respiratory care in Pakistan.

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Pleural effusion

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None of the committee members have any personal financial disclosure.

Scope, GRADE Methodology, and PICO Framework

This national guideline provides a standardized, evidence-based roadmap for the clinical approach to adult patients (aged 13 years and older) presenting with pleural effusion. It is designed to empower pulmonologists, thoracic surgeons, general physicians, emergency physicians, and postgraduate trainees across Pakistan to deliver safe, effective, and resource-stratified care.

Out-of-Scope Domains

- Management of pleural effusions in the pediatric population (under 13 years of age).
- Detailed technical steps of major open surgical procedures (e.g., formal thoracotomy for decortication), which are governed by specialized thoracic surgery curricula.

Literature Search Strategy

To assemble a robust and locally relevant evidence base, the Guideline Committee executed a systematic literature search across major international and regional indexes, including PubMed/MEDLINE, the Cochrane Library, and Embase.

- Search Terms: MeSH terms and keywords included "pleural effusion", "exudate", "transudate", "thoracentesis", "tuberculous pleurisy", "parapneumonic effusion", "empyema", "Light's criteria", "pleurodesis", and "thoracoscopy".
- Adaptation Framework: High-quality systematic reviews, randomized controlled trials (RCTs), and large-scale observational studies were prioritized. International guidelines from the British Thoracic Society (BTS), American College of Chest Physicians (CHEST), and European Respiratory Society (ERS) were critically appraised and adapted to fit the socio-economic and clinical realities of Pakistan's healthcare infrastructure.

GRADE Methodology

The recommendations compiled in this document are framed using a modified **GRADE (Grading of Recommendations, Assessment, Development, and Evaluation)** framework. This system explicitly decouples the statistical strength of a recommendation from the quality of the underlying clinical data, allowing the committee to issue strong recommendations in resource-limited settings where clinical benefit is clear despite a lack of localized RCTs.

Strength of Recommendation

- **Strong:** The committee is highly confident that the desirable effects of the intervention clearly outweigh its risks. These recommendations should be universally adopted as standard practice across all healthcare tiers in Pakistan.
- **Weak/Conditional:** The benefits and risks of the intervention are finely balanced, or the evidence is equivocal. Clinical choices should be individualized based on institutional resource availability and patient preferences.
- **Expert Consensus:** Recommendations formulated based on the collective clinical experience and consensus of the Pakistan Chest Society expert panel in scenarios where

direct clinical trial data is limited, yet clinical practice dictates a standardized approach.

Quality of Supporting Evidence

- **High Quality:** Data derived from multiple well-designed randomized controlled trials or high-powered meta-analyses. Further research is highly unlikely to alter our confidence in the estimated effect.
- **Moderate Quality:** Data from flawed RCTs, well-executed prospective cohort studies, or case-control studies. New research may impact on our confidence in the estimate and could potentially alter the recommendation.
- **Low Quality:** Data obtained from retrospective case series, observational registries, or historical controls. The estimate of the effect remains fundamentally uncertain.

PICO Framework

To guarantee clinical precision, the guideline addresses key diagnostic and therapeutic dilemmas structured around the **PICO** (Population, Intervention, Comparison, Outcome) format.

Chapter 01:
Anatomy and Physiology of the Pleural Space

This chapter establishes the anatomical and physiological basis for the diagnostic and therapeutic interventions discussed in later sections. Understanding the specialized drainage mechanisms and pressure dynamics is essential for managing pleural diseases in a GRADE-compliant framework.

1.1 Pleural Anatomy

The pleural cavity is a dynamic, highly organized potential space (approximately 10–20 µm thick) separating the lung from the chest wall[1,2].

- The Parietal Pleura: Lines the inner thoracic cage, mediastinum, and diaphragm. It is supplied by systemic circulation. Its most critical feature is the presence of lymphatic stomata (predominantly on the diaphragmatic and mediastinal surfaces), which serve as the primary exit route for fluid, protein, and cells [1, 3]. It is innervated by somatic nerves, providing acute sensitivity to pain[4].
- The Visceral Pleura: Firmly attached to the lung parenchyma. It receives its blood supply from the bronchial circulation [1, 5]. While it lacks sensory pain fibers, it contains mechanical receptors sensitive to lung stretch and volume changes[2,6].

Mesothelium: Both surfaces are covered by a single layer of mesothelial cells. These cells possess microvilli (up to 6 µm) that increase surface area for metabolic exchange and trap hyaluronic acid to create a friction-free sliding surface[5,7].

1.2 Pleural Physiology

The primary function of the pleural space is the mechanical coupling of the chest wall to the lung, ensuring efficient gas exchange.

1.2.1 Mechanical and Protective Functions

- Friction-free Sliding: A small volume of lubricant fluid (0.1–0.3 mL/kg) prevents mechanical erosions during the respiratory cycle[1,8].
- Lung Stabilization (FRC Dynamics): At Functional Residual Capacity (FRC), the pleural space maintains a negative pressure (typically -3 to -5 cmH2O). This is a result of the inward elastic recoil of the lung opposing the outward recoil of the chest wall[2,9].
- The Extra-pulmonary Reservoir: Due to its lower hydrostatic pressure compared to the lung interstitium, the pleural space acts as a "sink," sequestering excess fluid to preserve alveolar gas exchange[1,10].

1.2.2 Fluid Kinetics and Biochemical Characteristics

Pleural fluid is in a state of constant physiological turnover.

- Production and Reabsorption: In a healthy adult, approximately 15–20 mL of fluid is produced daily. The lymphatic system in the parietal pleura has a massive reserve capacity, capable of reabsorbing fluid at a rate significantly higher than baseline production[1,3].

- Normal Biochemical Profile: Under physiological conditions, the fluid is distinct from a simple plasma ultrafiltrate[1,2].

Parameter	Normal Physiological Value
pH	7.60 – 7.64 (Alkaline)
Protein	< 1.5 g/dL
Cell Count	~1,000 – 2,000 cells/mL (Predominantly Macrophages)
Glucose	Equivalent to Plasma
LDH	< 50% of Plasma LDH

Table 1.1: Physiological Reference Ranges for Pleural Fluid

1.3 Good Practice Points

- Clinicians should recognize that pleural fluid pH < 7.60 represents a deviation from normal physiology. A pH < 7.20 in the context of infection indicates a failure of local buffering and is a high-certainty predictor for the need for drainage [1, 11].
- Because the parietal pleura is the site of both lymphatic drainage and somatic pain sensation, diagnostic interventions (e.g., biopsy) must target the parietal surface to maximize yield and minimize parenchymal complications [1, 4].

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Chapter 02:
Pathophysiology of Pleural Effusion

The transition from physiological state to a clinical effusion occurs when the massive resorptive capacity of the parietal lymphatics—which is approximately 28 times greater than the baseline production rate—is overwhelmed by excessive fluid generation or mechanical drainage failure.[1,2]

2.1 Dynamics of Fluid Generation

Under healthy conditions, pleural fluid is a dynamic ultrafiltrate primarily originating from the parietal pleural capillaries.[3]

2.1.1 The Starling Equation

The movement of fluid across the pleural membranes is governed by the Starling Equation, which balances hydrostatic and oncotic pressures:

$$Qf = Lp.\ A.\ [(Pcap - Ppl) - \sigma(\pi cap - \pi pl)]$$

Qf: Net fluid motion.
Lp: Filtration coefficient (permeability).
A: Surface area of the membrane.
P: Hydrostatic pressure (capillary vs. pleural space).
π: Oncotic pressure (capillary vs. pleural space).
σ: Reflection coefficient for protein (the membrane's ability to restrict protein leakage)[5].

2.2 Mechanism-Based Classification of Effusions

Pleural effusions are broadly categorized by the underlying pathophysiological disruption. This distinction is critical for the application of Light's Criteria discussed in later chapters[1,4].

A. Alterations in Starling Forces (Typically Transudates)

In these states, the pleural membranes remain structurally intact and the reflection coefficient (σ) is near 1.0 (protein-restricted), but pressure gradients favor accumulation.[6]

- Increased Capillary Hydrostatic Pressure: Elevation in systemic or pulmonary venous pressure (e.g., Congestive Heart Failure) increases the filtration drive into the space.[7,8]
- Decreased Capillary Oncotic Pressure: Hypoalbuminemia (e.g., Nephrotic Syndrome, Cirrhosis) reduces the intravascular "pull," allowing fluid to escape into the pleura[1].
- Decreased Intrapleural Pressure: Significant atelectasis or "trapped lung" creates a highly negative pleural pressure, effectively "sucking" fluid into the space from the surrounding tissues.[9]

B. Alterations in Permeability and Drainage (Typically Exudates)

These involve inflammatory or structural damage to the pleura, altering the reflection coefficient and allowing protein-rich fluid to accumulate.

- Increased Capillary Permeability: Inflammatory mediators (Cytokines, VEGF) cause endothelial gaps, allowing proteins and cells to leak into the space (e.g., Pneumonia, Tuberculosis, Malignancy).
- Impaired Lymphatic Drainage: Physical blockage of the parietal stomata or mediastinal nodes (e.g., Malignancy/Lymphoma) prevents fluid exit[1,3].

- Peritoneal-to-Pleural Movement: Fluid (ascites) moves through microscopic diaphragmatic defects or "blebs" due to the pressure gradient (e.g., Hepatic Hydrothorax).[8]

2.3 Good Practice Points

- Clinicians should evaluate effusions based on the suspected physiological disruption. If Starling forces are the primary driver (e.g., Heart Failure), systemic treatment is the priority; if permeability is the driver (e.g., Infection), local pleural management is required[10,11].

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Chapter 03:
Clinical Presentation and Pathophysiology of Symptoms

The clinical manifestations of pleural effusion are highly variable. Clinicians must utilize symptom clusters and physical examination findings with known Likelihood Ratios (LR) to guide diagnostic certainty [1, 2].

3.1 Symptom Clusters and Diagnostic Accuracy

Symptoms are often present in clusters that suggest specific etiologies. While individual symptoms are sensitive, they lack specificity [2].

3.1.1 The Primary Symptom Cluster

- Dyspnea (LR+ 1.5–2.0): The most prevalent symptom. Driven by neuromechanical dissociation rather than simple volume displacement [3].
- Pleuritic Chest Pain: Indicates parietal pleural inflammation. If pain persists after the layers are separated by fluid, consider malignancy or necrotizing infection [1].
- Dry Cough: Triggered by compressive distortion of the lung parenchyma [2].

3.1.2 Physical Examination Likelihood Ratios

Physical findings are critical for the initial triage. The following LRs assist in "ruling in" or "ruling out" an effusion before imaging [4].

Table 3.1: Sensitivity and specificity of signs of pleural effusion

Finding	Sensitivity	Specificity	LR+ (Rule In)	LR- (Rule Out)
Dullness to Percussion	89%	81%	**4.7**	0.14
Reduced Vocal Fremitus	82%	86%	**5.7**	0.21
Asymmetrical Expansion	74%	91%	**8.1**	0.29
Absence of Breath Sounds	88%	83%	**5.2**	0.14

3.2 Red Flags: Indications for Urgent Intervention

Clinicians must identify presentations that suggest a complicated course or the need for immediate drainage (e.g., Empyema or Tension Pleural Effusion) [1,5].

BOX 3.1: Clinical Red Flags

- **Sepsis/Systemic Toxicity:** Suggests empyema or complicated parapneumonic effusion.
- **Tracheal Deviation (Away from effusion):** Suggests massive/tension effusion compromising hemodynamics.
- **Rapidly Progressive Dyspnea:** Risk of acute respiratory failure.
- **Chronic Weight Loss/Cachexia:** High suspicion for malignancy or Tuberculosis.
- **RAPID Score > 4:** High risk of 3-month mortality.

3.3 Pathophysiology of Symptoms

3.2.1 Neuromechanical Dissociation

The brain's respiratory centers sense a mismatch between the motor command to breathe and the restricted displacement of the lung. This results in the subjective sensation of air hunger[3,6].

3.2.2 Diaphragmatic and Hemodynamic Impact

- Diaphragmatic Inversion: Large effusions flatten the diaphragm, rendering it an inefficient pump. This increases the metabolic cost of breathing [7].
- Mediastinal Shift: Increases intra-thoracic pressure, reducing venous return (preload) and potentially leading to tachycardia and hypotension [8].

3.4 Good Practice Points

- Dullness to percussion is the most useful physical sign; its absence significantly reduces the probability of a large effusion (LR- 0.14) [4].
- In patients with trepopnea, clinicians should prioritize immediate ultrasound to assess for large-volume fluid causing V/Q mismatch [9, 10].

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Chapter 04:
Radiological Evaluation

Radiological assessment is the cornerstone of pleural disease management. In this GRADE-compliant framework, the choice of modality is dictated by diagnostic accuracy and procedural safety[1].

4.1 Chest Radiography (CXR)

CXR remains the standard initial screening tool. Clinicians must be aware of the volume thresholds required for visualization to avoid "false negative" interpretations in early or small effusions[1,2].

4.1.1 Detection Thresholds and Projections

- Lateral Decubitus View: The most sensitive radiographic projection; can detect as little as 5–10 mL of fluid[2].
- Lateral View: Blunting of the posterior costophrenic angle occurs at 50–75 mL.
- PA/Frontal View: Blunting of the lateral costophrenic angle requires 175–200 mL.
- Supine View: Often misses up to 500 mL, appearing only as a non-specific "hazy" increase in opacity (veiling opacification)[1].

4.1.2 Key Radiographic Signs

- Meniscus Sign: A concave upper border of the fluid, higher laterally than medially.
- Subpulmonic Effusion: Suggested by an apparent "elevation of the hemidiaphragm" with a laterally shifted peak[2].
- Massive Effusion: Complete opacification. Clinical Red Flag: Contralateral mediastinal shift suggests high pressure (tension) or malignancy[1,11].

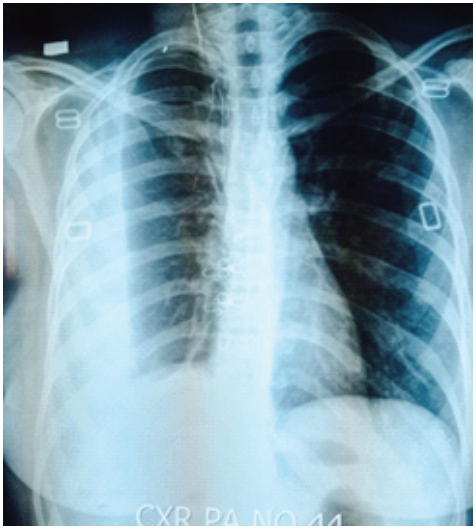

Figure 4.1: Right sided pleural effusion

4.2 Thoracic Ultrasound (TUS)

- TUS is now the mandatory standard for all pleural procedures and is superior to CXR for characterization [1,6]
- **Sensitivity:** Can detect as little as 20 mL of fluid [7].

Key Advantages:

- Distinguishes fluid from pleural thickening or lung consolidation [6].
- Identifies septations (fibrin strands) and loculations better than CT [8].
- Dramatically reduces the risk of accidental organ puncture and pneumothorax during thoracentesis [5,6].

- **Volume Estimation (Simplified Rule):** [9]

V(ml) = 20 x maximum anteroposterior diameter of pleural effusion at the lung base at end-expiration (mm)

- **Key Ultrasound Signs:**

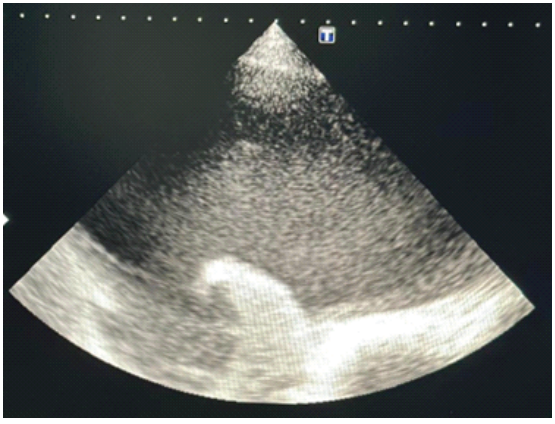

Figure 4.2: Jellyfish sign

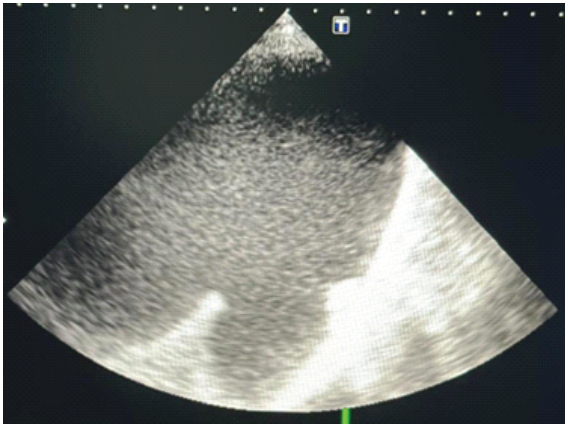

Figure 4.3: Pleural thickening and diaphragmatic nodule

- **Quad Sign:** A 2D-mode quadrilateral boundary confirming the presence of anechoic fluid between the chest wall and lung line[10].
- **Sinusoid Sign:** An M-mode wave-like motion of the visceral pleura toward the parietal pleura during respiration, confirming free-flowing fluid[10].
- **Spine Sign:** Visualization of the thoracic vertebral bodies above the diaphragm, made possible by fluid acting as an acoustic window[7].
- **Jellyfish Sign:** The appearance of a floating, wedge-shaped atelectatic lung within a large effusion, indicating lung mobility[6].
- **Plankton Sign:** Swirling hyperechoic debris within the fluid, highly suggestive of an exudate such as empyema, hemothorax, or malignancy[8,11].
- **Septation:** Fibrin strands or "honeycombing" within the fluid, indicating a complex effusion (e.g., Stage II parapneumonic effusion)[8].

While TUS provides strong clues, it cannot definitively replace biochemical analysis (Light's Criteria); however, it acts as a powerful non-invasive "rule-in" tool for exudates[11,12].

Table 4.1: Differentiating Transudates and Exudates on Ultrasound[6,7,11-13]

Feature	Transudate	Exudate
Echogenicity	Usually Anechoic. Pure fluid with low protein/cells	Often Complex. High protein and cellular debris create internal echoes
Septations	Extremely Rare. Presence virtually excludes a simple transudate	Common. Fibrin strands (Septation) are highly specific for an exudate
Plankton Sign	Absent	Frequent. Represents floating inflammatory or malignant cells
Pleural Thickening	Absent. Pleura remains thin (< 3mm)	Common. Thickening > 10 mm or nodularity is highly suggestive of malignancy/TB
Diaphragmatic Motion	Usually normal	May be restricted if there is significant inflamm - ation/trapped lung

PICO 4.1: In patients with suspected pleural infection or parapneumonic effusion (**P**), is Thoracic Ultrasound (**I**) superior to Contrast-Enhanced CT (**C**) for the detection of fibrin septations and loculations (**O**)?

- Recommendation: It is strongly recommended that thoracic ultrasound is the primary modality to characterize internal architecture and guide fibrinolytic therapy.
- Certainty of Evidence: Moderate (⊕ ⊕ ⊕ O).

- **Rationale:** TUS has a sensitivity of **100%** for identifying fibrin strands, whereas CT identifies them in only **25%** of cases[3, 14]. Visualizing these septations is a critical prerequisite for the use of intrapleural tPA/DNase. **The MIST-1 Trial (Rahman et al., 2006) was** primarily a fibrinolytic trial, it highlighted the failure of standard imaging to

predict which effusions were loculated [13]. A landmark comparative study showing Ultrasound detected septations in **100%** of cases where CT detected only **25%** [3, 14]. No direct RCT compares TUS to CT for outcome, but observational cohort studies are so definitive that the certainty is upgraded to **Moderate**.

PICO 4.2: In patients requiring pleural aspiration or drainage (P), does real-time Ultrasound guidance (I) reduce the risk of iatrogenic complications compared to the landmark-based "blind" technique (C)?

- **Recommendation:** It is strongly recommend that all pleural procedures be performed under direct Ultrasound guidance.
- **Certainty of Evidence:** High (⊕ ⊕ ⊕ ⊕).
- **Rationale:** Meta-analyses confirm that TUS-guided aspiration reduces the risk of iatrogenic pneumothorax from approximately **10%** to **<3%** and significantly reduces the incidence of accidental liver or spleen laceration [7, 8, 15]. **Gordon et al. (2010) conducted** a prospective study of 9,320 thoracenteses showing that Ultrasound guidance reduced the pneumothorax rate from **8.9% to 2.7%** [7,15]. Large-scale real-world evidence confirms a significant drop in "dry taps" and organ injury with US use. The evidence is so overwhelming that conducting a new RCT (randomizing patients to a blind arm) is now considered **unethical** in many jurisdictions.

4.3 Computed Tomography (CT)

- Contrast-enhanced CT (CECT) in the pleural phase (60–90s delay) is the preferred modality for undiagnosed effusions [1, 11]. It is the most sensitive modality, detecting >10 mL of fluid [14].
- Malignancy Indicators (The "CT Signs"): Nodular pleural thickening, circumferential thickening, parietal pleural thickening > 1cm, and mediastinal pleural involvement [1,13,14].
- Infection Indicators: The "Split Pleura Sign" (enhancement and separation of visceral and parietal layers) strongly suggests an exudative process like empyema [15].

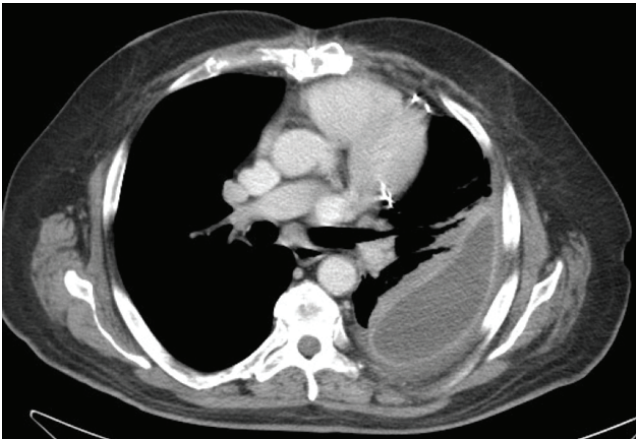

Figure 4.4: The split pleura sign

PICO 4.3: In patients with undiagnosed pleural thickening or nodules on CT (**P**), does Ultrasound-guided Pleural Biopsy (**I**) provide an equivalent diagnostic yield compared to CT-guided biopsy or Medical Thoracoscopy (**C**)?

- **Recommendation:** TUS-guided biopsy may be used (weak recommendation) as the first-line tissue-sampling strategy for accessible lesions (≥ 5 mm).
- **Certainty of Evidence:** Moderate (⊕ ⊕ ⊕O).

Rationale: TUS-guided biopsy offers a diagnostic yield of 85–92% for malignancy [11, 17]. It is preferred for its real-time visualization of the needle tip and lower cost compared to Thoracoscopy, though CT remains superior for deep-seated or paramediastinal lesions. Metintas et al. (2010) conducted an RCT comparing Medical Thoracoscopy to Ultrasound-Guided Pleural Biopsy (USPB). It showed that for patients with pleural thickening >5 mm, the diagnostic yield of USPB was equivalent to thoracoscopy (~90%) [16]. Ongoing/recent multi-center trial data (B-PLEUR) supporting image-guided biopsy as the first-line alternative to invasive surgery[17].

4.2 Comparative Diagnostic Sensitivity Table

Feature	CXR (PA/Lat)	Thoracic Ultrasound	CECT (Pleural Phase)
Smallest Volume	50 mL (Lat)	20 mL	10 mL
Septations	Not visible	Gold standard	Poor sensitivity
Parenchyma	Limited	Surface only	Gold standard
Split Pleura Sign	Absent	N/A	Specific for Empyema

PICO 4.4: In critically ill or mechanically ventilated patients (**P**), is Point-of-Care Ultrasound (**I**) more accurate than supine Chest Radiography (**C**) for diagnosing pleural effusion (**O**)?

- **Recommendation:** It is strongly recommend to integration POCUS into the standard bedside assessment of unstable patients.
- **Certainty of Evidence:** High (⊕ ⊕ ⊕ ⊕).

Rationale: Supine Chest X-rays often miss effusions up to 500 mL (appearing only as vague "veiling opacification"). POCUS has a sensitivity of >90% and can identify small volumes (<20 mL) that may be contributing to respiratory failure [12,18,19]. **Lichtenstein et al. (2004) conducted** the "BLUE Protocol" studies. This landmark research showed that Lung Ultrasound had a sensitivity of **92%** for effusion compared to **39%** for supine CXR in critically ill patients [18]. **The**

TUS-ICU Meta-analysis (2023) confirmed that POCUS significantly reduces time to diagnosis and reduces the need for "transport" CT scans, which carry high risk for unstable patients[19].

4.5 Good Practice Points

- The 1 cm Rule: If a patient with pneumonia has an effusion > 1 cm in depth on TUS or CXR, aspirate immediately. Do not "wait and watch," as this risks progression to an organized, irreversible fibrotic state [1, 10].
- TUS allows for real-time visualization of diaphragmatic excursions. Clinicians should time needle entry to occur when the safe zone is at its maximum during the respiratory cycle [6, 8].
- If CT shows rib crowding or a visceral peel > 2 mm, intrapleural fibrinolytics (tPA) are likely to fail. Early surgical consultation for decortication is required [5, 10, 11].

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Chapter 05:
Biochemical Analysis

Once a pleural effusion is confirmed, ultrasound-guided thoracentesis is performed to obtain fluid for biochemical analysis. This remains the definitive step in distinguishing the underlying etiology using the GRADE-standardized approach [1].

5.1 Macroscopic Appearance: Bedside Clues

While not definitive, the physical characteristics of the fluid provide immediate diagnostic redirection [1, 5].

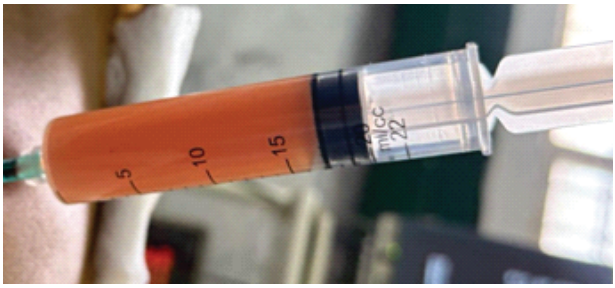

Figure 5.1: Serous pleural effusion

Table 5.1: Clinical association of appearance of pleural fluid

Appearance	Clinical Association
Straw-colored/Clear	Typically, transudative (e.g., Heart Failure)
Bloody (Sanguineous)	Malignancy, Pulmonary Infarction (PE), or Trauma
Brown (Anchovy Paste)	Ruptured Amoebic Liver Abscess.
Black	*Aspergillus niger,* Melanoma, or Esophageal Perforation.
Milky White	Chylothorax (supernatant remains milky after centrifugation).
Putrid Odor	Anaerobic Infection/Empyema [1, 5].

5.2 The Diagnostic Standard: Light's Criteria

Light's Criteria provides a sensitivity of ~97.5% for identifying exudates. The fluid is an exudate if ≥ 1 of the following are met [10]:

- Protein Ratio: Pleural Fluid Protein / Serum Protein 0.5
- LDH Ratio: Pleural Fluid LDH / Serum LDH > 0.6
- LDH Absolute Value: Pleural Fluid LDH > 2/3 of the Upper Limit of Normal (ULN) for Serum LDH.

5.2.1 The "Pseudo-exudate" and the Albumin Gradient

PICO 5.1: In patients with suspected Heart Failure on diuretics (P), is the Albumin Gradient or NT-proBNP (I) more accurate than Light's Criteria (C) for identifying a true transudate (O)?

- **Recommendation:** Use the **Serum-Effusion Albumin Gradient (SEAG)** or Pleural **NT-proBNP** when clinical suspicion of heart failure conflicts with exudative Light's Criteria.
- **Certainty of Evidence: High** (⊕ ⊕ ⊕ ⊕).
- **SEAG > 1.2 g/dl:** Confirms Transudate[2,3].
- **NT-proBNP > 1500 pg/mL:** Confirms Heart Failure[3].

PICO 5.2: In high-burden TB regions (**P**), is Pleural Adenosine Deaminase (**ADA**) (**I**) an effective surrogate for pleural biopsy/culture (**C**) in diagnosing TB pleurisy (**O**)?

- **Recommendation: Conditional Recommendation.** Use ADA in lymphocytic exudates.
- **Certainty of Evidence:** Moderate (⊕ ⊕ ⊕O).
- **Threshold: ADA > 35–40 U/L** is highly suggestive of TB in the appropriate clinical context[1,6].

PICO 5.3: Should pleural fluid pH be measured via blood gas analyzer (I) or pH indicator strips/litmus (C)?

- **Recommendation: Strong Recommendation.** pH must be measured using a **heparinized syringe** and a **blood gas analyzer.**
- Certainty of Evidence: High (⊕ ⊕ ⊕ ⊕).
- **Rationale:** pH strips are inaccurate and can lead to inappropriate management of parapneumonic effusions[1,7].

5.4 Specialized Biochemical Markers

Table 5.2: Biomarkers of pleural effusion

Marker	Clinical Significance	Diagnostic Threshold
pH	Indicator of pleural inflammation/infection	< 7.20 suggests empyema or complicated parapneumonic effusion (requires drainage). > 7.64 may suggest Proteus infection
Glucose	Low levels indicate high metabolic activity (bacteria/cells)	< 60 mg/dL suggests TB, Malignancy, or Rheumatoid pleurisy
Adenosine Deaminase (ADA)	Crucial for the high-burden TB context of Pakistan	> 35–40 U/L is highly suggestive of Tuberculosis; also elevated in empyema and RA

Amylase	Elevated in specific pathologies	Pleural/Serum ratio > 1.0 suggests Pancreatitis, Esophageal Rupture, or Malignancy
Triglycerides	Used to diagnose Chylothorax	> 110 mg/dL confirms a chyle leak
NT-proBNP	Useful for Heart Failure diagnosis when systemic fluid is present	> 1500 pg/mL in pleural fluid is diagnostic of Congestive Heart Failure

5.5 Good Practice Points

- If the fluid is milky, centrifuge it. If the supernatant clears, turbidity was due to cells/debris. If it remains milky, it confirms a Chyle leak[1].
- If lymphocytes constitute > 50% of the count, the primary differentials are Malignancy, TB, and Lymphoma[1,3].
- If the pleural fluid is bloody, check the hematocrit. A pleural-to-blood hematocrit ratio > 0.5 defines a Hemothorax[1].

5.5 Specimen Handling

pH: Must be collected in a heparinized syringe and analyzed in a blood gas machine immediately. Do not use pH indicator strips, as they are inaccurate[1,12].

Glucose/Protein/LDH: Collected in plain or gel-top tubes.

Table 5.3: Differentiating chylothorax from pseudochylothorax[1]

Feature	Chylothorax	Pseudochylothorax
Triglycerides	High > 1.10 mmol/L (110 mg/dL)	Low
Cholesterol	Low	High > 5.18 mmol/L (200 mg/dL)
Cholesterol Crystals	Absent	Often present
Chylomicrons	Usually present	Absent

Table 5.4: Etiological Classification of Pleural Effusions by Incidence and Biochemical Type

Category	Transudates	Exudates
Common Causes	Heart failure Liver cirrhosis	Malignancy Pneumonia post-surgry will be from next line. like this: Tuberculosis (High prevalence in Pakistan) Post-surgery (cardiothoracic, abdominal) Pericardial diseases
Less Common Causes	Hypoalbuminemia Nephrotic syndrome Pulmonary arterial hypertension Atelectasis Volume overload (e.g., in ESRF) Non-expandable lung* Peritoneal dialysis	Trauma Idiopathic Pulmonary embolism# Abdominal diseases Autoimmune diseases Uremic pleural effusion

Rare Causes	Superior vena cava syndrome* Constrictive pericarditis* Urinothorax* Cerebrospinal fluid (CSF) leak Non-cirrhotic portal hypertension Extravascular migration of CVC	Esophageal perforation Chylothorax# Gynecological conditions (e.g., Meigs syndrome, Endometriosis, OHS) Drugs (e.g., Amiodarone, Methotrexate) Benign asbestos pleural effusion Viral infections Sarcoidosis Amyloidosis# Thoracic radiotherapy

* They may also be exudate
# They may also be transudate

Table 5.5: Causes of Lymphocytic Pleural Effusion
A lymphocytic predominant effusion is typically defined as a pleural fluid where lymphocytes constitute >50% of the total white cell count.

Malignancy
Tuberculosis (TB)
Lymphoma
Congestive Cardiac Failure
Post-coronary Bypass Graft
Rheumatoid Arthritis
Chylothorax
Yellow Nail Syndrome

Table 5.6: Causes of Bilateral Pleural Effusion
Bilateral effusions are frequently associated with systemic diseases rather than primary pleural pathology. When present, they are often (though not exclusively) transudative in nature[1].

Congestive Cardiac Failure
Hypoalbuminaemia
Renal Failure
Liver Failure
SLE and Autoimmune Diseases
Widespread Malignancy
Bilateral Pulmonary Embolus
Drugs

Table 5.7: Causes of Chylothorax and Pseudochylothorax

Condition	Category	Specific Etiologies
Chylothorax	Trauma	Thoracic surgery (especially involving the posterior mediastinum, e.g., oesophagectomy), thoracic injuries
	Neoplasm	Lymphoma or metastatic carcinoma
	Miscellaneous	Disorders of lymphatics (including lymphangioleiomyomatosis), Tuberculosis, Cirrhosis, obstruction of the central veins, chyloascites
	Idiopathic	Approximately 10% of cases
Pseudochylothorax		Tuberculosis, Rheumatoid Arthritis

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Chapter 06:
Management of Pleural Infection and Empyema

Pleural infection is a complex disease progressing through three distinct phases: Exudative (sterile filtrate), **Fibrinopurulent** (bacterial translocation and loculation), and **Organizing** (fibroblast proliferation forming a restrictive peel).

6.1 Management Algorithm for Pleural Infection

- Clinical Suspicion: Risk factors (Diabetes, GORD, poor oral hygiene) + pneumonia symptoms[1].
- **TUS-Guided Thoracocentesis:**
  - **pH > 7.30 and Glucose > 60mg/dL:** Simple parapneumonic effusion: Antibiotics alone[1].
  - **pH ≤ 7.20 and Glucose ≤ 60 mg/dL and LDH > 1000 IU/L:** Complicated effusion: Mandatory Drain + Antibiotics[1,2].
  - **Frank Pus / Positive Gram Stain:** Empyema: Urgent Drain + Antibiotics[1,3].
- **Assessment at 48–72 Hours:**
  - **Improvement:** Continue medical therapy.
  - **Failure (Sepsis/Loculation):** IPFT (tPA/DNase) or Thoracoscopy (Medical/VATS)[4,5].

Clinical presentations are variable. The classical presentation is that of a relatively young patient with few comorbidities, with fever, rigors, symptoms of an acute respiratory illness, and a non-resolving pneumonia, anorexia, malaise, etc[1].
Several risk factors, such as immunosuppression, diabetes, poor oral hygiene, gastro-oesophageal reflux, alcohol excess and intravenous drug use, are known to independently predict increased risk of progression of pneumonia to pleural infection[1,2].
There are three phases of pleural infection:

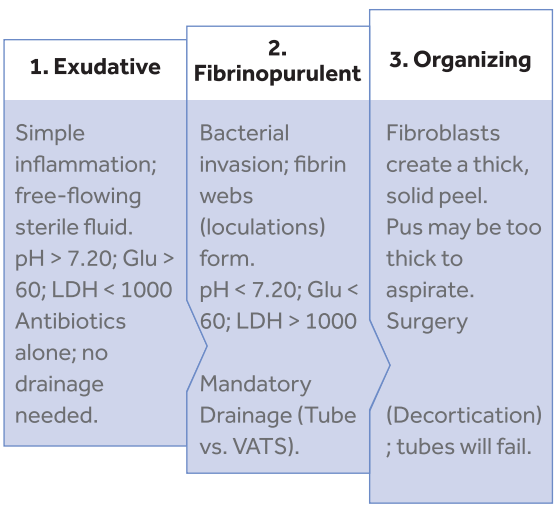

Figure 6.1: Different phases of pleural effusion

Pleural fluid culture, to date, is the recommended modality for microbiology. Although it has a yield of 30–40%, this increases to 60% when inoculated into blood culture bottles[1,3]. Peripheral blood cultures are important and may be the only positive source of culture (as seen in about 12% of cases in the MIST-1 study (First Multicentre Intrapleural Sepsis Trial)[4].

6.1 Microbiology of Pleural Infection

The microbiology of pleural infection is distinct from pneumonia, characterized by high diversity and a significant prevalence of polymicrobial growth[1,5].

6.1.1 Emerging Pathogens

- Staphylococcus aureus: Has surpassed Viridans streptococci as the most common pathogen; approximately 60% of these cases are MRSA[1,6].
- Streptococcus pneumoniae: Remains the leading cause of monomicrobial community-acquired infections[1].
- Anaerobes: Frequently implicated but often underreported due to standard culture limitations. Metagenomic studies (e.g., TORPIDS) suggest an incidence of polymicrobial infection as high as 79%[7].

6.1.2 Community vs. Hospital Acquired

- Community-Acquired: Predominantly mixed anaerobes, Gram-negative bacteria, and S. pneumonia[1,8].
- Hospital-Acquired: Higher prevalence of Gram-negative organisms and S. aureus[1,6].
- Atypical Organisms: (e.g., Legionella, Mycoplasma) are rarely identified in the pleural space; therefore, atypical antibiotic cover is generally not required[1].

6.1.3 Prognostic Value of Microbiology

The causative organism is a powerful predictor of clinical outcomes:

- Higher Mortality/Longer Stay: Associated with S. aureus, Enterobacteriaceae, and non-streptococcal infections[9].
- Better Survival: Associated with the Streptococcus anginosus group and anaerobic infections[9].

6.1.4 Clinical Recommendations

- Broad-Spectrum Coverage: Initial empirical therapy must include anaerobic cover for all patients[1,10].
- Culture Techniques: Use of blood culture bottles for pleural fluid is strongly recommended to increase the yield of fastidious organisms and anaerobes[1,3].

6.1.5 TB empyema

TB empyema is a chronic, active infection of the pleural space characterized by thick, turbid, or purulent fluid [11]. It usually results from the rupture of a subpleural cavitary focus or via the progression of a neglected TB pleurisy into a fibropurulent stage[11,12]. Patients typically present with a more chronic course compared to pyogenic empyema, often exhibiting weight loss, night sweats, and a productive cough[11]. Physical examination reveals signs of a large effusion or significant pleural thickening[12].

Diagnostic Evaluation

Although TB pleural effusion is paucibacillary, in TB endemic areas also get pleural fluid AFB smear and Xpert MTB/Rif assay, AFB culture[13]. The primary reason TPE is paucibacillary is that the effusion is not typically caused by a high-burden bacterial infection of the pleural space itself. Instead, it is a delayed-type hypersensitivity reaction (Type IV)[14].

- **Mechanism:** A small subpleural focus of Mycobacterium tuberculosis (MTB) ruptures into the pleural space. This release of a small number of bacilli (and their antigens) triggers an intense local cell-mediated immune response. T-lymphocytes and macrophages flood the area, releasing cytokines (like IFN-□ and TNF-α). This inflammatory storm increases capillary permeability, leading to fluid accumulation. Because the fluid is a result of the immune response to a few antigens rather than a massive bacterial overgrowth the actual number of bacilli present in the fluid is extremely low[14,15].

TB empyema may have high mycobacterial load and test positive on AFB smear and Xpert MTB/Rif assay [11,13]. Ultrasound is essential to check for pleural thickening and loculations, that may guide drainage [1,8]. On

CT scan one may find crowded ribs, pleural calcifications, and presence of bronchopleural fistula [12].

Management Strategies
Standard antituberculous treatment regimens should be initiated immediately. Minimum treatment duration is 6 months but may extend due to poor drug penetration into the thickened pleural peel [11,16].

Often large-bore chest tubes are required for thick pus, though the success rate of simple drainage is lower than in pyogenic empyema due to extensive fibrosis [11]. Evidence regarding use of fibrinolytics is less robust [1,11].

For multiseptated, multiloculated empyema perform medical thoracoscopy under local anesthesia [8,17]. It will serve both diagnostic and therapeutic purposes. If patient is not candidate for medical thoracoscopy then get surgical input for VATS decortication [1,18]. Thoracoplasty/ open window thoracostomy are reserved for chronic, recalcitrant cases or when a bronchopleural fistula is present in an unfit surgical candidate [19].

6.2 Antimicrobial Management of Pleural Infection
Empirical antibiotic therapy should be initiated immediately upon suspicion of pleural infection. It must cover both aerobic and anaerobic pathogens, as the latter are frequently under-detected by standard culture techniques [1,10].

6.2.1 Community-Acquired Infection
For patients presenting with infection acquired outside the hospital setting:

- **Recommended Agents:** A combination of a parenteral second or third-generation cephalosporin (e.g., Ceftriaxone 2g daily) plus Metronidazole (500mg TDS), or an aminopenicillin/beta-lactamase inhibitor (e.g., Co-amoxiclav) [1,10].
- **Atypical Coverage:** Routine coverage for Legionella or Mycoplasma is generally not required, as these organisms rarely cause pleural infection [1].
- In any patient with an "empyema" that fails to respond within 5–7 days, tuberculosis must be ruled out via GeneXpert MTB/RIF, and/ or pleural biopsy [11,13].

6.2.2 Hospital-Acquired / Post-Procedural Infection
These are frequently caused by multi-drug resistant (MDR) organisms, including Pseudomonas aeruginosa and MRSA [1,6].

- **Recommended Agents:** Anti-pseudomonal coverage is mandatory. Options include Piperacillin-tazobactam, Cefepime (plus metronidazole), or Carbapenems (e.g., Meropenem) [1,10].
- **MRSA:** Vancomycin or Linezolid should be added if there are specific risk factors or if local prevalence is high [1].
- If the patient is septic despite therapeutic vancomycin levels, switch to linezolid (600mg IV q12h). Linezolid has significantly better lung and pleural fluid penetration [1,20].

6.2.3 Pharmacokinetics and Dosing
The pleural barrier dictates drug choice in pleural infections. Penicillins, cephalosporins, carbapenems, and metronidazole achieve excellent concentrations in the pleural fluid [1,21]. Beta-lactams enter the pleural space via passive diffusion. To get enough drug into a fibrin loculation, high concentration gradient is needed. Use higher doses [21].

Aminoglycosides should be avoided for pleural infection. The acidic environment of an empyema inactivates aminoglycosides and renders them ineffective [1,21]. Currently, there is insufficient evidence to recommend the routine administration of antibiotics directly into the pleural space [1].

6.2.4 Route and Duration of Therapy
While drainage is the primary therapeutic intervention, the duration of antibiotics remains a subject of debate.

- Start with intravenous (IV) therapy [1,10].
- Step-down to oral antibiotics is appropriate when:
    - Chest drain is out
    - There is clear clinical improvement and defervescence.
    - Inflammatory markers (CRP) are significantly falling.

- The pleural space has been successfully drained [1,22].
- The total duration is usually 3 to 6 weeks [1,10]. The pleura has a poor blood supply; it takes weeks to sterilize the fibrotic peel covering the lung [22].

6.2.5 Microbiological Directed Therapy

Once culture results are available, the antibiotic spectrum should be narrowed. However, anaerobic coverage should be continued even if anaerobic cultures are negative, due to the high rate of "culture-negative" anaerobes in pleural fluid [1,5].

Clinical pearls:

- If the patient is still spiking fevers after 5 days of antibiotic, do not change the drug. First check whether the pus is undrained. Re-image with Ultrasound and re-drain [1].
- If the pleural fluid pH > 7.30 (simple parapneumonic), use standard pneumonia antibiotic durations (5–7 days). If pH < 7.20, commit to the 3–6 weeks rule [1].

PICO 6.1: In patients with pleural infection (**P**), does empiric anaerobic coverage (**I**) improve resolution (**O**) compared to aerobic coverage alone (**C**)?

Recommendation: It is strongly recommended to use initial empiric antibiotics covering both aerobic and anaerobic pathogens.

- **Strength: Strong | Certainty: High** (⊕⊕⊕⊕)

Evidence: Meta-genomic studies show anaerobic incidence up to 79% [7]. Beta-lactams and metronidazole achieve excellent pleural concentrations, while aminoglycosides are inactivated by the acidic environment [43].

6.3 Therapeutic Pleural Aspiration (Thoracentesis)

The traditional standard for managing pleural infection is Intercostal Drain (ICD) insertion. However, Repeated/Iterative Therapeutic Thoracentesis (TT) has emerged as a potential alternative for specific patient populations [23]:

- **Low RAPID Score:** Patients at low risk of poor outcomes.
- **Stable Hemodynamics:** No evidence of systemic sepsis or septic shock.
- **Small to Moderate Volume:** Effusions that are easily accessible via ultrasound.
- **Early Presentation:** Simple parapneumonic effusions before the development of thick septations or a pleural rind.

Clinical pearls

- ICD insertion remains the preferred primary management for complicated parapneumonic effusions and empyema [1].
- Iterative TT may be considered in resource-limited settings or in highly selected, stable patients where close monitoring and daily ultrasound are available [23].
- All repeat aspirations must be ultrasound-guided to minimize the cumulative risk of pneumothorax or lung laceration [1,24].

6.4 Chest Drain Insertion and Management

Closed thoracic drainage remains the global standard of care for pleural infection. Since the early 20th century, this intervention has reduced mortality in streptococcal pleural infections from 30% to approximately 3.4% [1]. The indications for chest drain insertion are:

- Pleural fluid pH ≤ 7.2
- Pleural fluid LDH > 1000 IU/L
- Pleural fluid glucose ≤ 4 mmol/L

A CT score devised by Porcel et al can also be used to predict need for chest drainage in pleural infection [25]:

Table 6.1: CT score to predict need of chest tube in pleural infection

CT Finding	Points
Pleural contrast enhancement (Parietal pleura)	3 points
Pleural microbubbles (Gas bubbles within the fluid)	1 points
Increased extra-pleural fat attenuation	1 points
Fluid volume ≥ 400 mL	1 points

- Total Score ≥ 3: High probability of a complicated parapneumonic effusion.

Clinical Significance: A score of 3 or more has been shown to have a high positive likelihood ratio (~3.4) for needing a chest tube [25].

6.4.1 Technique and Guidance

- All chest drains must be inserted under ultrasound guidance to identify the optimal pocket of fluid and avoid organ injury [1,24].
- Seldinger technique is the preferred method of insertion. It is less invasive, better tolerated by patients, and associated with fewer complications than blunt surgical dissection [1,24]. Cost of equipment is major hindrance.

The triangle of safety is the anatomical region recommended as the preferred site for the insertion of a chest tube to minimize risk to major structures like the heart, major arteries and lymphatics. It is bound by:

- **Anterior border:** The lateral edge of the **pectoralis major** muscle
- **Posterior border:** The anterior edge of the **latissimus dorsi** muscle
- **Inferior border:** The line of the **5th intercostal space**
- **Apex:** The **axilla**

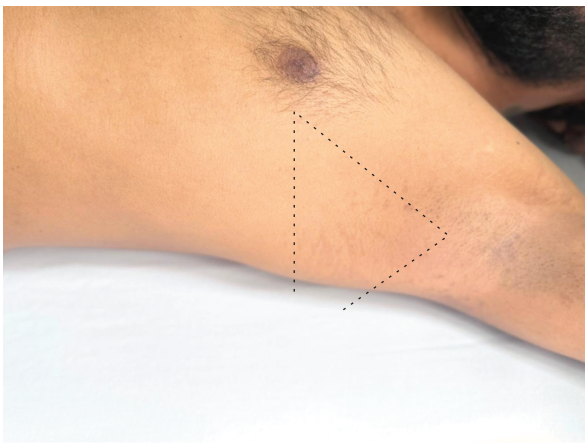

Figure 6.2: Safe triangle
While the "Safe Triangle" is the standard for most effusions and pneumothoraces. Current standard is to use thoracic ultrasound to guide any procedures. Triangle of safety is fixed anatomical area while the fluid moves or may be loculated [1,24].

6.4.2 Chest Tube Size: The "Small vs. Large"

International consensus defines:

- Small-bore Drains: ≤14 Fr.
- Large-bore Drains: ≥ 18 Fr.

Small-bore drains (10–14 Fr) are recommended as the first-line choice for pleural infection. Data from the MIST-1 and MIST-2 trials confirm there is no difference in clinical outcomes (mortality or need for surgery) between small and large-bore drains [4,26]. Large-bore drains, especially those inserted via blunt dissection, are associated with significantly higher pain scores [24]. Small-bore drains are less painful and are sufficient for the administration of intrapleural fibrinolytics and enzymes [26].

- While Poiseuille's Law dictates that flow increases exponentially with radius (r^4), clinical trials show that small-bore catheters (12–14F) are just as effective as large-bore tubes for draining infected pleural fluid, provided they are managed with regular flushing (30 ml saline every 6 hourly)

and, if necessary, intrapleural fibrinolysis to address fluid viscosity. For empyemas keep chest tube on active suction, - 20 cmH2O.

PICO 6.2: In patients requiring drainage (**P**), are small-bore drains (≤14Fr) (**I**) as effective as large-bore drains (> 20Fr) (**C**) in treating empyema (**O**)?

Recommendation: Small bore drains are first line intervention for draining empyema.

- **Strength: Strong | Certainty: High** (⊕⊕⊕⊕)
- **Evidence:** MIST trials confirm no difference in mortality or surgical rates between sizes, with significantly less pain reported for small-bore catheters [3].
- Failure of chest tube drainage of effusion should be declared if, after 48–72 hours of drainage and appropriate antibiotics, the patient meets any of the following objective criteria:
    - Persistent Sepsis: Ongoing fever, tachycardia, or rising inflammatory markers (WBC/CRP) despite a patent drain.
    - Minimal fluid output (<100 mL/day) despite imaging (Ultrasound/CT) showing a significant remaining collection.
    - Follow-up imaging shows persistent loculations or a trapped lung that do not expand.

Leaving an ineffective tube in for weeks is a common error. It creates a chronic sinus tract, acts as a nidus for secondary hospital-acquired infections, and causes the pleural to become thicker and more vascular. A non-functional tube at day 3 will remain non-functional on week 3. Plan early LAT where available or refer to thoracic surgeon for VATS.

6.4.3 Maintenance and patency

In Pakistan, mostly the patients present late with fibrinopurulent or organizing stage of empyema. A major concern with small-bore drains is the risk of occlusion by thick pus or fibrin (occlusion rates reach up to 63% in some series)[27].

- Saline Flushes: Regular flushing (e.g., 20–30 mL of sterile saline three times daily) is advocated to maintain patency[1].
- Intrapleural Irrigation: Emerging evidence suggests that large-volume saline irrigation (e.g., 250 mL three times daily) may improve radiological clearance and reduce the need for surgical referral[28].

Clinical Pearls:

In our resource-constrained environments, where advanced digital drainage systems are not always available, the clinician must be an expert in interpreting the signs of the water seal. To manage a chest tube, the clinician must distinguish between old air being evacuated and new air from an active fistula[29-31].

6.4.4 Re-expansion Pulmonary Edema (RPE)

RPE is a form of non-cardiogenic pulmonary edema that occurs when a chronically collapsed lung (due to large effusion or pneumothorax) is re-inflated too rapidly [33]. The pathophysiology involves a sudden shift in pressure and a reperfusion injury to the lung tissue. When a lung has been collapsed for a long period (typically >3–7 days), the pulmonary capillaries become fragile. Rapid re-expansion causes a sudden increase in blood flow and a dramatic drop in pleural pressure. The sudden mechanical stretching of the alveolar-capillary membrane leads to its disruption, allowing protein-rich fluid exudation into alveoli. Re-oxygenation of the collapsed lung triggers the release of free radicals and inflammatory mediators (like IL-8 and leukotrienes), further increasing permeability[33,34].

REPE follows a classic timeline. Immediate relief following drainage and lung re-expansion. Symptoms typically appear within 1–2 hours (rarely up to 24h). Key signs are persistent, wracking cough, pink, frothy sputum (pathognomonic for alveolar flooding), sudden tachypnea and hypoxia [33]. Radiological hallmark for REPE is unilateral, alveolar infiltrates limited strictly to the lung that was re-expanded. Prevention is the only effective management for REPE. For large pleural effusions, do not remove more than 1.0 to 1.5 Liters in a single session. For chronic pneumothorax or massive effusions, avoid applying active suction during the initial 24 hours. Use an underwater seal (gravity drainage) only. If the patient develops chest tightness or a persistent cough during drainage, stop immediately, even if you have drained less than 1 Liter. This is an early sign of shifting pleural pressures[33,34].

If REPE occurs, treatment is supportive, as there is no pharmacological cure: Place the patient with the affected side up. This reduces blood flow to the leaky lung and improves ventilation-perfusion matching in the healthy lung. High-flow O2 or Non-Invasive Ventilation (CPAP/BiPAP) to provide positive end-expiratory pressure. Severe cases may require intubation and mechanical ventilation. Diuretics are generally not recommended, as these patients are often intravascularly depleted despite the edema in the lung[33].

6.5 Intrapleural Fibrinolytic and Enzyme Therapy (IPFT)
In the infected pleural space, inflammatory mediators (tPA-inhibitors and TNF-α) promote heavy fibrin deposition. This leads to increased fluid viscosity and the formation of loculations, which make standard drainage difficult[26,35]. Approximately 6–27% of patients fail standard care (antibiotics + drain) and require further intervention. Evidence comes from the MIST trials. The intrapleural enzymes is not available currently in Pakistan.

- Monotherapy (Fibrinolytics alone): The MIST-1 trial (427 patients) and a major Cochrane review (993 patients) showed that fibrinolytics (like Streptokinase or Urokinase) alone do not improve mortality or reduce the need for surgery[4,36].
- Combination Therapy (The MIST-2 Protocol): The MIST-2 trial revolutionized management by combining a fibrinolytic (tPA) to break fibrin membranes with an enzyme (DNase) to reduce the viscosity of DNA-rich pus[26].
- According to MIST-2, tPA + DNase results in[26]:
    - 77% reduction in the need for surgical referral.
    - 6.7-day reduction in the length of hospital stay.
    - Significant improvement in radiographic (CXR/CT) pleural clearance.

6.5.1 Administration Protocol (MIST-2 Dosing)
This is the standard regimen for a non-draining or loculated infected pleural space [26]:
- tPA (Alteplase): 10 mg injected into the pleural space via the chest tube.
- Flush: Follow with 10 mL of 0.9% NaCl.
- DNase (Pulmozyme): 5 mg injected immediately after.
- Flush: Follow with another 10 mL of 0.9% NaCl.
- Clamp: The drain is clamped for 1 hour to allow the drugs to work.
- Frequency: Administered twice daily (12-hourly) for up to 3 consecutive days (maximum 6 doses).

Note: Some newer studies (ADAPT-1 & 2) suggest that lower doses (e.g., 5 mg tPA) or once-daily dosing may be equally safe and effective[37].

6.5.2 Safety and Bleeding Risk
The risk of pleural hemorrhage is low (~3.8% to 4.2%) and mostly can be managed by simple blood transfusion and do not require surgery[26]. Use caution and consider halving the tPA dose in patients with:
- Renal failure or dialysis.
- Low platelet count (< 100 x 10^9/L).
- Concurrent systemic anticoagulation.
- High RAPID scores.

PICO 6.3: In patients with loculated empyema (**P**), does combination tPA/DNase (**I**) reduce surgical referral (**O**) compared to monotherapy (**C**)?

Recommendation: It is recommended to use the combination of tPA and DNase for non-draining or loculated effusions.

Strength: Strong | Certainty: Moderate (⊕ ⊕ ⊕ ⊕)
Evidence: Combination therapy (10mg tPA + 5mg DNase BD) resulted in a 77% reduction in surgical referrals. Monotherapy with fibrinolytics alone is not recommended[3].

6.6 Medical thoracoscopy
The use of LAT/ MT (Local anesthetic thoracoscopy/ medical thoracoscopy) in pleural infection is an area of growing interest, particularly for multiloculated collections. Studies report success rates upto 98%[35,38].

LAT allows for mechanical disruption of septations, direct-vision biopsy (improving yield), and precise chest tube placement [38]. Complications rate is very low. It may be considered in centers with high expertise for patients with multiseptated/ multiloculated pleural effusion or in patients with diagnostic uncertainty[1]. As availability of IPFT is a major obstacle in treatment of such cases in Pakistan.

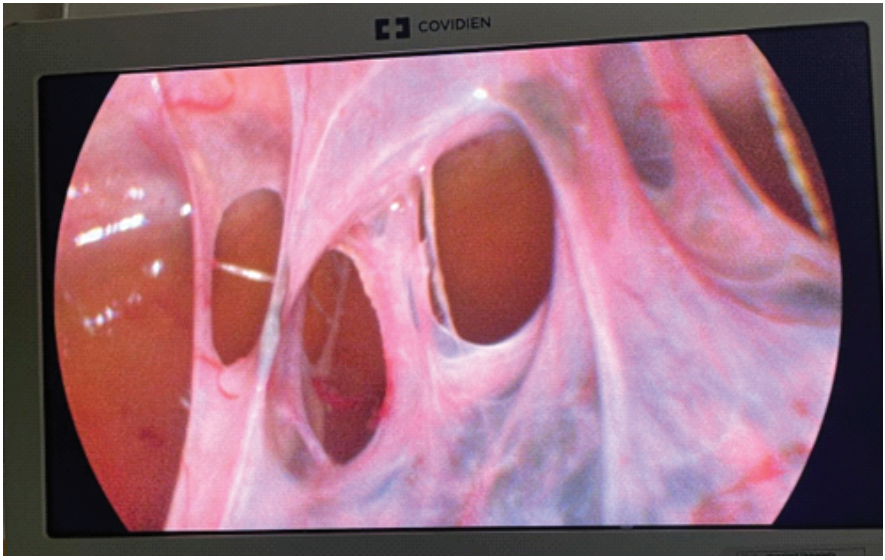

Figure 6.3: Thoracoscopic view of pleural effusion with overlying thick intrapleural septations

6.7 Surgical Management of Pleural Infection

Despite optimal medical therapy (antibiotics and drainage), approximately 15–20% of patients with pleural infection will require intervention [[1]]. If there is stage 3 empyema, trapped lungs or patient is not willing for local anesthetic procedure or thoracoscopy expertise/ equipment are unavailable then may be referred to thoracic surgeon for VATS decortication [1,10,18].

6.7.1 Indications for Surgery

Surgery should be considered in the following clinical scenarios [1,10,18]:

- Failure of fever defervescence and persistently elevated inflammatory markers despite patent drainage and appropriate antibiotics.
- Persistent fluid collections on imaging (TUS/CT) that cannot be accessed by chest tubes or managed with IPFT.
- Presence of extensive loculations (fibrinopurulent stage) or a thick fibrous rind (organizing stage).
- A thick visceral pleural rind preventing lung re-expansion, which requires decortication.

6.7.2 Surgical Modalities

- Video-Assisted Thoracoscopic Surgery (VATS): Now the preferred approach for managing pleural infection [1,18,39].
  - Advantages: Reduced postoperative pain, shorter hospital stays, less blood loss, fewer respiratory complications, and lower costs compared to open surgery.
  - Function: Allows for effective debridement and evacuation of infected material.
- Open Thoracotomy (Decortication): Reserved for advanced chronic empyema where VATS is technically impossible due to a dense, mature pleural rind that requires manual stripping to allow lung expansion [1,39].
- Open Window Thoracotomy / Thoracoplasty: Salvage procedures for debilitated patients with chronic pleural space infections who cannot tolerate major decortication [19].

PICO 6.4: In patients failing medical therapy (P), is VATS (I) superior to open thoracotomy (C) in respect to complications (O)?

Recommendation: VATS is the preferred surgical modality for debridement and decortication.

- **Strength: Strong | Certainty: Moderate** (⊕ ⊕ ⊕O)

Evidence: VATS is associated with reduced pain and fewer complications. Surgery should be considered early (within 5–7 days) if medical therapy fails[5,8].

PICO 6.5: In patients with multiloculated pleural infection (**P**), is Medical Thoracoscopy (**I**) superior to chest tube drainage alone (**C**) in treating empyema (**O**)?
Recommendation: It is recommended that medical thoracoscopy under local anesthesia is a therapeutic option where IPFT is unavailable.

- **Strength: Weak/Conditional | Certainty: Moderate** (⊕ ⊕ ⊕ ⊕)

Evidence: MT allows mechanical disruption of septations with success rates up to 98% in early stages[1,3,9].

6.7.3 Timing and Risk Stratification

- Delaying intervention is associated with poorer outcomes. Early consultation with a thoracic surgeon is advised if medical therapy does not show objective improvement within 5–7 days[1].

PICO 6.6: In patients with parapneumonic effusion (**P**), does immediate drainage within 24 hours of admission (**I**) improve outcomes (**O**) compared to delayed drainage (**C**)?
Recommendation: early pleural drainage is recommended for all complicated effusions and empyemas.

Strength: Strong | Certainty: High (⊕ ⊕ ⊕ ⊕)
Evidence: Delay in drainage of ≥ 2 days from diagnosis is independently associated with higher 30-day and 90-day mortality[1,42,44].

6.8 Indwelling Pleural Catheters (IPC)
For advanced, chronic pleural infections where "trapped lung" is present:

- IPCs combined with prolonged antibiotic therapy can be used as a "salvage" strategy to manage symptoms and provide long-term drainage[40].
- Data remains sparse and robust recommendations cannot be made; use should be individualized.

6.9 Intrapleural Antibiotics

- Currently not recommended for routine pleural infection[1].
- Evidence is limited largely to post-pneumonectomy infections. Systemic antibiotics (IV/Oral) remain the standard due to adequate pleural penetration of most recommended agents[1,21].

6.10 Role of Corticosteroids
Theoretically their role is to modulate the high levels of inflammatory mediators (IL-6, TNF-α, VEGF) in the infected space. The STOPPE trial (a feasibility study) did not demonstrate clear clinical benefits for using steroids in parapneumonic effusions[41]. Routine use of steroids in bacterial pleural infection is not recommended. (Note: This differs from Tuberculous Pleurisy, where steroids may have a specific role in highly symptomatic patients).

PICO 6.7: In adults with bacterial pleural infection (**P**), do systemic corticosteroids (**I**) reduce the need for surgery (**O**) as compared to no steroids (**C**)?

Recommendation: Do not routinely use corticosteroids in bacterial pleural infection.

Strength: Strong | Certainty: Moderate (⊕ ⊕ ⊕O)

- Evidence: The STOPPE trial did not demonstrate clinical benefits; steroids may mask sepsis signs[1,41].

6.11 Salvage Surgical Options

For patients with chronic empyema and bronchopleural fistula (BPF) who are unfit for VATS/ Decortication[19]:

- **Open Window Thoracotomy:** Creating a permanent or semi-permanent opening in the chest wall for drainage and dressing changes.
- **Thoracoplasty:** Removal of ribs to collapse the chest wall into the infected space to obliterate the cavity.

6.12 Risk Stratification and Future Directions

Despite therapeutic advances, the mortality of pleural infection remains high. The traditional "one-size-fits-all" approach is being challenged by early risk stratification[1].

6.12.1 The Cost of Delay

Timely intervention is the most significant modifiable factor in survival. A delay in pleural drainage of just 2 days from diagnosis is associated with significantly worse mortality at 30 and 90 days[1]. Late surgical referral increases the rate of conversion from VATS to open thoracotomy, leading to higher morbidity and mortality[1].

6.12.2 The RAPID Score

The RAPID score is the only prospectively validated tool for predicting mortality in pleural infection[42]. It should be calculated for every patient at the time of admission to guide the therapy[9].

Table 6.2: The RAPID Score

Parameter	Description	Points
Renal	Serum Urea <5 mmol/L (0); 5–8 mmol/L (1); >8 mmol/L (2)	0–2
Age	<50 years (0); 50–70 years (1); >70 years (2)	0–2
Purulence	Purulent fluid (0); non-purulent fluid (1)	0–1
Infection Source	Community-acquired (0); Hospital-acquired (1)	0–1
Dietary	Serum Albumin >30 g/L (0); <27 g/L (1)	0–1

- Low Risk (Score 0–2): 3-month mortality ~2.3%.
- Medium Risk (Score 3–4): 3-month mortality ~9.2%.
- High Risk (Score 5–7): 3-month mortality ~29.3%.

Practical points

- **When to drain parapneumonic effusion?**
  - Distinguish between a sterile, passive filtrate and an active, acid-producing environment. Pneumonia releases cytokines that make the nearby pleural capillaries "leaky." This is a passive process. The fluid is essentially plasma that has leaked into space. There are no bacteria "living" in the fluid to consume energy. Hence the pH remains > 7.30 and glucose is > 60 mg/dL.Do not drain this effusion. As the antibiotics treat pneumonia, the cytokine storm is turned off, the capillaries tighten, and the lymphatics naturally pump the fluid away over 2–4 weeks. Once bacteria or a massive load of neutrophils enters space, the fluid transitions from passive filtrate to active metabolism. The bacteria consume glucose and forms lactic acid and CO2. The pH turns acidic. Low pH triggers the coagulation cascade, turning fibrinogen into solid fibrin. The fluid begins to loculate. Tube Thoracostomy is Mandatory.

- **What to do if pleural fluid pH is not available?**
  - Use glucose as substitute. Glucose diffuses freely into the pleura. The only reason for pleural glucose to be low is if a massive bacterial load is consuming it faster than the blood can replace it.

- **Glucose is very low, but patients are not septic. What is the cause?**
  - Think Rheumatoid Pleurisy. RA causes defects in the GLUT-1 glucose transporters in the pleura. The transport of sugar is completely blocked. Do not place a chest tube in a Rheumatoid effusion solely based on low glucose. It is a sterile, chronic inflammatory state, not an acute infection.

- **Can pleural fluid LDH help in deciding for tube thoracostomy?**
  - Yes. Pleural fluid Lactate Dehydrogenase (LDH) is an intracellular enzyme. It only reaches the pleural space when cells burst and die. If the LDH is > 1000 IU/L in a parapneumonic effusion, the fluid is complicated regardless of the pH. An LDH > 1000 mandates a chest tube. If a patient has a massive effusion but no fever or signs of infection, a sky-high LDH points toward specific, rapidly dividing cancers. Consider a Tunneled Pleural Catheter (TPC) in cases of malignancy.

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Chapter 07:
Management of Malignant Pleural Effusion (MPE)

7.1 Pathophysiology & Clinical Goal

Malignant pleural effusion (MPE) develops by imbalance of pleural fluid production and the capacity of lymphatic absorption.[1] While initial theories focused primarily on impaired drainage caused by tumor invasion of the parietal pleural stomata or mediastinal lymph nodes, current evidence highlights increased vascular hyperpermeability as a critical driver. Most MPEs arise from hematogenous spread, typically invading the visceral pleura first. [2, 3] The accumulation of fluid is dictated by a complex tumor–host interaction that triggers pro-inflammatory and pro-angiogenic pathways, primarily controlled by transcription factors like NF-κB and STAT3. [3]

Among the various vasoactive mediators involved, vascular endothelial growth factor (VEGF) is the most potent, inducing vasodilation and endothelial fenestration that results in significant plasma extravasation. [1-3] Other tumor-derived molecules, such as osteopontin (OPN), promote vascular leakage independently of VEGF. [1,3] Additionally, mast cells contribute by releasing mediators like tryptase AB1 and IL-1β, which trigger further fluid accumulation and tumor proliferation. [1,2] Host-derived factors, including interleukin (IL)-5, recruit eosinophils and myeloid suppressor cells that enhance vascular permeability and support tumor cell survival. This combination of cytokine-driven hyperpermeability and the physical obstruction of lymphatics by tumor cells ensures the persistent accumulation of protein-rich exudate within the pleural space. [1-3]

7.2 The Diagnostic & Management Algorithm

Step 1: Initial Assessment

When an effusion is suspected to be malignant, the first step is a Transthoracic Ultrasound (TUS) followed by a guided pleural aspiration [5]. Send fluid for biochemistry and cytology [1,6]. The first cytology sample has the highest yield; the second sample adds ~15%. A third is rarely useful [1,12]. In Pakistan, always rule out Tuberculosis [7]. Inconclusive fluid workup requires further investigation [11].

Pleural fluid cytology is a test of tumor shedding. The likelihood of finding malignant cells depends entirely on the cohesive nature of the tumor type [1,8].

Table 7.1: Likelihood of positive cytology

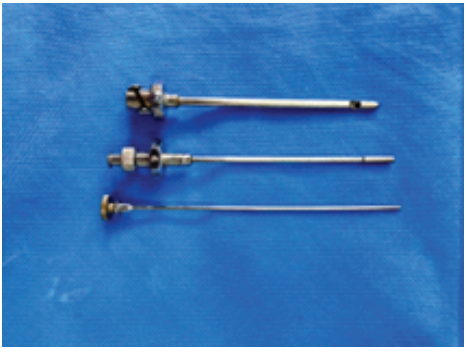
Tumor Type	Cohesion	Shedding	Cytology Yield
Adenocarcinoma (Lung/Breast)	Low: Cells detach easily	High: Floats freely in fluid	High Also order cell block for EGFR, ALK, ROS1

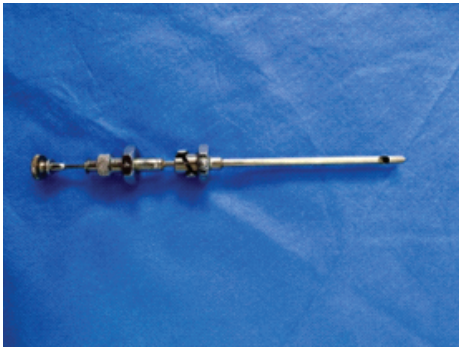
Mesothelioma	High: Forms a solid "rind."	Low: Tightly bound to the wall	Low When suspected gets pleural biopsy
Squamous Cell	Variable: Usually obstructive	Low: Rarely invades pleura directly	Very Low
Lymphoma	Low: Individual cells shed	High: Mimics inflammation	High (if Flow cytometry used: suggests all lymphocytes are monoclonal)

Step 2: Definitive Tissue Diagnosis

If cytology is non-diagnostic after two samples but suspicion remains high:The Abram's needle

PICO 7.1: In patients with undiagnosed exudative effusion (**P**), does IGPB (**I**) provide a higher diagnostic yield for malignancy (**O**) than blind CNB (**C**)?





The Abram's needle

Recommendation: Image guided (US or CT guided) is recommended over blind closed needle biopsy for suspected malignancy.

Strength: Strong | Certainty: High (⊕ ⊕ ⊕ ⊕)

- **Evidence:** IGPB sensitivity reaches 85–90% compared to <40% for CNB, as malignant deposits are often patchy[1,13,14].

PICO 7.2: In patients with non-diagnostic fluid cytology and negative image-guided biopsies (**P**), does Medical Thoracoscopy (**I**) improve the definitive diagnostic yield for malignancy and mesothelioma (**O**) compared to repeated image-guided biopsies (**C**)?

- **Recommendation:** Medical Thoracoscopy is the definitive diagnostic step for undiagnosed exudative effusions.
  Strength: Strong | Certainty: High (⊕ ⊕ ⊕ ⊕)

- **Evidence:** Thoracoscopy has a yield >95% and is essential for **Mesothelioma,** where deep biopsies including underlying fat/muscle are required for pathological diagnosis [17,18,19]. If medical thoracoscopy is unavailable, VATS is the surgical alternative [20].

Step 3: Prognostication (The LENT Score)

Before choosing a permanent intervention, use the **LENT Score** to set realistic goals.

Table 7.1: The LENT score

Variable	Cohesion	Points
L (LDH)	Pleural Fluid LDH < 1500 IU/L	0
E (ECOG)	Pleural Fluid LDH > 1500 IU/L	1
	ECOG 0	0
	ECOG 1	1
N (NLR)	ECOG 2	2
T (Tumor)	ECOG 3–4	3
	Neutrophil-to-Lymphocyte Ratio < 9	0
	Neutrophil-to-Lymphocyte Ratio ≥ 9	1
	Lung Cancer / Mesothelioma	1
	Other Cancers (Breast, Ovary, etc.)	2
	High-Sparing Cancers (Hematological)	0

Risk Stratification and Survival Rates

The total score (0–7) correlates strongly with median survival, allowing for realistic goals-of-care discussions with patients and their families [21,22].

Risk Group	Score	Median Survival	Clinical Implication
Low Risk	0–1	319 Days	Consider definitive pleurodesis or IPC.
Moderate Risk	2–4	130 Days	Preference-based (IPC vs. pleurodesis).
High Risk	5–7	44 Days	Focus on minimally invasive palliation (IPC or large volume thoracentesis- LVT).

While highly accurate, the LENT score should not be used in isolation. Clinical judgment regarding the patient's nutritional status, presence of "trapped lung," and individual preferences must remain central to the decision-making process.

PICO 7.3: In patients with confirmed MPE **(P),** does the application of the LENT Score **(I)** more accurately predict survival and guide selection of palliative interventions **(O)** compared to clinical judgment alone **(C)**?

Recommendation: Calculate the **LENT Score** for all patients with MPE.

Strength: Strong | Certainty: High (⊕ ⊕ ⊕ ⊕)

Evidence: Survival is objectively categorized into **Low Risk** (Score 0-1, ~319 days), **Moderate Risk** (Score 2-4, ~130 days), and **High Risk** (Score 5-7, ~44 days).[21,22]

Step 4: Diagnostic Drainage

Dyspnea in MPE is primarily due to **diaphragmatic failure** rather than lung collapse.[33]

Perform a **Large-Volume Thoracentesis (max 1.5L).** Measure the **Borg Scale** before and 2 hours after. If dyspnea persists despite drainage, do not perform pleurodesis. Investigate other causes like **Pulmonary Embolism** or **Endobronchial Obstruction.**[34]

Step 5: Selecting Definitive Intervention
Success depends on whether the lung is expandable (visceral pleura reaches the chest wall).
Scenario A: The Expandable Lung
PICO 7.4: In patients with an expandable lung requiring pleurodesis **(P)**, does the use of sterile graded talc **(I)** result in higher successful pleurodesis rates **(O)** compared to other agents **(C)**?
Recommendation: Use sterile graded talc for pleurodesis of expandable lung.
Strength: Strong | Certainty: High (⊕⊕⊕⊕)
Evidence: Success rates reach 80–90% [27, 28, 29]. Large-particle talc (>15 microns) must be used to mitigate ARDS risks.[30]

Table 7.2: Comparison of Common Pleurodesis Agents in Clinical Practice.[27,29,30,31]

Agent	Dose	Dose	
Sterile Talc (Slurry)	4g in 50–100mL Normal Saline	70–80% Success. Induces intense mesothelial inflammation.	Most effective agent. Must use graded (large particle) talc to avoid ARDS
Sterile Talc (Poudre)	4g (via Thoracoscopy)	80–90% Success. Uniform distribution under direct vision.	Requires medical thoracoscopy or VATS
Doxycycline	500mg in 50mL Saline	60–70% Success. Chemical irritation.	Widely available in Pakistan; useful if talc is unavailable. Highly painful; requires lidocaine
Bleomycin	60,000 Units (60mg)	50–60% Success. Sclerotic agent.	Expensive; lower success rate than talc. Avoid in younger patients
Povidone-Iodine	20mL of 10% solution	70–80% Success.	Cheap and accessible. Risk of visual loss/neurotoxicity (rare)

- Talc slurry via a small-bore chest tube is the standard. Large-bore tubes are not necessary for pleurodesis. Pleurodesis is painful. Administer systemic analgesia (e.g., NSAIDs) and instil 20–25mL of 1% Lidocaine intrapleurally 15 minutes before the sclerosing agent. Inject the talc slurry through the chest tube. the tube is clamped for 1–2 hours and the patient rotated. The tube can be unclamped after 1–2 hours or left to drain to underwater seal immediately. Remove the chest tube once drainage falls below the baseline (usually <150mL/24h) and the X-ray shows lung expansion.
- Pain is the most common side effect. Aggressive local and systemic analgesia is mandatory. Fever is common within the first 24 hours due to systemic inflammatory response. A rare but severe complication of pleurodesis is ARDS. It is strictly associated with small-particle talc (<15 microns). Our guidelines specify the use of graded, large-particle sterile talc to mitigate this risk. Ensure strict aseptic technique during instillation to avoid secondary empyema.

Scenario B: The Non-Expandable (Trapped) Lung
If the lung is restricted by a mature collagen peel (often from old TB), pleurodesis will fail [35].
PICO 7.5: In symptomatic patients with MPE **(P),** is the use of an IPC **(I)** as effective at relieving dyspnea **(O)** as chemical talc pleurodesis **(C)**?
Recommendation: IPC is the first-line option for trapped lung or patients wishing to minimize hospital stays.
Strength: Strong | Certainty: High (⊕ ⊕ ⊕ ⊕)
Evidence: AMPLE and TIME2 trials confirm IPCs are equivalent to pleurodesis for breathlessness but reduce hospital days.[3,25,26] Low pleural pH (<7.30) or glucose often predicts pleurodesis failure, favoring IPC.[23,24]
PICO 7.6: In patients with MPE and expandable lungs **(P),** does combining IPC with talc administration **(I)** lead to faster pleurodesis **(O)** compared to IPC alone **(C)**?
Recommendation: Hybrid approach (IPC + Pleurodesis) is recommended for patients desiring rapid outpatient pleurodesis.
Strength: Weak | Certainty: Moderate (⊕ ⊕ ⊕ ◯)
Evidence: AMPLE-2 showed higher 5-week pleurodesis rates with the hybrid method.[32]

7.6 MPE Symptomatology
In malignant pleural effusion (MPE), the size of the effusion on an X-ray does not always correlate with the severity of the patient's dyspnea. Treating the image instead of the patient leads to unnecessary procedures that fail to provide palliative relief. The primary cause of dyspnea is not the collapse of the lung itself, but the failure of the hemidiaphragm.[33] When the weight of a massive effusion becomes too great, it flattens or inverts the diaphragm. The diaphragm's length-tension relationship is destroyed. It can no longer contract effectively, leaving the patient feeling suffocated even if their oxygen saturation is normal. Before performing a definitive procedure like Talc Pleurodesis or an Indwelling Pleural Catheter (IPC), you must perform a Diagnostic Drainage Trial. Perform a Large-Volume Therapeutic Thoracentesis (maximum 1.5L). Measure the patient's breathlessness (Borg Scale) before and 2 hours after the tap. If dyspnea is resolved, the fluid is the cause. Proceed with a definitive pleural procedure (IPC/Talc). If dyspnea is not resolved, do not perform a pleurodesis. You will

subject a dying patient to a painful procedure with zero benefit. If dyspnea doesn't settle after therapeutic pleural aspiration, look for the causes [34]:

1. **Pulmonary Embolism (PE):** Cancer is the ultimate pro-thrombotic state. A sudden worsening of dyspnea in an MPE patient is a PE until proven otherwise.
2. **Lymphangitic Carcinomatosis:** The tumor has infiltrated the microscopic lymphatics of the lung, making the lung tissue stiff and incapable of easy expansion.
3. **Malignant Pericardial Effusion:** The cancer may be attacking the heart, causing cardiac tamponade.
4. **Endobronchial Obstruction:** A central tumor may be plugging the airway. No amount of pleural drainage will re-inflate a lung with an obstructed bronchus.

7.7 The trapped lung vs lung entrapment

Understanding the distinction between trapped lung and lung entrapment is essential for proper pleural management.[31] Trapped Lung is a chronic, mechanical condition resulting from remote injuries like old tuberculosis or surgery, which heal into avascular collagen peel. This mature scar prevents lung expansion, creating a vacuum that pulls in a transudative effusion. During drainage, these patients experience a rapid drop in pleural pressure (> 14.5 cmH2O per liter), leading to sharp, sucking chest pain early in the procedure as the vacuum pulls on the chest wall and mediastinum. On ultrasound, this is confirmed by a thickened visceral pleura that lacks the normal pleural sliding. Management must avoid aggressive suction or pleurodesis, which are ineffective; instead, it focuses on symptom relief via an indwelling pleural catheter (IPC) or surgical decortication to remove the fibrous peel.

Conversely, Lung Entrapment represents active inflammation, such as malignancy or empyema, where the lung is restricted by active tumor growth or fibrin. In this state, the resulting fluid is exudate. Unlike the trapped lung, pleural pressures remain neutral or high initially and only drop sharply at the very end of drainage. This is a medical emergency requiring aggressive treatment of the underlying cause—such as chemotherapy or intrapleural enzymes—to dissolve the restriction before it transitions into permanent, irreversible fibrosis.[35]

A critical diagnostic pitfall is the Pneumothorax Ex Vacuo,.[36] which often appears on X-ray after draining a trapped lung. This air is not caused by an accidental lung puncture but by the intense vacuum pulling gases out of the surrounding tissues or through the needle track to fill the rigid void. It is characterized by a thick, lobulated lung margin and a perfectly horizontal air-fluid level. Clinicians must recognize this as a stable mechanical finding and not insert a chest tube. Applying suction to a trapped lung will never expand the lung and will only subject the patient to unnecessary pain.

7.3 Clinical Pitfalls to Avoid

1. Pneumothorax Ex Vacuo: Air on X-ray following drainage of a trapped lung is a mechanical vacuum effect. Do not insert a chest tube; it will not expand the lung and may cause harm.[31,35,36]
2. Paramalignant Effusion: Rule out pneumonia, tuberculosis, etc before labeling an effusion malignant based solely on the presence of cancer elsewhere.[34]

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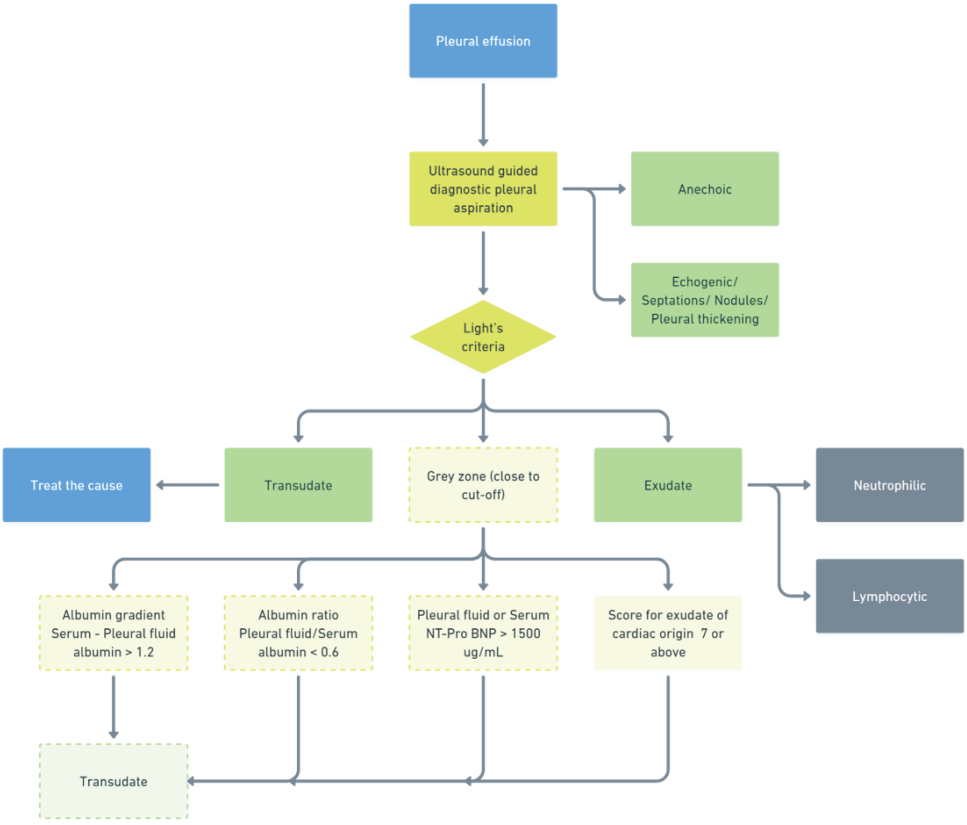
Section 08:
Algorithms

8.1 Differentiating exudate from transudate effusion

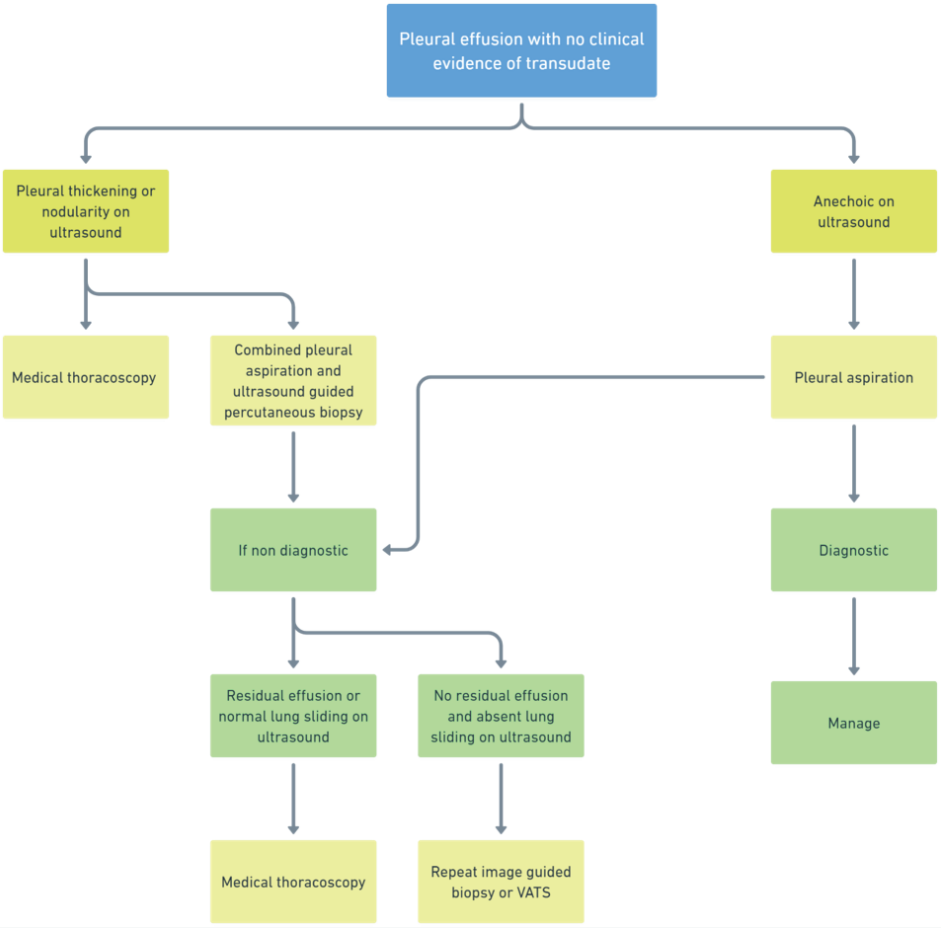


core for exudate of cardiac origin (Adopted from Porcel et al.)

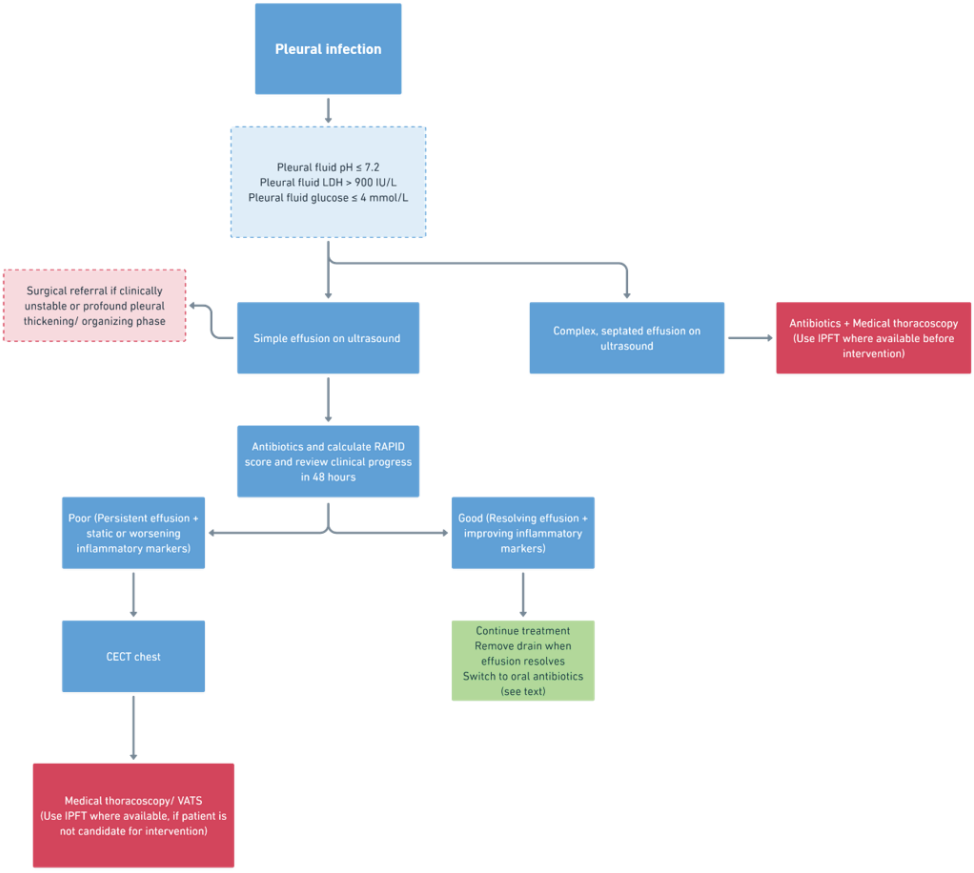
Risk Group	Score
Age ≥ 75 years	3
Albumin gradient > 1.2 g/dLa	3
PF LDH < 250 U/Lb	2
Bilateral pleural effusion on chest X-ray	2
Protein gradient > 2.5 g/dLc	1

a = serum albumin minus PF (pleural fluid) albumin
b = this figure represents two-thirds of the upper limit of normal for serum LDH in the laboratory the score was derived in
c = serum protein minus PF (pleural fluid) protein

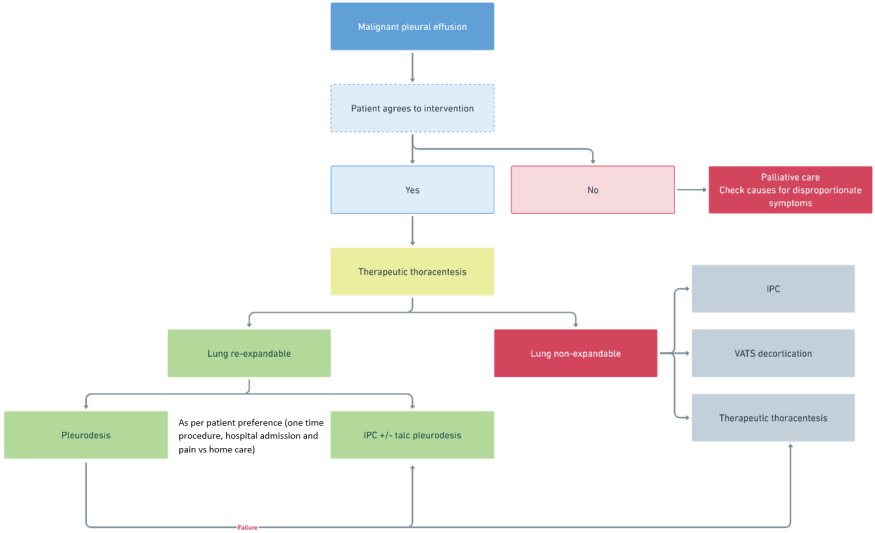
8.2 Pleural effusion with no clinical evidence of transudate



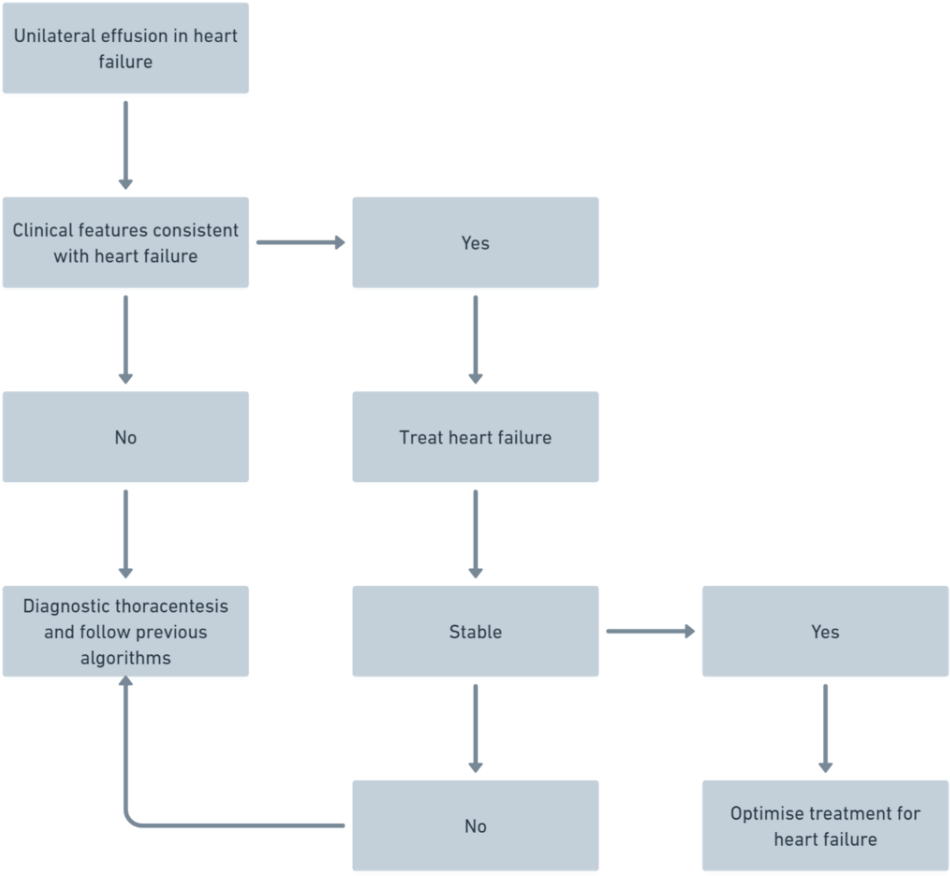
8.3 Pleural infection



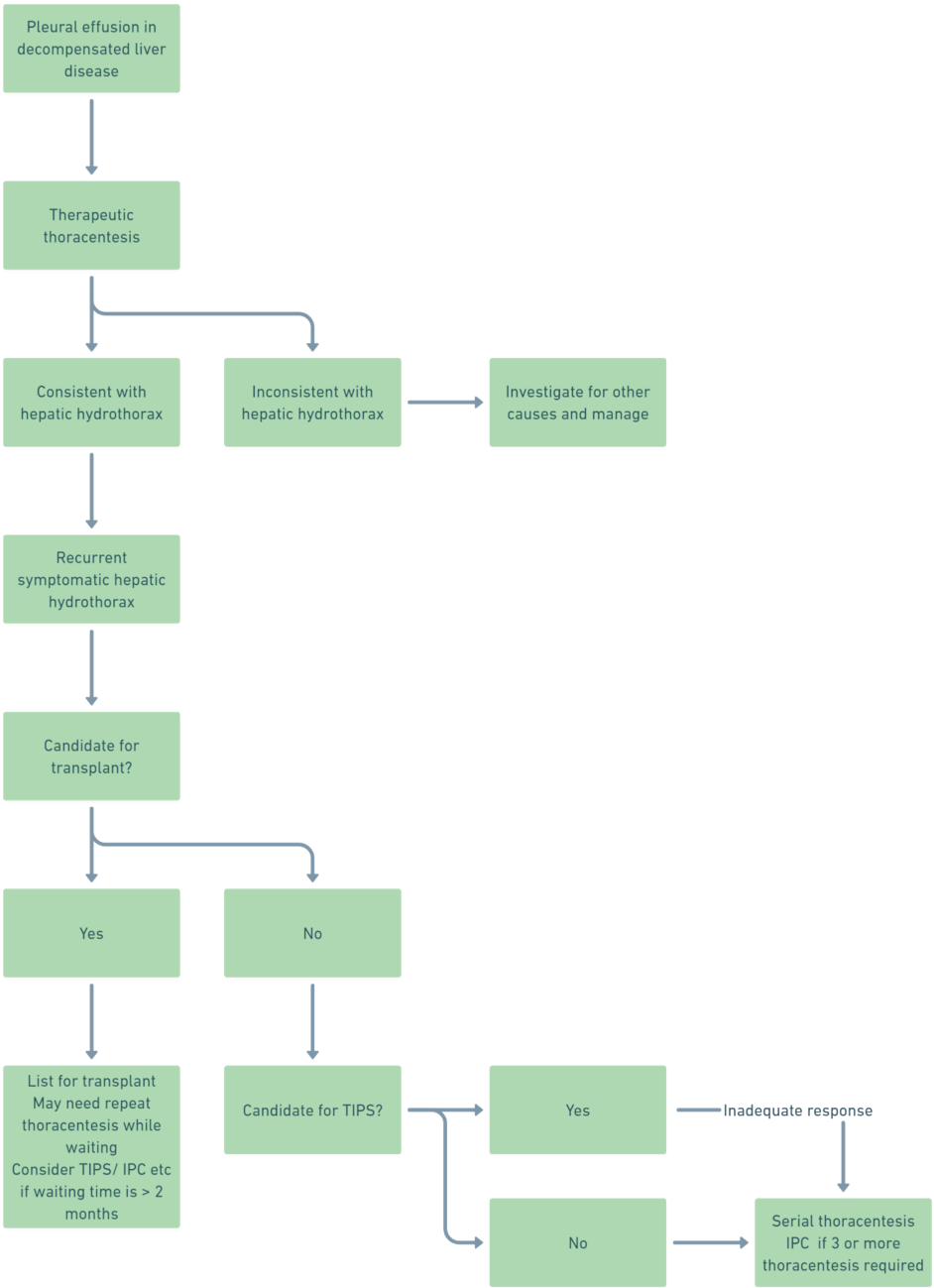
8.4 Malignant pleural effusion



8.5 Unilateral effusion in heart failure



8.6 Hepatic hydrothorax



8.7 Pleural effusion in End stage renal failure