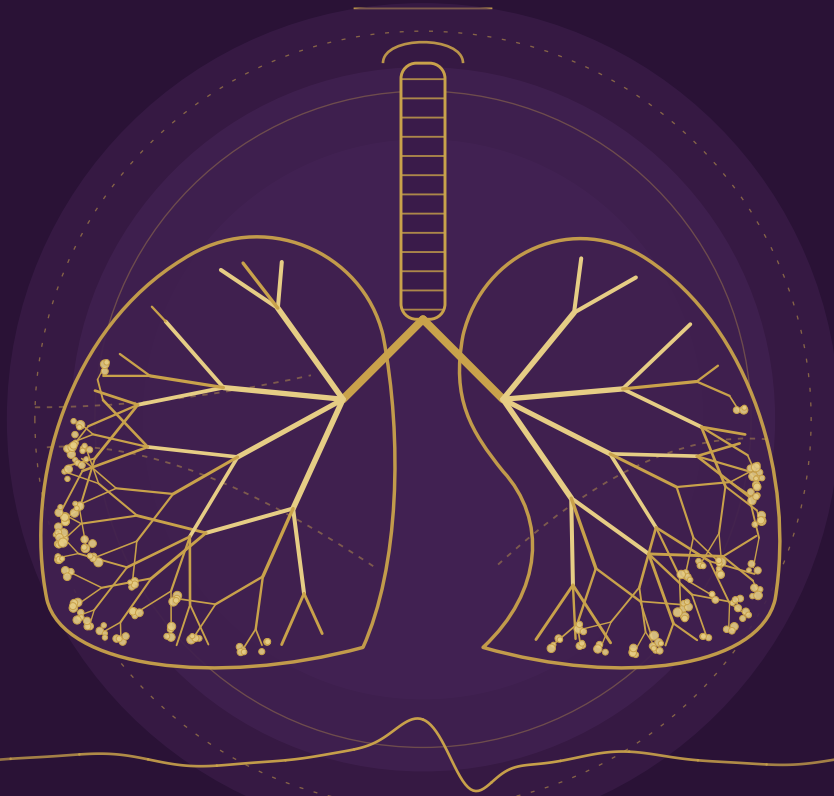




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EXIT EXAMINATION

DNB Respiratory Medicine

Solved Previous-Year Questions

VOLUME 1

Basic Science, Clinical Evaluation and Interventional Pulmonology

Part 1 · Basic Science, Physiology, Acid-Base and Research Methods

Part 2 · Clinical Evaluation, Imaging and Lung Function

Part 3 · Interventional Pulmonology and Thoracic Surgery

WRITTEN & REVIEWED BY

Dr. Anshuman Bedi

DNB Respiratory Medicine

Dr. Naresh Kumar

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Based on Murray & Nadel's Textbook of Respiratory Medicine, 7th ed. · current guidelines

UPDATED TILL OCTOBER 2026

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Answers are written from Murray & Nadel's Textbook of Respiratory Medicine (7th ed.), with printed page numbers cited in each answer, and from current guidelines found on official society and journal sites, cited [W#] and listed in the Web-Sourced Facts Register.

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HOW TO USE

Each answer groups every year the question was asked and is written to the most demanding version. Badges show how often a topic was asked. Each answer ends with one Sources block: the Murray & Nadel 7e chapter and printed pages used, and the guideline/web sources (also listed in the register at the end). Section B lists this volume question by question; C lists high-yield topics.

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PART 1**Basic Science, Physiology, Acid–Base and Research Methods****1. Blood supply of the lung – pulmonary and bronchial circulations****ASKED 2*** · Intermediate answer

Asked in: Jun 2021 P-I Q7(a) [4] · Oct 2023 P-I Q2(b) [5]

Q: The bronchial circulation. [4]

Q: Blood supply of lung. [5]

Definition

- Lung has a **dual blood supply**: the pulmonary (functional, gas-exchange) circulation and the bronchial (systemic, nutritive) circulation.
- The bronchial circulation is the systemic arterial supply to the lung's own structural tissues.

Bronchial circulation**Territory supplied**

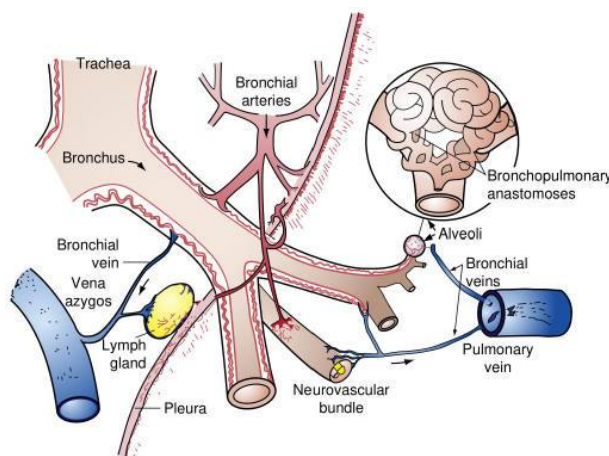
- The bronchial circulation supplies the trachea (and esophagus), mainstem bronchi, and pulmonary vessels entering the lung.
- It also supplies the visceral pleura in humans, which is thick.
- Scar tissue and tumours larger than 1 mm in diameter receive their blood through it.

Quantity and anatomy

- Flow is **0.5–1.5% of cardiac output**, mostly to the large airways.
- Bronchial arteries branch into capillary networks in three places:
 - the lamina propria
 - the submucosa
 - the region external to the bronchial cartilage
- A capillary network also lies in the lamina propria of neighbouring pulmonary arteries.

Venous drainage

- Venous blood from the trachea and large airways enters bronchial venules.
- The venules converge into bronchial veins, which drain into the **azygos or hemiazygos veins**.
- Most bronchial blood therefore returns to the right heart.
- Deeper in the lung, bronchial blood passes through short anastomotic vessels into the pulmonary venules.
- This blood reaches the left heart and contributes to **venous admixture** (physiological shunt).



eFigure 1.1 — Murray & Nadel 7e, pr.23.e2. Schematic illustration of the components of the bronchial circulation. Flow from capillary beds supplying large airways and lymph glands drains to bronchial veins and into the azygos vein and superior vena cava. Intrapulmonary flow drains into the pulmonary circulation at the level of the alveoli (bronchopulmonary anastomoses) or pulmonary veins (bronchopulmonary veins). (From Deffebach ME, Charan NB, Lakshminarayan

Functional importance

- The bronchial circulation has **enormous growth potential**. The pulmonary circulation is unresponsive to growth signals after childhood.
- It is therefore the main source of new vessels for repair after lung injury.
- Flow is greatly increased in long-standing inflammatory and proliferative disease, such as bronchiectasis and carcinoma.
- These hypertrophied vessels are the usual source of haemoptysis in such disease.

Pulmonary circulation

Anatomy

- The pulmonary artery enters each lung at the hilum, in a loose connective tissue sheath next to the main bronchus.
- It runs beside and branches with each airway generation, down to the **respiratory bronchiole**.
- This arrangement links perfusion to ventilation.
- Pulmonary veins follow "Miller's dictum": inside the lung they lie as far from the airways as possible.
- Peripherally, arteries enter the terminal respiratory unit and veins lie in the surrounding connective tissue envelope.
- Each small muscular artery supplies a specific volume of respiratory tissue. Each vein drains parts of several such zones.

Table 1.3 Quantitative Data on Intrapulmonary Blood Vessels in Humans

Vessel Class (With Diameter)	Volume (mL)	Surface Area (m ²)	Reference
Arteries (>500 µm)	68	0.4	69
Arterioles (13–500 µm)	18	1.0	69
Capillaries (10 µm)	60–200	50–70	70
Venules (13–500 µm)	13	1.2	71
Veins (>500 µm)	58	0.1	71

Table 1.3 — Murray & Nadel 7e, pr.9. Table 1.3 Quantitative Data on Intrapulmonary Blood Vessels in Humans

Table 1: Quantitative data on human intrapulmonary vessels

Vessel (diameter)	Volume (mL)	Surface area (m ²)
Arteries (>500 µm)	68	0.4
Arterioles (13–500 µm)	18	1.0
Capillaries (10 µm)	60–200	50–70
Venules (13–500 µm)	13	1.2
Veins (>500 µm)	58	0.1

- Most blood volume lies in the larger vessels, but nearly all the surface area lies in the smaller vessels.
- Capillary surface area is about 20 times that of all other vessels, which maximises the area for gas exchange.

Pressures and resistance

- Lung height at FRC is about **24 cm**, so intravascular pressure varies by about 24 cm H₂O from top to bottom.

- Pulmonary arterial pressure at mid-lung is about 20 cm H₂O (15 mmHg). It is about 12 cm H₂O near the apex and about 36 cm H₂O near the base.
- Pulmonary venous (left atrial) pressure at mid-lung is about 8 cm H₂O. It is −4 cm H₂O at the apex and +20 cm H₂O at the base.
- Blood volume is greater at the base, because higher luminal pressure distends the vessels.
- This distension also lowers the basal vessels' contribution to total pulmonary vascular resistance.
- The pulmonary circulation is a **low-resistance circuit** from birth through adulthood.
- Alveolar capillaries hold **35–45%** of total pulmonary vascular resistance at FRC.
- In the systemic circulation, the major drop in resistance is across the arterioles.
- Smooth muscle surrounds the pulmonary vessels, so vasoactivity regulates local blood flow in relation to ventilation.

Comparison

Table 2: Bronchial versus pulmonary circulation

Feature	Bronchial	Pulmonary
Role	Nutritive, systemic	Gas exchange
Share of cardiac output	0.5–1.5%	Whole right ventricular output
Supplies	Trachea, bronchi, large pulmonary vessels, visceral pleura, tumours and scar >1 mm	Respiratory units (alveoli)
Venous return	Azygos/hemiazygos to right heart; part to pulmonary veins	Pulmonary veins to left atrium
Growth potential	Large, forms new vessels after injury	Unresponsive to growth signals after childhood
Pressure	Systemic	Low

Clinical correlates

- Bronchial arteries dilate and proliferate in bronchiectasis and carcinoma.
- Part of bronchial venous drainage enters the left heart, adding to venous admixture.
- Distal to pulmonary arterial obstruction, the bronchial supply helps maintain the tissue.

PEARLS

- The bronchial circulation carries about **0.5–1.5% of cardiac output**.
- Bronchial veins drain to the azygos or hemiazygos veins, so most bronchial blood returns to the right heart.
- Bronchopulmonary anastomoses add to **venous admixture**.
- The bronchial circulation is the main source of new vessels after lung injury. It also supplies tumours and scars larger than 1 mm.
- Pulmonary arteries accompany the airways down to the respiratory bronchiole. Veins lie away from the airways.
- Pulmonary arterial pressure at mid-lung is about 15 mmHg. It varies by about 24 cm H₂O from apex to base.
- **35–45%** of pulmonary vascular resistance lies in the alveolar capillaries at FRC.
- Capillary surface area is **50–70 m²**.

Sources

- Textbook: Murray & Nadel 7e — Ch 1 Anatomy, §Airways / Pulmonary Circulation — pp. 8–9
- Textbook: Murray & Nadel 7e — Ch 1 Anatomy, §Humans And Mice — pp. 23.e2

2. Bronchopulmonary segments of the human lung

ASKED 1* · Intermediate answer

Asked in: Jun 2025 P-I Q1(a) [5]

Q: Bronchopulmonary segments of human lung. [5]

Bronchopulmonary segments of the human lung

NOT IN TEXTBOOK

Textbook pages searched for "bronchopulmonary segments" and "segmental bronchi anatomy". The pages supplied (Ch 26, bronchoscopy) only mention that the segmental bronchi of the five lobes are inspected. They give no segment names or anatomy. The answer below is therefore web-sourced.

Definition

- A **bronchopulmonary segment** is the largest subdivision of a lobe. It is supplied by its own segmental (tertiary) bronchus and its own branch of the pulmonary artery.
- It is a discrete anatomical and surgical unit of lung. Connective tissue septa, the intersegmental septa, separate it from its neighbours.
- Each segment is named after the segmental bronchus that supplies it.

Anatomical features

- Each segment is **pyramidal**. Its apex points to the hilum and its base to the pleural surface.
- The segmental bronchus and pulmonary artery lie together at the centre of the segment.
- The pulmonary veins run in the intersegmental septa and drain adjacent segments.
- The segment has its own lymphatic drainage.
- The connective tissue septa limit collateral air drift between segments, but only partly.
- Segmental topography is constant.
- Each segmental bronchus gives rise to two or three subsegmental bronchi.
- The bronchial tree is as follows:
 - Trachea → main bronchi → lobar bronchi (**3 right, 2 left**) → segmental bronchi → subsegmental bronchi.
 - Segmental bronchi are generation 4. They have cartilage in their walls.

Number of segments

- The right lung has **10** segments.
- The left lung has **8** segments (8–10 in some descriptions, depending on how segments are combined).
- The left lung has two fewer for two reasons:
 - The apical and posterior bronchi share a common stem, giving the **apicoposterior** segment.
 - The medial basal bronchus is usually absent as a separate branch, giving the **anteromedial basal** segment.

Table 1: Bronchopulmonary segments of the right and left lung

Lobe	Right lung	Left lung
Upper	Apical (1), posterior (2), anterior (3)	Apicoposterior (1+2), anterior (3)
Middle / lingula	Middle lobe: lateral (4), medial (5)	Lingula: superior (4), inferior (5)
Lower	Superior (6), medial basal (7), anterior basal (8), lateral basal (9), posterior basal (10)	Superior (6), anteromedial basal (7+8), lateral basal (9), posterior basal (10)
Total	10	8

- The **lingula** is the left upper lobe's equivalent of the right middle lobe.
- The right middle lobe lies between the horizontal and oblique fissures.
- The left lung has only an oblique fissure.

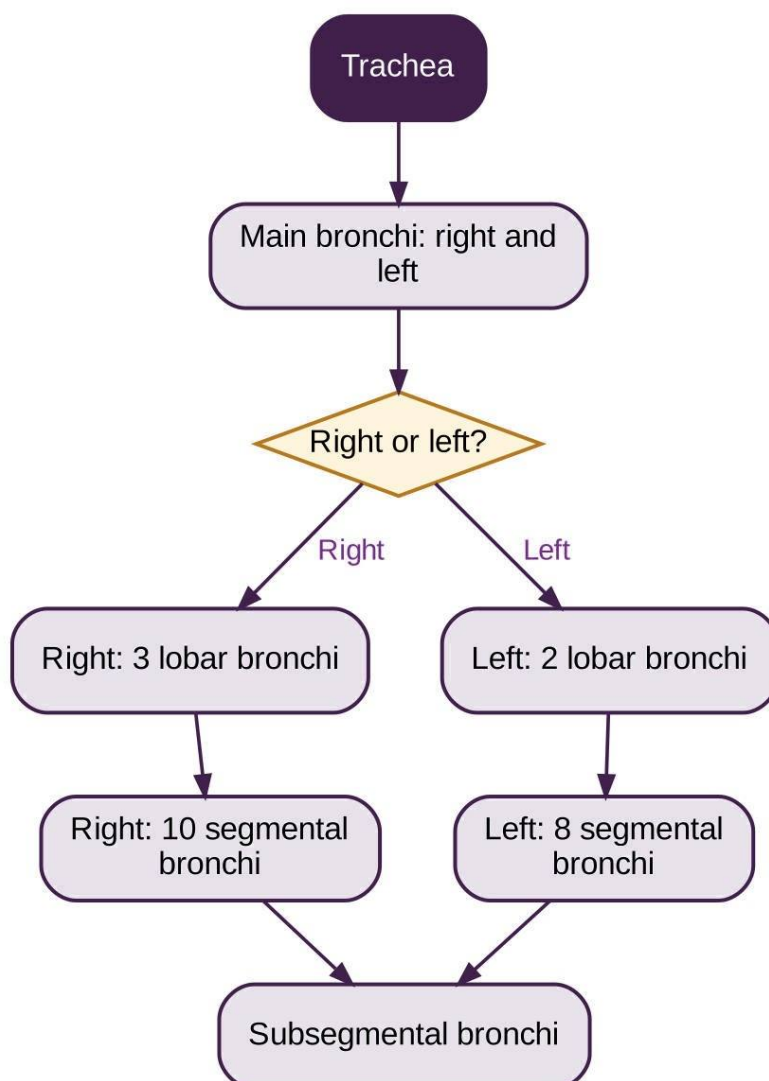
Bronchoscopic relevance

- The right upper lobe bronchus arises about 2 cm from the carina.
- The right main bronchus continues as the **bronchus intermedius**. This gives off the middle lobe bronchus, which divides into medial and lateral branches, and then the lower lobe bronchus.
- The left upper lobe bronchus arises about 5 cm from the carina. It has a superior division (apicoposterior, anterior) and a lingular division (superior, inferior).
- Standard fiberoptic bronchoscopy examines the segmental bronchi of all five lobes systematically.
- Variants occur, such as a tracheal bronchus. This is an apical right upper lobe bronchus arising from the trachea.

Clinical importance

- **Surgery:** segmentectomy removes one segment without disturbing adjacent segments, preserving lung function.
- **Localisation:** radiological and bronchoscopic lesions are described by segment (for example RB6, the superior segment of the right lower lobe).
- **Postural drainage:** physiotherapy positions are based on segmental orientation.
- **Aspiration:** the right main bronchus is wider, shorter and more vertical, so aspirated material goes there more often.
- **Infection and collapse:** disease is often segmental, for example middle lobe or lingular collapse.
- **Lymph nodes:** hilar (station 10) nodes lie next to the hilar vessels and main bronchus. These are N1 nodes.

Flowchart



PEARLS

- There are **10 right** and **8 left** bronchopulmonary segments.
- The left lung lacks a separate apical and posterior pair, and a medial basal segment. These become the apicoposterior and anteromedial basal segments.
- The lingula (superior and inferior segments) belongs to the left upper lobe and corresponds to the right middle lobe.
- The right middle lobe has two segments: lateral and medial.
- The segmental bronchus and artery run centrally. Veins run in the intersegmental septa.
- A segment is the unit of segmentectomy. It is pyramidal, with its apex at the hilum.
- Segmental bronchi are generation 4. They are named from the 1949 London nomenclature, revised in 1960.
- The right upper lobe bronchus arises about 2 cm from the carina and the left about 5 cm.

Sources

- Textbook: Murray & Nadel 7e — Ch 26 Diagnostic Bronchoscopy: Basic Techniques, §Procedure › Approach — p. 370
- [w1] NCBI StatPearls — Anatomy, Thorax, Lungs — <https://www.ncbi.nlm.nih.gov/sites/books/NBK470197/>
- [w2] NCBI StatPearls — Anatomy, Thorax, Bronchial — <https://www.ncbi.nlm.nih.gov/sites/books/NBK537353/>
- [w3] PMC — Anatomical considerations in bronchoscopy (J Thorac Dis) — <https://pmc.ncbi.nlm.nih.gov/articles/PMC5696545/>
- [w4] Diseases of the Chest — Nomenclature of the Bronchopulmonary Segments and Their Blood Supply (1960 revision) — [https://journal.chestnet.org/article/S0096-0217\(16\)31355-3/abstract](https://journal.chestnet.org/article/S0096-0217(16)31355-3/abstract)
- [w5] Thoracic Surgery Clinics — Lobes, Fissures, and Bronchopulmonary Segments — <https://www.sciencedirect.com/science/article/abs/pii/S1547412706001125>

3. Collateral ventilation

ASKED 1* · Intermediate answer

Asked in: Dec 2025 P-I Q3(b) [5]

Q: Collateral ventilation. [5]

Collateral ventilation

Definition

- **Collateral ventilation (CV)** is ventilation of alveoli through channels that bypass the normal anatomical airway.
- Gas reaches a lung unit through neighbouring alveoli or lobules instead of its own feeding bronchus.
- It is clinically important in bronchoscopic lung volume reduction (BLVR). A target lobe that still receives gas through collateral channels will not collapse after its airway is occluded.

Anatomical pathways

- **Pores of Kohn** are the interalveolar connections. They keep pressures similar across adjacent alveoli.
- The pores of Kohn are found in both human and mouse lungs.
- In humans the number of pores **increases with age**. In the mouse it does not change with age.
- The other classical channels are:
 - **Canals of Lambert** (bronchiole–alveolar).
 - **Channels of Martin** (interbronchiolar).
 - **Interlobar channels** through incomplete fissures.
- Humans have about 500 million alveoli. Mice have about 15 million.
- Interlobar CV depends on **fissure integrity**. A complete fissure means low CV between lobes.

Physiological significance

- **Beneficial effects:**
 - It maintains ventilation behind an obstructed airway.

- It limits atelectasis.
- It equalises pressures between units.
- **Harmful effects in emphysema:**
 - Destroyed septa and enlarged pores increase CV.
 - Air is trapped through leak pathways.
 - CV makes the target lobe stay inflated after valve placement.
- Collateral resistance is high in normal human lungs. It falls in emphysema, so CV is more prominent.

Relevance to bronchoscopic lung volume reduction

- **Endobronchial valves** (Zephyr, IBV) are one-way valves. They let air leave a segment but block re-entry, so the diseased lobe deflates.
- The ability to deflate the lung, and so the benefit, depends on **absence of collateral ventilation** to the target segment.
- If CV is present, air enters the target lobe through the collateral channels. The lobe then does not collapse and the valve fails.
- Pneumothorax after valve placement reflects effective lobar collapse. It was seen only in the valve group (26.5%, all in the first 45 days).

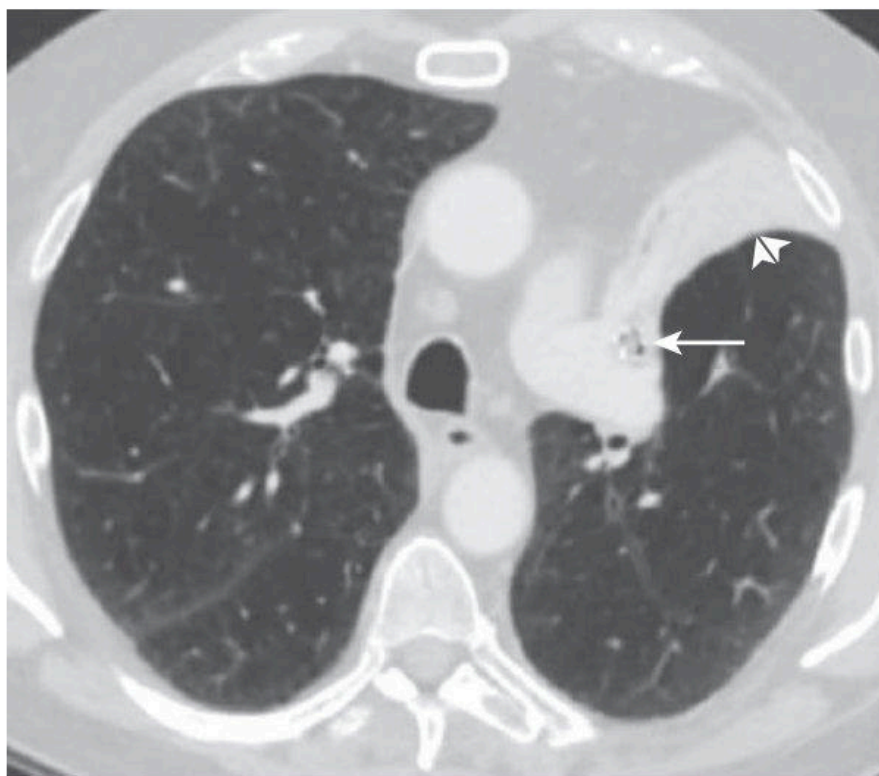


Figure 28.5 — Murray & Nadel 7e, pr.396. Complete left upper lobe collapse after endobronchial valve placement. The valve was placed in a patient with COPD for lung volume reduction. Axial chest computed tomography displayed in lung windows shows complete collapse of the left upper lobe (arrowheads) after placement of left upper lobe endobronchial valves (arrow). (Courtesy Steve Tseng, DO, Pulmonary and Critical Care Medicine, University of Arizona College)

Assessment of collateral ventilation

- **Chartis system (Pulmonx)** is a bronchoscopic balloon catheter system.
 - The balloon is inflated to block the target airway.
 - Flow, resistance and pressure are measured beyond the balloon.
 - The flow falls gradually to zero if there is no CV (CV negative).
 - It predicts clinical improvement after lobar occlusion with an effectiveness of about 75%.
 - All patients in LIBERATE were shown to have little or no CV with Chartis before randomisation.
- **HRCT fissure integrity** is a non-invasive assessment. The EMPROVE trial used chest CT to assess fissure integrity.
- Quantitative CT analysis and V/Q scan data help to choose the target lobe.

Techniques and their dependence on collateral ventilation

Table 1: Bronchoscopic lung volume reduction techniques and collateral ventilation

Technique	Mechanism	Reversible?	Needs absent CV?
Endobronchial valves (Zephyr, IBV)	One-way valve, lobar deflation	Yes	Yes
Lung volume-reduction coils (nitinol)	Fold and retract parenchyma	No	No
Biologic sealant (AeriSeal)	Polymeric foam collapses emphysematous lung	No	No, because the sealant may block collateral sites
Thermal vapor ablation	Steam causes inflammation, fibrosis, atelectasis	No	No

- Coils were not FDA approved. In RENEW the benefit was modest, with a higher rate of major complications.
- The ASPIRE sealant trial was terminated for financial reasons.
- **LIBERATE:** the primary outcome was at least a 15% improvement in post-bronchodilator FEV1, achieved in **47.7%** with valves versus **16.8%** of controls.
- Zephyr valves were FDA approved in June 2018 for heterogeneous emphysema with minimal collateral ventilation. IBV was approved in December 2018.

Management and clinical use

GUIDELINE

GOLD — Global Strategy for Diagnosis, Management and Prevention of COPD — 2026 report. Bronchoscopic lung volume reduction is graded Evidence A for patients without interlobar collateral ventilation (confirmed via PubMed-indexed 2026 review).

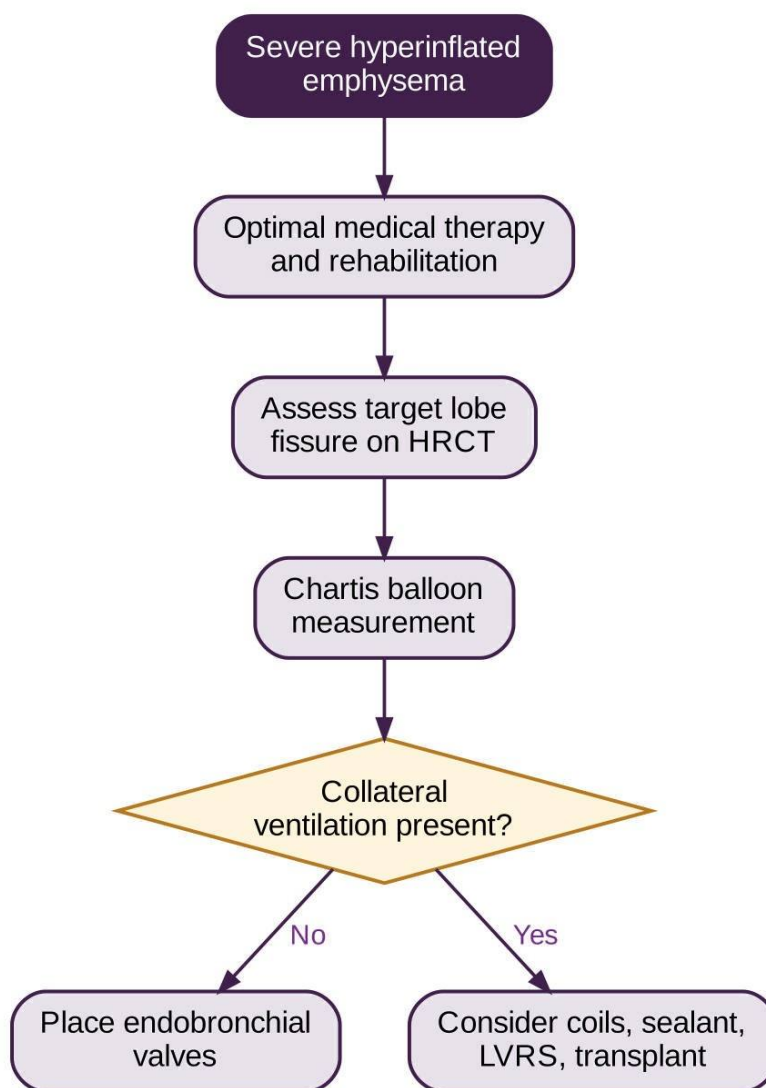
- **Patient selection:**
 - Severe emphysema with hyperinflation.
 - Symptomatic despite optimal medical therapy.
 - **Absent interlobar CV** in the target lobe (Chartis or CT fissure integrity).
- In patients without CV, valves improve FEV1, exercise capacity and quality of life.
- Pneumothorax is the commonest serious complication (about 26%). It indicates effective lobar occlusion.
- Patients with CV positive lobes are not candidates for valves. Options for them are:
 - Coils, sealant or vapor ablation, which do not depend on CV (limited availability and data).
 - Lung volume-reduction surgery or transplantation in suitable patients.
 - Research is exploring conversion of CV-positive patients to CV-negative.

Other uses of valves

- IBV valves are used for **persistent air leak** after lobectomy or segmentectomy.
 - Multiple valves are often needed because many patients have some collateral ventilation.
 - They are removed after 6 weeks.

Flowchart

Flowchart 1: Selecting emphysema patients for endobronchial valves



PEARLS

- **Pores of Kohn** are the main interalveolar collateral channels. Their number increases with age in humans.
- Valves work only if there is **no collateral ventilation** to the target lobe.
- **Chartis** measures CV bronchoscopically (about 75% predictive). HRCT fissure integrity is the non-invasive alternative.
- LIBERATE: $\geq 15\%$ FEV1 gain in **47.7%** with valves versus **16.8%** of controls.
- Pneumothorax (**26.5%**, within 45 days) is the most common serious adverse event.
- Coils, sealant and thermal vapor ablation are **irreversible** but do not depend on CV. Valves are **reversible**.
- Persistent air-leak valves are usually removed after **6 weeks**.

Sources

- Textbook: Murray & Nadel 7e — Ch 1 Anatomy, §Humans And Mice — pp. 22
- Textbook: Murray & Nadel 7e — Ch 28 Therapeutic Bronchoscopy: Interventional Techniques, §Managing Other Indications — pp. 396–398
- [w1] Diagnostics (Basel) / PubMed-indexed review — Endobronchial Valves for BLVR in Severe Emphysema — 2026 — <https://pubmed.ncbi.nlm.nih.gov/42279507/>
- [w2] PubMed — Bronchoscopic and Surgical Interventions for Patients With COPD: A State-of-the-Art Review — <https://pubmed.ncbi.nlm.nih.gov/42606276/>

4. Congenital agenesis of the lung

ASKED 1* · Intermediate answer

Asked in: Oct 2023 P-I Q3(a) [5]

Q: Congenital agenesis of lung. [5]

Congenital agenesis of the lung

Definition

- Congenital agenesis is **complete absence of one or both lungs**. Bronchus, parenchyma and pulmonary vasculature are all missing.
- It is the extreme end of the **agenesis–aplasia–hypoplasia complex**, which is failure of lung bud development.
- It is rare. Unilateral agenesis has an incidence of about **1:15,000**, affects both sides and both sexes equally, and is compatible with survival.
- Bilateral agenesis is incompatible with life.

Embryology and pathogenesis

- Trachea and paired lung buds appear at about **4 postconceptual weeks**, arising from the ventral foregut endoderm.
- Lung specification needs canonical **Wnt2/Wnt2b** → **β-catenin** signalling, which maintains **Nkx2-1**, the earliest marker of respiratory fate.
- After specification, **FGF10** signalling is essential for budding.
 - Loss of Fgf10 (mouse) gives lung agenesis with the trachea preserved.
- Retinoic acid controls budding by regulating WNT, TGF-β and FGF10 signalling.
- Human genes tied to lung agenesis or severe hypoplasia:
 - **RSPO2** (WNT pathway)
 - **STRA6** (retinoic acid pathway)
 - **FGF10**
 - **TBX4**
- A vascular hypothesis proposes abnormal blood flow in the dorsal aortic arch at the fourth week.
- Lung hypoplasia is a related but separate entity with secondary causes:
 - congenital diaphragmatic hernia (1 in 3500 live births)
 - skeletal dysplasia
 - pleural effusion
 - oligohydramnios from premature rupture of membranes or fetal bladder outlet obstruction

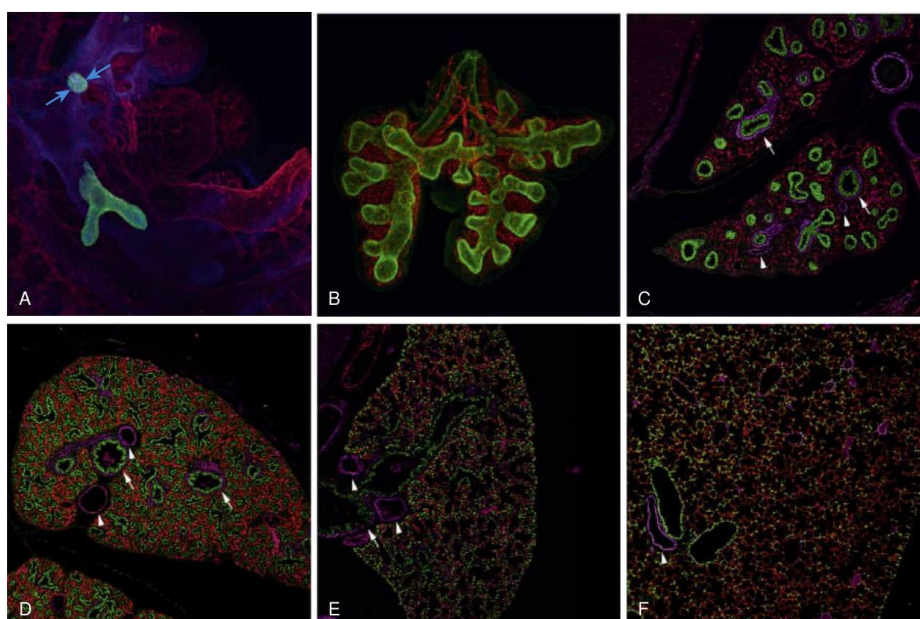


Figure 2.2 — Murray & Nadel 7e, pr.26. Morphology of the stages of lung development. Mouse lungs from the indicated developmental stages were stained with an antibody against Nkx2-1 to identify epithelial cells in the respiratory lineage (green), an antibody against endomucin to identify vascular cells (red), and an antibody against α -smooth muscle actin to identify smooth muscle cells (magenta). An antibody against E-cadherin identifies the foregut endod

Classification

Table 1: Schneider–Boyden classification of pulmonary underdevelopment

Type	Term	Carina/bronchus	Lung tissue and vessels
1	Agenesis	Absent	Absent
2	Aplasia	Rudimentary blind-ending bronchus	No parenchyma
3	Hypoplasia	Variable bronchial tree	Reduced parenchyma, variable vessels

- Boyden's groups 1–3 correspond to these three types.
- Unilateral cases may be right- or left-sided. One review reports the left side in about 70%.

Clinical features

- Presentation varies widely.
- **Neonate:** respiratory distress needing resuscitation and support.
- **Infant/child:** recurrent lower respiratory tract infections and breathlessness.
- Some patients are asymptomatic and are found incidentally. Survival to adulthood is reported, the oldest case being 72 years.
- Rarer complications are pneumothorax, pulmonary hypertension and haemoptysis.
- Associated congenital anomalies are common, especially cardiovascular, skeletal and gastrointestinal.
- Signs on the affected side:
 - flattened hemithorax with narrow intercostal spaces
 - tracheal and mediastinal shift towards the affected side
 - absent breath sounds
 - compensatory hyperinflation of the other lung

Investigations

Table 2: Investigations in lung agenesis

Test	Finding	Meaning
Chest X-ray	Opaque hemithorax, mediastinal shift, raised diaphragm, contralateral hyperinflation	Volume loss, not effusion
CT/HRCT chest	Absent lung, absent or blind bronchus, contralateral lung herniating across midline	Confirms the diagnosis
CT pulmonary angiography	Absent ipsilateral pulmonary artery	Shows the vascular status
Bronchoscopy	Absent carinal orifice or blind-ending main bronchus	Separates agenesis from aplasia
Echocardiography	Associated cardiac defects, pulmonary hypertension	Looks for associated anomalies
Antenatal ultrasound/MRI	Absent lung, mediastinal shift	Early detection

- Bronchography and angiography are older confirmatory tests.
- Look for associated anomalies in other systems.

Differential diagnosis

- Lung or lobar collapse, for example endobronchial obstruction
- Pneumonectomy or destroyed lung
- Thickened pleura or fibrothorax
- Large pleural effusion (the mediastinum shifts away, not towards)
- Unilateral absence of the pulmonary artery
- Congenital pulmonary airway malformation or sequestration

Management

GUIDELINE

No dedicated society guideline exists for this rare anomaly. The approach below follows published reviews: Respiratory Medicine pictorial review of developmental lung anomalies in adults, and the Schneider–Boyden reviews on PubMed/PMC.

- **Neonate in distress:** airway and respiratory support, including ventilation if needed.
- **Asymptomatic patients:** expectant management with follow-up.
- **Recurrent infections:**
 - prompt antibiotics
 - chest physiotherapy
 - vaccination
 - nutritional support
- Treat associated cardiac or other anomalies.
- Avoid insults to the single functioning lung, such as smoking and infections.
- Monitor for pulmonary hypertension and scoliosis.
- Surgery is not curative.

Prognosis

- Prognosis depends on associated anomalies and on the side affected.
- Many reviews report right-sided agenesis as more severe, because the mediastinal shift distorts the airway and heart more.
- Mortality is high in infancy, mainly from infection and cardiac anomalies.

PEARLS

- Agenesis means no bronchus, no lung and no vessels. Aplasia has a blind rudimentary bronchus.
- Chest X-ray shows an opaque hemithorax with shift **towards** the lesion. An effusion pushes the mediastinum away.
- Key genes are **FGF10, TBX4, RSPO2 and STRA6**.
- Lung bud specification needs **Wnt2/2b → β-catenin → Nkx2-1**.
- Fgf10 loss gives lung agenesis with the trachea spared.
- Hypoplasia is commonly secondary, as in diaphragmatic hernia or oligohydramnios.
- Confirm with CT and bronchoscopy. CT angiography shows the vessels.
- Asymptomatic cases need no treatment. Treat infections early.
- Associated anomalies, especially cardiac, determine outcome.

Sources

- Textbook: Murray & Nadel 7e — Ch 2 Lung Growth and Development, §Introduction — p. 24
- Textbook: Murray & Nadel 7e — Ch 2 Lung Growth and Development, §Molecular Mechanisms › Embryonic Stage — p. 26
- Textbook: Murray & Nadel 7e — Ch 2 Lung Growth and Development, §Morphogenesis — p. 31
- [w1] Respiratory Medicine — Developmental lung anomalies in adults: a pictorial review — <https://www.sciencedirect.com/science/article/pii/S0954611119302355>
- [w2] PMC — Agenesis of lung, a report of two cases — <https://pmc.ncbi.nlm.nih.gov/articles/PMC2853047/>
- [w3] PMC — Left pulmonary aplasia with left pulmonary artery agenesis in a child (Nepal) — <https://pmc.ncbi.nlm.nih.gov/articles/PMC12924539/>
- [w4] PMC — Primary Pulmonary Hypoplasia — <https://pmc.ncbi.nlm.nih.gov/articles/PMC6337051/>
- [w5] Radiology — Aplasia of the Lung — <https://pubs.rsna.org/doi/10.1148/67.5.751>

- [w6] Diseases of the Chest — Agenesis of the Lung —
[https://journal.chestnet.org/article/S0096-0217\(16\)30770-1/fulltext](https://journal.chestnet.org/article/S0096-0217(16)30770-1/fulltext)

5. Congenital diaphragmatic hernia

ASKED 1* · Intermediate answer

Asked in: Apr 2023 P-I Q7(a) [5]

Q: Congenital diaphragmatic hernia. [5]

Congenital diaphragmatic hernia

Definition

- **CDH** is an opening (defect) in the diaphragm that lets abdominal organs herniate into the chest.
- The result is **pulmonary hypoplasia** and a hypoplastic pulmonary vasculature.
- Incidence is about **1 in 3500 live births** (Murray & Nadel). Newer reviews quote about 1 in 3000 live births.
- Mortality is about 30%, from pulmonary hypoplasia and pulmonary hypertension (PH).

Pathogenesis

- The lungs and pulmonary vessels are underdeveloped through two mechanisms:
 - Mechanical compression by the herniated viscera.
 - Intrinsic defects in **branching morphogenesis, septation and vascular development**.
- Pulmonary hypertension complicates CDH, as it does alveolar capillary dysplasia and preterm birth with or without BPD.
- PH in CDH has two components: reduced vascular number, and failure of normal pulmonary vascular smooth muscle relaxation after birth.
- Most cases are sporadic. Genetic causes range from aneuploidy to complex chromosomal aberrations and specific mutations. These often give a multiple-malformation phenotype.

Types and anatomy

- **Bochdalek hernia** is posterolateral, in the posterior mediastinum.
 - It appears on the **left** side, presumably because the liver prevents herniation on the right.
 - It is the common CDH.
- **Morgagni hernia** goes through the foramen of Morgagni.
 - It produces a **cardiophrenic angle mass**, usually on the right, in the anterior mediastinum.
 - It is the rarer, anterior form.
- Hiatal hernia can also appear as a mediastinal mass.

Anterior/Prevascular Mediastinum	Middle/Visceral Mediastinum	Posterior/Paravertebral Mediastinum
Thymic neoplasms	Lymphadenopathy	Neurogenic tumors
Germ cell tumors	Reactive and granulomatous inflammation	Meningocele
Teratoma	Metastasis	Diaphragmatic hernia (Bochdalek)
Seminoma	Angiofollicular lymphoid hyperplasia (Castleman disease)	Extramedullary hematopoiesis
Nonseminomatous germ cell tumors	Lymphoma	Lymphadenopathy
Embryonal cell carcinoma	Developmental cysts	Lesions arising from posterior spine
Choriocarcinoma	Pericardial cyst	Metastases
Lymphoma	Foregut duplication cysts	Discitis/osteomyelitis
Hodgkin lymphoma	Bronchogenic cyst	Thoracic duct cyst
Non-Hodgkin lymphoma	Enteric cyst	
Thyroid neoplasms/goiter	Others	
Parathyroid neoplasms	Vascular enlargements (i.e., descending aortic aneurysm)	
Mesenchymal tumors	Diaphragmatic hernia (hiatal)	
Lipoma	Esophageal lesions	
Fibroma	Carcinoma	
Lymphangioma	Diverticula	
Hemangioma	Varices	
Mesothelioma		
Sarcoma		
Diaphragmatic hernia (Morgagni)		
NUT midline carcinoma		
Lymphadenopathy		
Vascular lesions		

NUT, nuclear protein in testis.

Table 115.2 — Murray & Nadel 7e, pr.1596. Table 115.2 Disorders Presenting as a Mass in the Mediastinum

Associations

- Extralobar sequestration is associated with CDH. Associated anomalies occur in about 50–60% of extralobar sequestrations.
- Other CDH associations include:
 - Congenital heart disease, which strongly worsens outcome.
 - Congenital cystic adenomatoid malformation.
 - Vertebral defects.
 - Pulmonary hypoplasia.
- After neonatal repair, **chylothorax** may develop. The textbook lists CDH repair among the surgical causes of chylothorax.

Clinical features

- Presentation is usually in the newborn, with respiratory distress, hypoxaemia and persistent pulmonary hypertension.
- Many cases are now diagnosed on routine prenatal ultrasound.

Investigations

Table 1: Investigations in CDH

Test	Finding	Meaning
Prenatal ultrasound	Stomach or bowel in the chest, mediastinal shift	Antenatal diagnosis and referral to a tertiary centre
Chest radiograph	Bowel loops in the hemithorax, shifted mediastinum	Confirms the hernia
Echocardiography	Pulmonary hypertension, RV or LV dysfunction, cardiac anomaly	Guides vasodilator or inotrope therapy and prognosis
Karyotype and genetics	Aneuploidy or syndromic variants	Associated anomalies and counselling

- Prognostic factors:
 - **Defect size** (graded A–D at surgery).
 - **Severe cardiac anomaly**.

Management

GUIDELINE

CDH EURO Consortium — Standardized Postnatal Management of Infants with CDH in Europe, Consensus 2015 Update (Neonatology 2016;110:66–74). It remains the standard reference, alongside the Japanese Clinical Guidelines for CDH 2021.

- **Antenatal care:**
 - Deliver at an experienced tertiary centre. The consensus specifies a high-volume centre (>6 CDH deliveries per year).
 - Fetal tracheal occlusion (**FETO**) stimulates fetal lung growth. It is an investigational prenatal therapy for severe hypoplasia.
- **Delivery room:**
 - Start resuscitation with **FiO₂ < 1.0**.
 - Avoid routine neuromuscular blockade after delivery.
 - Avoid high airway pressures.
- **Ventilation:**
 - Use **gentle ventilation**.
 - Conventional mechanical ventilation is the initial mode.
 - **HFOV** is the rescue mode.
- **Pulmonary hypertension:**
 - Therapies that work in usual PPHN are not widely successful in CDH.
 - Options include inhaled nitric oxide, sildenafil and others, individualised by echocardiographic findings.

- **ECMO/ECLS** is used for refractory cases.
- **Surgery:**
 - Repair is done only after cardiorespiratory stabilisation. It is not an emergency.
 - The defect is closed primarily or with a patch.
- **Follow-up:**
 - Monitor for pulmonary hypertension, chronic lung disease, chylothorax, recurrence, GERD and growth.
 - Follow-up should be multidisciplinary.

Differential diagnosis

Table 2: Chest masses in the newborn that mimic CDH

Condition	Distinguishing feature
CPAM	Cystic lesion, connects to the airway
Bronchopulmonary sequestration	No tracheobronchial connection, systemic arterial supply
Eventration of the diaphragm	Diaphragm is intact but elevated
Lung hypoplasia from other causes	Oligohydramnios, skeletal dysplasia, pleural effusion or omphalocele

PEARLS

- CDH occurs in about **1 in 3500** births. The lung is hypoplastic on both sides, and worse on the side of the hernia.
- The **left posterolateral (Bochdalek)** hernia is the common type, because the liver blocks the right.
- Morgagni hernia is anterior, usually right, and appears as a cardiophrenic angle mass.
- The main causes of death are **pulmonary hypoplasia and pulmonary hypertension**, not the hernia itself.
- Stabilise first. Use gentle ventilation, $\text{FiO}_2 < 1.0$ and HFOV as rescue. Operate later.
- Defect size and cardiac anomalies are the strongest prognostic factors.
- FETO is a prenatal option for severe cases.
- Chylothorax is a recognised complication of CDH repair.
- CDH is a cause of pulmonary hypertension in the newborn, alongside ACD/MPV and BPD.

Sources

- Textbook: Murray & Nadel 7e — Ch 2 Lung Growth and Development, §Morphogenesis — pp. 31–32
- Textbook: Murray & Nadel 7e — Ch 88 Pulmonary Vascular Anomalies, §Malformations › Treatment — pp. 1215–1215
- Textbook: Murray & Nadel 7e — Ch 111 Chylothorax, §Thoracic Duct — pp. 1552–1552
- Textbook: Murray & Nadel 7e — Ch 115 Mediastinal Tumors and Cysts, §Mediastinal Mass — pp. 1596–1603
- [w1] CDH EURO Consortium — Standardized Postnatal Management of Infants with CDH in Europe, 2015 Update — 2016 — <https://pubmed.ncbi.nlm.nih.gov/33881212/>
- [w2] Greenough A — Management of infants with CDH and pulmonary hypertension (Pediatr Res) — 2023 — <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10313509/>
- [w3] Narrative review of controversies in neonatal management of CDH — <https://pmc.ncbi.nlm.nih.gov/articles/PMC8192986/>
- [w4] Genetics of diaphragmatic hernia — <https://pubmed.ncbi.nlm.nih.gov/34621023/>
- [w5] Standardized reporting for CDH, international consensus — <https://www.sciencedirect.com/science/article/abs/pii/S0022346813006751>

6. Stages of lung development – prenatal stages, postnatal alveolarisation, development of airways and blood vessels

ASKED 4* · Intermediate answer

Asked in: Jun 2020 P-I Q6(a) [5] · Dec 2022 P-I Q4(b) [5] · Jun 2025 P-I Q2(a) [5] · Dec 2025 P-I Q5(a) [5]

Q: Stages of lung development. [5]

Q: Post natal lung development. [5]

Q: Development of the airways and blood vessels. [5]

Q: Stages of lung development. [5]

Definition and overview

- Lung development is divided into two processes: **budding and branching morphogenesis**, which forms the conducting airways, and **septation and alveologenesi**s, which forms the distal gas-exchange surface.
- It is classically divided into **five stages**: embryonic, pseudoglandular, canalicular, saccular and alveolar.
- The stages blend into one another, because the cellular and molecular programmes change smoothly.
- Epithelium arises from **endoderm**. Mesenchyme and endothelium arise from **mesoderm**.
- The airways are complete well before birth. About **95% of the gas-exchange surface area is added after birth**.

MAJOR STAGES OF LUNG DEVELOPMENT

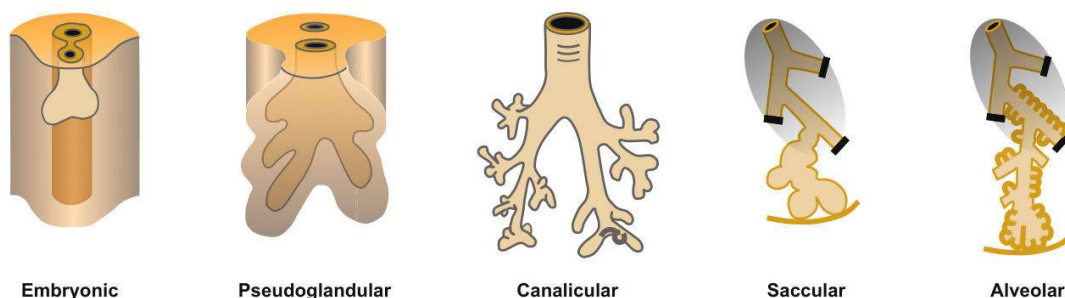


Figure 2.1 — Murray & Nadel 7e, pr.25. Diagrams of key features of the lung at progressive developmental stages, from the embryonic, pseudoglandular, canalicular, sac-cular, to alveolar stages. See text for stages and details of these events of lung development. (Modified from Swarr DT, Wert SE, Whitsett JA. Molecular determinants of lung morphogenesis. In Wilmott RW, Deterding R, Li A, et al, editors. Kendig's Disorders of the Respiratory Tract in Child

Stages of lung development

Table 1: Stages of human lung development (PCW = postconceptual weeks)

Stage	Human timing	Mouse timing	Key events
Embryonic	PCW 4–7	E8.5–11.5	Respiratory specification, lung buds, trachea–oesophagus separation
Pseudoglandular	PCW 5–17	E11.5–15.5	Branching morphogenesis; proximal airways formed
Canalicular	PCW 16–26	E15.5–16.5	Air spaces and capillaries expand; AT1/AT2 differentiate; surfactant first made
Saccular	PCW 24–38	E16.5–P3	Terminal air spaces enlarge; primary septa; surfactant stored
Alveolar	Begins around term, continues after birth	–	Secondary septation increases surface area

Embryonic stage

- Ventral foregut endoderm cells are specified to a respiratory fate. The earliest marker is **Nkx2-1**.
- The respiratory primordium buds into the surrounding mesenchyme to form the **left and right lung buds**.
- The foregut tube divides into the **trachea (ventral)** and **oesophagus (dorsal)**.
- Left–right asymmetry of the lung buds is already specified at budding.

- **Wnt2/Wnt2b** act through β -catenin to maintain Nkx2-1. Their loss causes failure of trachea and lung development in mice.
- **FGF10** is essential for budding. Fgf10 loss causes lung agenesis, with the trachea preserved.
- Retinoic acid controls budding through WNT, TGF- β and FGF10.
- Human mutations in **RSPO2, STRA6, FGF10 and TBX4** are linked to lung agenesis or severe hypoplasia.
- The lungs acquire their pleural covering at budding. The pleural cavity separates from the pericardial and peritoneal spaces by 9 weeks.

Pseudoglandular stage

- The primary event is **branching morphogenesis**, which is under mesenchymal guidance.
- Branching uses three subroutines: **domain branching, planar bifurcation and orthogonal bifurcation** (90° to the previous plane).
- The programme is stereotyped in mice and more variable in humans.
- Mesenchymal **FGF10** promotes proliferation and chemotaxis of distal tip epithelium. It acts through FGFR2 and ETV4/5 to induce Shh, and Shh in turn inhibits Fgf10.
- This feedback loop contributes to the repeated bifurcation programme.
- The **proximal–distal pattern** is marked by proximal **Sox2** and distal **Sox9**.
- In humans, SOX2 overlaps distally with SOX9 until about 20 weeks.
- Airway epithelium differentiates in a set order. **Pulmonary neuroendocrine cells** come first, followed by **basal cells**, which are the adult airway progenitors.
- Mesenchyme differentiates into cartilage and smooth muscle.
- By the end of this stage most proximal airways are formed.

Canalicular stage

- The programme switches from branching to **septation of distal air spaces**.
- The distal epithelium still undergoes three final rounds of branching.
- Air spaces lengthen and widen, and capillaries grow.
- Mesenchymal thinning brings epithelium and capillaries together, forming the **alveolar–blood interface**.
- Epithelium differentiates into **AT1 and AT2 cells**.
- **Surfactant** is first detected at **PCW 22–24**. This is the key milestone for survival of premature infants, and antenatal steroids can enhance it.

Saccular stage

- Branching is complete and the airways are laid out.
- Terminal air spaces increase in volume and the mesenchyme is thinned.
- **Primary septa** are lined by AT1 cells with interspersed AT2 cells, and are underlined by a capillary basket.
- AT2 cells increase surfactant stored in **lamellar bodies**.
- Amniotic fluid peaks at about PCW 34. In mice its pressure promotes alveolar epithelial differentiation.
- Fusion of epithelial and endothelial basal laminae brings AT1 cells and capillaries into close contact.

Alveolar stage

- Formation, lengthening and thinning of **secondary septa** markedly increase epithelial surface area.
- Human lungs at term are at the **beginning of the alveolar stage**. Mouse lungs at term are at the saccular stage.

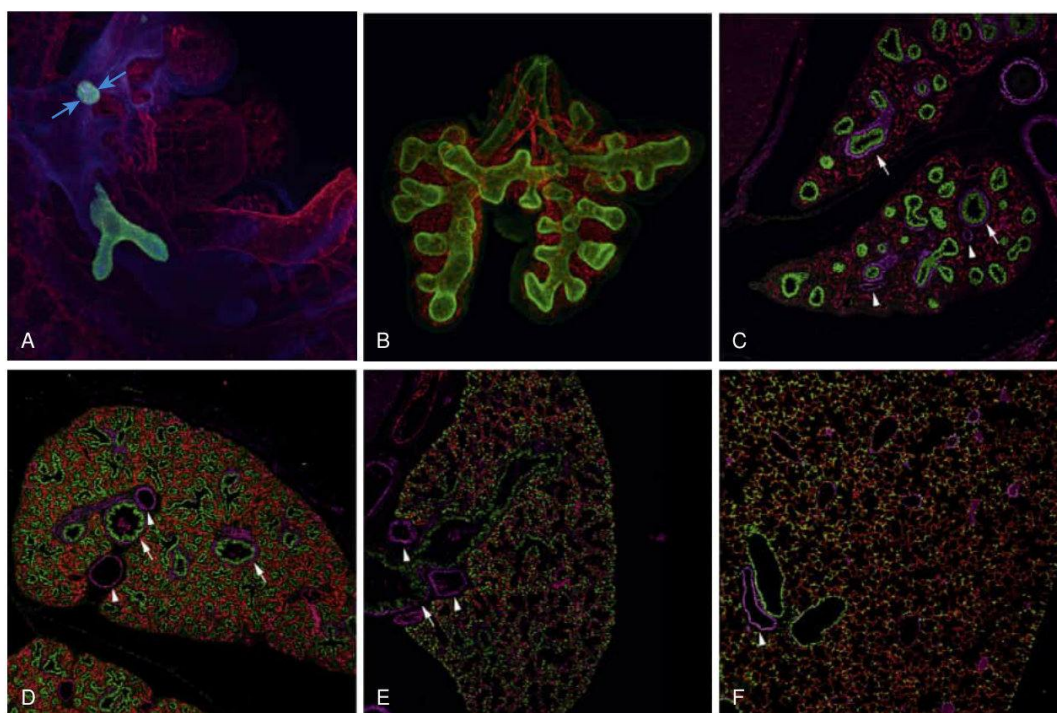


Figure 2.2 — Murray & Nadel 7e, pr.26. Morphology of the stages of lung development. Mouse lungs from the indicated developmental stages were stained with an antibody against Nkx2-1 to identify epithelial cells in the respiratory lineage (green), an antibody against endomucin to identify vascular cells (red), and an antibody against α -smooth muscle actin to identify smooth muscle cells (magenta). An antibody against E-cadherin identifies the foregut endod

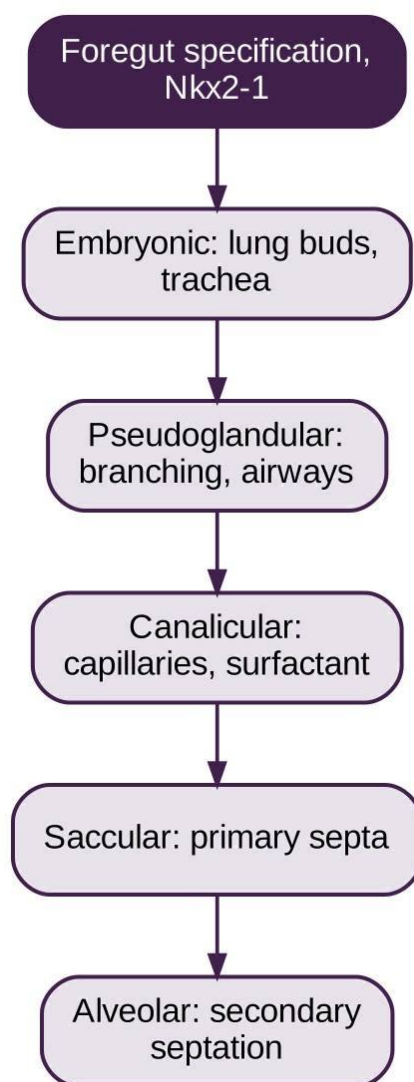
Development of the airways

- The airways develop by **iterative bud formation, extension and dichotomous bifurcation**.
- The basement membrane (collagen IV, laminin, fibronectin, nidogen, HSPGs, netrin) coordinates branching.
- At the tips, the basement membrane thins and **low-sulfated HSPG** allows FGF10 diffusion, which favours branching.
- At the neck, **highly sulfated HSPG and netrin** limit FGF10 signalling, which prevents branching.
- Distal mesenchyme induces branching when placed next to proximal tracheal epithelium. Tracheal mesenchyme prevents branching when placed at a distal bud.
- Human mesenchymal defects: **FOXF1** mutation causes alveolar capillary dysplasia, and **TBX4** mutation causes acinar hypoplasia.

Development of the blood vessels

- Pulmonary endothelium gives rise to **three vascular networks**: pulmonary (carries deoxygenated blood to the lung), bronchial (systemic, nourishes lung cells) and lymphatic (fluid homeostasis and antigen conduit).
- The pulmonary vasculature branches **in parallel with the airways**. Vascular precursors form a plexus around the epithelium from the embryonic stage.
- **Vasculogenesis** forms distal vessels from mesenchymal cells. **Angiogenesis** connects them to proximal vessels.
- Textbook chapter 5 places vascular emergence at the start of the canalicular stage (**16–24 weeks**).
- The distal vessels align with air spaces to form the **alveolar–capillary unit**.
- **FGF and VEGF** are required for vessel formation. Epithelial VEGF is stored in the mesenchyme and released by MMP cleavage.
- The ECM composition drives vasculogenesis and angiogenesis.

Flowchart 1: Sequence of human lung development



Postnatal lung development

- At birth about **5% of the final surface area** exists. The remaining **95% is added after birth**.
- The conventional view is that alveolar surface area is complete by **6–7 years**.
- A more recent study shows **new alveoli continue to be added into the 20s**.
- The adult lung has about **480–500 million alveoli** and a surface area of about **130 m²**.
- Secondary septation is the main mechanism of postnatal growth.
- AT2 cells produce surfactant and can give rise to **AT1 cells**, which cover about 95% of the surface area.
- In humans, pores of Kohn increase with age.
- Disrupted development can follow genetic mutations, early respiratory infections, and exposure to pollutants, cigarette smoke or e-cigarette vapour.
- **Bronchopulmonary dysplasia (BPD)** is a common consequence of preterm birth. Its deficit often persists into adulthood.
- Reduced lung capacity from poor early growth can cause premature decline in function in later life, as in COPD.

Clinical correlates

- Surfactant protein deficiencies and BPD are developmental lung diseases.
- Lung hypoplasia occurs with defective branching.
- Childhood ILD and pulmonary vascular disease are developmental diseases.

PEARLS

- Five stages in order: embryonic, pseudoglandular, canalicular, saccular, alveolar.
- **Nkx2-1** is the earliest marker of respiratory fate.
- **FGF10** is needed for both budding and branching. Fgf10 loss gives lung agenesis with the trachea preserved.
- All conducting airways are formed by the end of the pseudoglandular stage. The canalicular stage adds only three final rounds of branching.
- **Surfactant** appears at **PCW 22–24** (canalicular stage). Antenatal steroids enhance it.
- Preterm infants born at 27–36 weeks are in the saccular stage, which explains their need for respiratory support.
- About **95% of gas-exchange surface area is added after birth**, and alveoli are added into the 20s.
- **FOXF1** mutation causes alveolar capillary dysplasia. **TBX4** mutation causes acinar hypoplasia or lung hypoplasia.
- **Sox2** marks proximal airways and **Sox9** marks distal tips.
- Mouse lungs at term are saccular, whereas human lungs at term are at the start of the alveolar stage.

Sources

- Textbook: Murray & Nadel 7e — Ch 1 Anatomy, §Humans And Mice — p. 22
- Textbook: Murray & Nadel 7e — Ch 2 Lung Growth and Development, §Introduction; Molecular Mechanisms — pp. 24–27
- Textbook: Murray & Nadel 7e — Ch 5 Lung Mesenchyme, §Lung Mesenchyme in Development — p. 70

7. Stocker classification of congenital pulmonary airway malformation (CPAM)

ASKED 1* · Intermediate answer

Asked in: Oct 2023 P-I Q4(a) [5]

Q: Stockers classification of Congenital Pulmonary Airway Malformation (CPAM). [5]

Stocker classification of congenital pulmonary airway malformation (CPAM)

NOT IN TEXTBOOK

Textbook search terms: "Stocker classification", "CPAM", "congenital pulmonary airway malformation", "congenital cystic adenomatoid malformation". Murray & Nadel 7e (Ch 2) only names CPAM as the most common congenital lung mass. It does not give the Stocker types, so the type-wise detail below comes from the web sources listed.

Definition

- **CPAM** (formerly CCAM) is a hamartomatous cystic or solid lung lesion caused by abnormal airway branching morphogenesis.
- It connects to the normal tracheobronchial tree.
- Its blood supply comes from the pulmonary circulation.
- It is the most common congenital lung mass.
- It arises from defective lung initiation and branching. Congenital lung masses occur in 1 in 10,000 to 35,000 live births.
- Stocker first classified it in 1977 into 3 types, using cyst size and histology.
- In 2002 Stocker added types 0 and 4 and renamed CCAM as CPAM.
- The basis of the classification is the level of the tracheobronchial tree at which development is arrested or aberrant, matched to cyst size and epithelium.

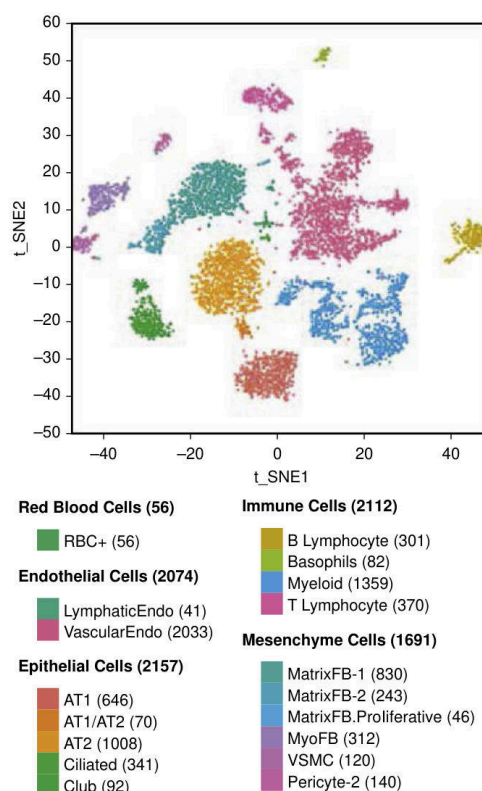


Figure 2.4 — Murray & Nadel 7e, pr.30. Representative single-cell RNAseq *t*-distributed stochastic neighbor embedding (tSNE) plot to demonstrate cell-type-based clustering. Data from single-cell analysis of whole mouse normal lung at post-natal day 3 (beginning of alveologenesis phase). On the tSNE plot, each dot represents a cell placed in *in silico* space based on its RNA transcript profile. Cells with similar transcriptional profiles are placed near each other.

Modified Stocker classification

Table 1: Modified Stocker classification of CPAM (types 0–4)

Type	Origin / level	Gross features	Histology	Frequency	Prognosis
0	Trachea/bronchi (acinar dysplasia)	Small, firm, solid lungs; no true cysts (<0.5 cm)	Ciliated pseudostratified epithelium, cartilage, glands	<2% (rarest)	Incompatible with life
1	Distal bronchus / proximal bronchiole	One or more large cysts >2 cm (up to 10 cm)	Pseudostratified ciliated epithelium with mucous cells; cartilage rare	60–70% (commonest)	Good; resectable
2	Bronchiolar	Multiple small cysts 0.5–2 cm, sponge-like	Resemble dilated bronchioles, cuboidal/columnar lining; striated muscle in 5%	10–15%	Depends on associated anomalies (renal, cardiac)
3	Bronchiolar–alveolar duct	Solid-looking bulky mass; cysts <0.5 cm	Non-ciliated cuboidal epithelium	5–10%	Poor (large mass, hydrops, pulmonary hypoplasia)
4	Distal acinar (alveolar)	Peripheral cysts up to 7 cm, may involve more than one lobe	Flattened alveolar-type lining; no cartilage	<10%	Link to pleuropulmonary blastoma

- Frequencies vary between sources: type 2 is quoted as 10–15% or 15–20%, and type 3 as about 5% or 5–10%.

Key points by type

- **Type 0:**
 - It is now recognised as acinar dysplasia, with FGFR2 and FGF10 mutations.
 - It involves all lung tissue and is fatal.
- **Type 1:**
 - It often presents late.
 - Mucinous cell clusters carry a risk of transformation to mucinous adenocarcinoma.

- Somatic **KRAS** mutations have been found.
- **Type 2:**
 - It presents in neonates.
 - Other malformations are common, and these determine the outcome.
- **Type 3:**
 - It is a solid lesion.
 - It may cause mediastinal shift and hydrops.
 - KRAS mutations have also been reported.
- **Type 4:**
 - It is now regarded as type I pleuropulmonary blastoma, so it is no longer counted as CPAM.
 - Cysts are peripheral and may be bilateral.
 - It can present with pneumothorax.

Practical classification and management

- Many centres now simply label CPAM as macrocystic (large, >2 cm) or microcystic (small, <2 cm).
- Macrocystic lesions have the better prognosis.
- Poor prognostic factors are hydrops fetalis, microcystic CPAM and larger lesion size.
- Fetal intervention is used when the mass impairs normal lung development or cardiac function.
- After birth, CPAMs are typically resected even if asymptomatic, because of the risk of malignant transformation.
- Some centres now observe asymptomatic lesions with serial imaging.
- The extent of resection (segmentectomy or lobectomy) depends on lesion size and location.

Differentiation from other congenital lung masses

Table 2: CPAM versus bronchopulmonary sequestration

Feature	CPAM	Sequestration
Bronchial communication	Present	Absent
Blood supply	Pulmonary	Systemic

- Bronchogenic cysts often do not communicate with the airway and may have either a pulmonary or a systemic blood supply.

PEARLS

- Stocker (1977) described 3 types. Types 0 and 4 were added in 2002.
- **Type 1** is the commonest (60–70%) and has cysts >2 cm.
- **Type 2** has cysts of 0.5–2 cm and associated anomalies.
- **Type 3** is a solid lesion with cysts <0.5 cm and carries a poor prognosis.
- **Type 0** is acinar dysplasia and is lethal.
- **Type 4** is cystic pleuropulmonary blastoma, which is now a separate entity.
- The classification is based on cyst size and histology.
- CPAM has a pulmonary blood supply and communicates with the airway. Sequestration has a systemic blood supply and does not communicate.
- Type 1 carries a risk of mucinous adenocarcinoma.
- Resection is standard.

Sources

- Textbook: Murray & Nadel 7e — Ch 2 Lung Growth and Development, §Morphogenesis — pp. 30–31
- [w] PMC — Clinical and histopathological spectrum of CPAM: a case series — <https://pmc.ncbi.nlm.nih.gov/articles/PMC11342210/>

- [w2] PMC — Adult CPAM presenting with a large cystic lung lesion — <https://pmc.ncbi.nlm.nih.gov/articles/PMC13492259/>
- [w3] PMC — Pleural loculated empyema masking a CPAM 3 in a newborn — <https://pmc.ncbi.nlm.nih.gov/articles/PMC6197727/>
- [w4] PMC — Spectrum of CCAM, North India — <https://pmc.ncbi.nlm.nih.gov/articles/PMC10553778/>
- [w5] PMC — RAS-MAPK pathway mutations in CPAM — <https://pmc.ncbi.nlm.nih.gov/articles/PMC11146530/>
- [w6] PMC — Characterization of 45 cases of congenital lung malformation — <https://pmc.ncbi.nlm.nih.gov/articles/PMC12019245/>

8. The ageing lung

ASKED 2* · Intermediate answer

Asked in: Jun 2020 P-I Q4(b) [5] · Dec 2022 P-I Q3(b) [5]

Q: Aging lung. [5]

Q: Aging lung. [5]

Aging lung

NOT IN TEXTBOOK

Searched in the textbook pages supplied (terms: aging lung, ageing lung, senescence, elderly lung function, age-related decline). The pages are from Ch 2, Lung Growth and Development. They cover the alveolar stage and early-life origins of adult disease, but not senescent changes in the adult lung. The body of this answer is from review literature (PubMed/PMC), with the textbook used only for the developmental background.

Definition

- The aging lung is the progressive, non-pathological change in lung structure, mechanics, gas exchange, control of breathing and immunity that occurs with advancing age.
- It is also called **senile lung**.
- The lung matures by age **20–25 years**. After that, function declines progressively.
- Peak function is reached at about age 20 in females and 25 in males.
- Normal ageing is hard to separate from age-related comorbidity. "Normal" function in the elderly is also quite variable.

Developmental background (textbook)

- About **95%** of alveolar surface area is added after birth.
- Alveologenesis continues into the early 20s.
- Early exposure to pollution, secondhand smoke and e-cigarette vapour damages existing alveoli. It also truncates formation of new alveoli.
- Reduced lung capacity from abnormal early growth predisposes to premature functional decline, as in COPD.
- So the "peak" reached in young adulthood sets how much reserve is available to lose with age.

Structural changes (after about age 50)

- Elastic elements of the lung degenerate.
- Elastin fibres in the bronchioles are disrupted and lost. Collagen–elastin cross-linking is altered.
- Alveolar ducts and bronchioles dilate. This is **senile emphysema**: airspace enlargement with loss of parenchymal tissue and a reduced gas-exchange surface, but without destructive inflammation.
- Small airways enlarge as the collagen network around them expands.
- Chest wall compliance falls because of thoracic spine deformity and calcification. Intercostal muscle mass and force are reduced.
- Defective protein folding in the endoplasmic reticulum is a proposed cause of tissue degeneration and a possible therapeutic target.

Molecular drivers

- Hallmarks of lung senescence include:
 - oxidative stress
 - telomere attrition
 - genomic instability
 - epigenetic modification
 - loss of proteostasis
 - impaired macroautophagy
- These link ageing to COPD, IPF, asthma and non-IPF fibrosis.

Physiological changes

Table 1: Age-related changes in respiratory mechanics and function

Parameter	Change with age	Mechanism
Static elastic recoil	Reduced	Loss of elastic fibres
Lung compliance	Increased	Airspace enlargement
Chest wall compliance	Decreased	Spine and rib cage stiffening
Respiratory muscle strength	Reduced	Muscle mass and force loss
FEV1	Progressive decline	Reduced recoil and airway closure
Alveolar dead space	Increased	Loss of gas-exchange surface
Gas exchange	Arterial oxygen affected	Dead space and V/Q change
CO2 elimination	Not impaired	Compensation

- Reduced static elastic recoil, decreased chest wall compliance and weak respiratory muscles underlie almost all other age-related changes.
- Adaptive changes in breathing frequency and tidal volume maintain adequate ventilation at rest.
- The reserve is lower, so decompensation is easier under stress.

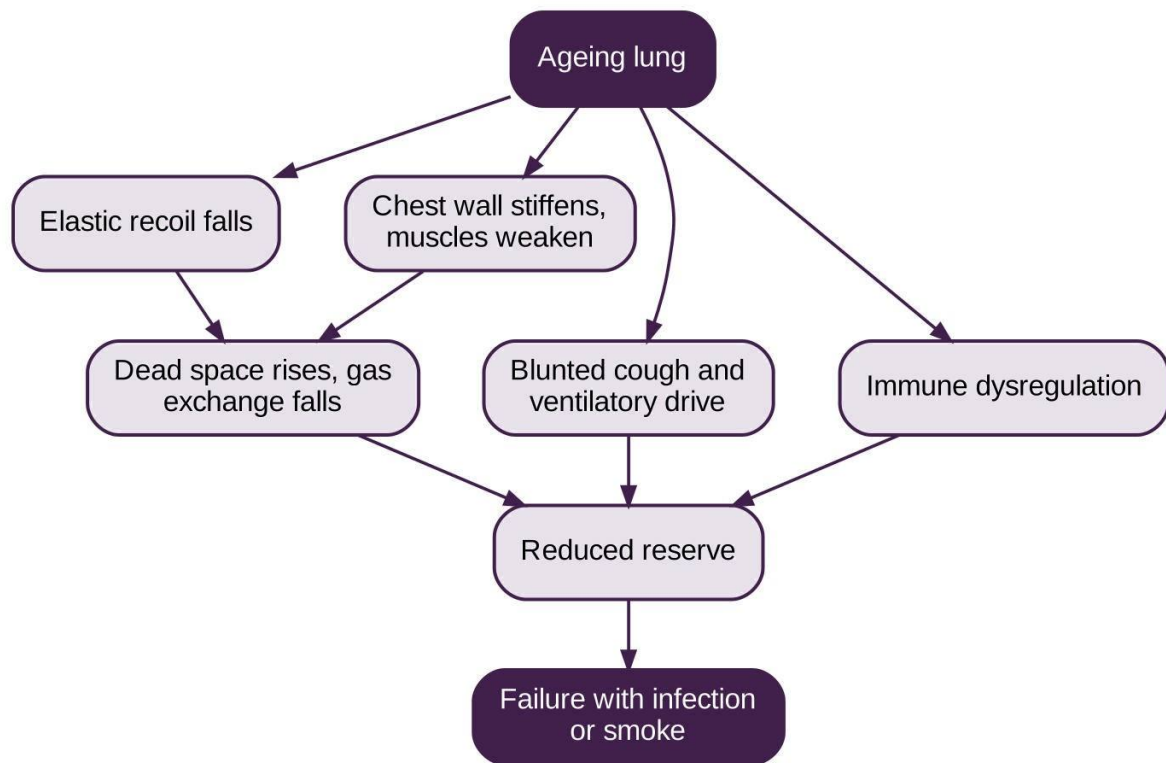
Control of breathing and defences

- **Ventilatory responses** to hypoxia and hypercapnia are depressed.
- **Dyspnoea perception** is reduced, so the elderly are vulnerable to ventilatory failure in heart failure or pneumonia.
- **Cough reflex** is depressed.
- **Sleep:** sleep cycles change. Sleep apnoea and periodic breathing are commoner, and loop gain is impaired.
- **Innate immunity** is disturbed. This predisposes to pulmonary inflammation.
- BAL shows more neutrophils and fewer macrophages.
- Persistent low-grade inflammation causes proteolytic and oxidant injury to the matrix. This adds to alveolar loss.
- Airway receptors respond less to the drugs used in younger patients.

Clinical implications

- Chronic lower respiratory disease is the **third leading cause of death** in those aged 65 or older.
- Lower reserve increases vulnerability to impairment after tobacco smoke or respiratory infection.
- Lifetime exposures (tobacco, infections, air pollution, occupational dusts) add to the age-related loss.
- Age is a major risk factor for COPD, IPF, asthma and non-IPF interstitial fibrosis.
- Hypoxaemia and hypercapnia may be missed because dyspnoea perception and ventilatory drive are blunted.
- Aspiration and pneumonia risk is raised by the weak cough and immune dysfunction.
- Use age-adjusted reference values when interpreting spirometry. Apply them cautiously, because "normal for age" values may hide real impairment.

Flowchart 1: How ageing leads to respiratory vulnerability

**PEARLS**

- Lung function peaks at about 20–25 years and then declines steadily.
- The key changes are lower elastic recoil, a stiffer chest wall and weaker respiratory muscles.
- Ageing raises lung compliance but lowers chest wall compliance.
- Senile emphysema is airspace enlargement without destructive inflammation.
- Dead space rises and arterial oxygen falls, but CO₂ elimination is maintained.
- Ventilatory responses to hypoxia and hypercapnia, and dyspnoea perception, are blunted.
- Cough and innate immunity are impaired, so pneumonia risk is higher.
- Early-life exposures that stunt alveolar growth lower the peak. This predisposes to COPD later.
- Sleep-disordered breathing is commoner with age.

Sources

- Textbook: Murray & Nadel 7e — Ch 2 Lung Growth and Development, §Introduction — p. 24
- Textbook: Murray & Nadel 7e — Ch 2 Lung Growth and Development, §Molecular Mechanisms › Alveolar Stage — p. 28
- [w1] Frontiers review — The aging respiratory system: pulmonary structure, function and neural control (Respir Physiol Neurobiol) — <https://www.sciencedirect.com/science/article/abs/pii/S1569904813000918>
- [w2] PMC — Aging Lung: Molecular Drivers and Impact on Respiratory Diseases, a Narrative Clinical Review — <https://pmc.ncbi.nlm.nih.gov/articles/PMC11673154/>
- [w3] PMC — Respiratory Impairment and the Aging Lung: A Novel Paradigm for Assessing Pulmonary Function — <https://pmc.ncbi.nlm.nih.gov/articles/PMC3297762/>
- [w4] PubMed — Effect of aging on respiratory system physiology and immunology — <https://pubmed.ncbi.nlm.nih.gov/18046878/>
- [w5] PubMed — The aging lung — <https://pubmed.ncbi.nlm.nih.gov/24235821/>
- [w6] ScienceDirect — The Aging Respiratory System (Clin Geriatr Med) — <https://www.sciencedirect.com/science/article/abs/pii/S0749069018309637>

9. Alveolar epithelium – type I and type II pneumocytes (structure and functions)

ASKED 2* · Intermediate answer

Asked in: Dec 2021 P-I Q1(b) [5] · Dec 2021 P-I Q8(b) [5] · Jun 2025 P-I Q3(a) [5]

Q: Type 2 alveolar epithelial cell structure and functions. [5]

Q: Alveolar Epithelium. [5]

Q: Pneumocytes. [5]

Alveolar epithelium – type I and type II pneumocytes

Definition

- The alveolar epithelium lines the anatomic alveoli. It is made of **alveolar type 1 (AT1)** cells, **alveolar type 2 (AT2)** cells and a minor subpopulation of **alveolar epithelial progenitors (AEPs)**.
- All of these sit on a shared basal membrane, with the subjacent capillaries and fibroblasts.
- Alveolar macrophages lie free in the alveolar lumen. They are not part of the epithelial lining.

Cell numbers versus surface area

- **AT2 cells** are about 15% of total peripheral lung cells.
- **AT1 cells** are about 8–10% of total peripheral lung cells.
- AT1 cells cover about **90–95% of the alveolar surface area**, so AT2 cells are more numerous but cover much less area.

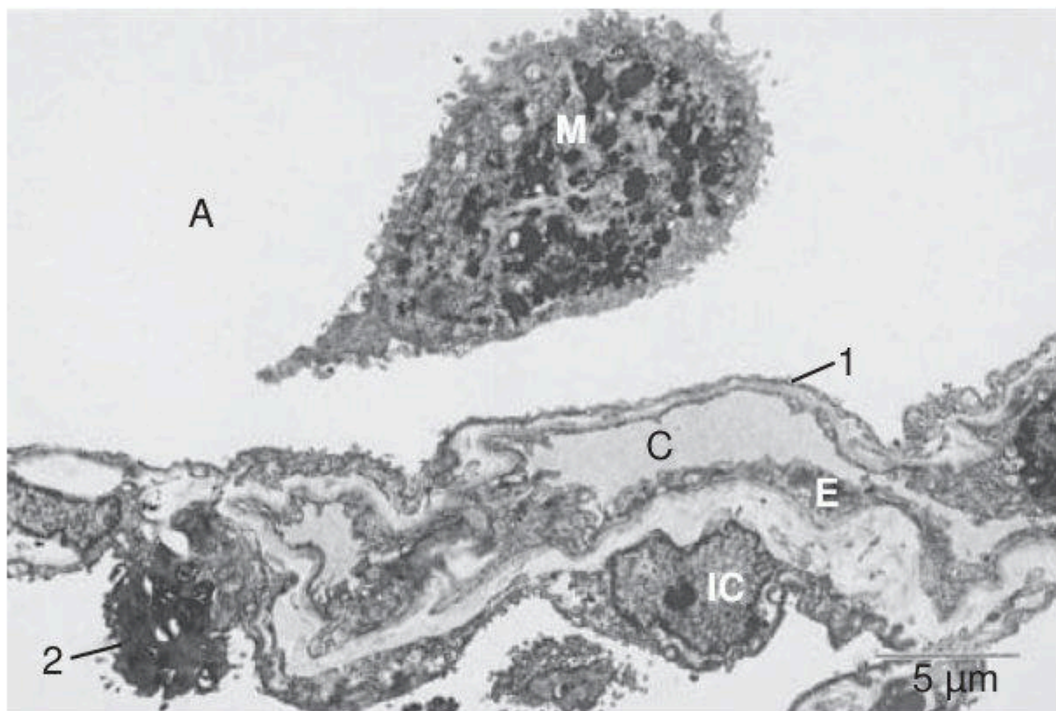


Figure 1.27 — Murray & Nadel 7e, pr.16. Cells of the terminal respiratory unit. An alveolar macrophage (M) is located in an alveolus (A). Alveolar macrophages are the air space scavengers that are cleared either up the mucociliary escalator or into the interstitium. These cells can be activated to express and secrete cytokines, which may interact with other cells. Cells of the alveolar wall are the lining alveolar type 1 and 2 cells (1 and 2, respectively)

Type 1 pneumocyte (AT1)

- **Structure**
 - Cells have extensive, attenuated cytoplasmic processes. These form a large, thin surface for gas exchange.
 - Tight junctions join them to neighbouring AT2 cells. This forms a relatively impermeable seal between alveolar air and the interstitium.
 - The cytoplasm contains many small non-clathrin-coated vesicles (**caveolae**). These open to the lumen or interstitium, or lie free in the cytoplasm.

- Caveolae contain the scaffolding protein **caveolin-1**. Caveolin-1 can bind free cholesterol and modulate cholesterol efflux.
- Caveolae sequester growth factor receptors, G proteins, calcium receptors and pumps.
- **Functions**
 - They provide the thin barrier for gas diffusion.
 - They express water channels, epithelial sodium channels and Na-K-ATPase. These regulate pulmonary water flux and lung liquid.
 - Stretch raises intracellular calcium in AT1 cells. The signal spreads through gap junctions to adjacent AT1 and AT2 cells and increases surfactant secretion.
- **Vulnerability**
 - They have limited proliferative capacity and are sensitive to injury.

Type 2 pneumocyte (AT2)

- **Structure**
 - They are small cuboidal cells of about **300 μm^3** , with short stubby apical microvilli.
 - The cytoplasm holds **lamellar bodies**. These are membrane-bound inclusions of 0.1–2.5 μm diameter, made of stacked layers of membrane-like material. They store surfactant.
 - AT2 cells are specialised for production and recycling of surfactant proteins and phospholipids.

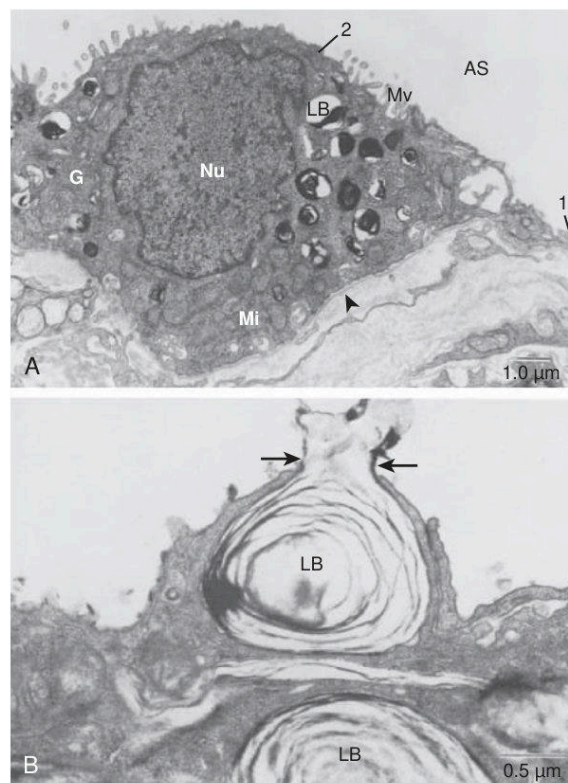


Figure 1.29 — Murray & Nadel 7e, pr.17. Cellular structure of alveolar type 2 cells. (A) Alveolar type 2 (or granular) cells (2) are cuboidal epithelial cells that contain characteristic lamellar bodies (LB) in their cytoplasm and have stubby microvilli (Mv) that extend from the apical surface into the alveolar air space (AS). Other prominent cytoplasmic organelles in alveolar type 2 cells are mitochondria (Mi) and Golgi apparatus (G). Adjacent to the al

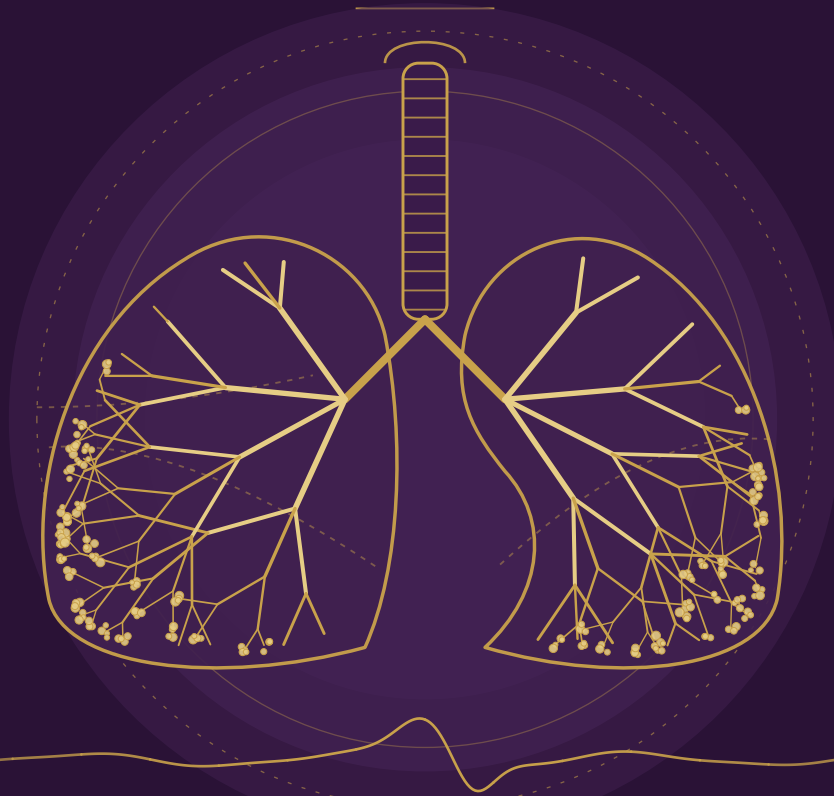
- **Functions**
 - They synthesise, secrete and recycle **all components of surfactant**.
 - They are the major synthesising and secreting "factory" of the alveolar epithelium.
 - They repair the epithelium by proliferating. This is the key reparative function after AT1 injury.
 - They contribute to innate lung immunity through surfactant proteins SP-A and SP-D.

Surfactant synthesis, secretion and turnover

- About **10–20% of the surfactant pool is secreted hourly**.
- Secretion needs active extrusion of lamellar body contents. The lamellar body fuses with the plasma membrane.



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Part 6 · Obstructive Airway Disease

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Answers are written from Murray & Nadel's Textbook of Respiratory Medicine (7th ed.), with printed page numbers cited in each answer, and from current guidelines found on official society and journal sites, cited [W#] and listed in the Web-Sourced Facts Register.

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HOW TO USE

Each answer groups every year the question was asked and is written to the most demanding version. Badges show how often a topic was asked. Each answer ends with one Sources block: the Murray & Nadel 7e chapter and printed pages used, and the guideline/web sources (also listed in the register at the end). Section B lists this volume question by question; C lists high-yield topics.

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Part 5 — Tuberculosis and Nontuberculous Mycobacteria	47 answers	114
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B • This volume, question by question

1. Approach to non-resolving / non-responding pneumonia Asked in: Jun 2022 P-II Q8(b) [5] · Dec 2025 P-II Q3(b) [5]	2×	13
2. COVID-19 therapeutics – repurposed drugs, remdesivir, IL-6 and JAK inhibitors, monoclonal antibodies and convalescent plasma Asked in: Jun 2020 P-IV Q6(b) [5] · Jun 2021 P-IV Q2(b) [5] · Jun 2021 P-IV Q5(b) [5] · Jun 2021 P-IV Q7(a) [5] · Jun 2021 P-IV Q7(b) [5] · Dec 2021 P-IV Q5(a) [5] · Dec 2022 P-IV Q8(b) [5]	4×	17
3. COVID-19 vaccines – types, side effects, precaution dose, vaccine hesitancy and prevention strategies Asked in: Dec 2020 P-IV Q8(b) [5] · Jun 2021 P-I Q5(a) [7] · Jun 2021 P-I Q5(b) [3] · Dec 2021 P-IV Q3(a) [5] · Apr 2023 P-IV Q10(b) [5]	4×	20
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7. Corticosteroids (glucocorticoids) in COVID-19 Asked in: Jun 2021 P-IV Q10(b) [5] · Dec 2022 P-IV Q8(a) [5]	2×	39
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9. Melioidosis Asked in: Dec 2022 P-IV Q5(b) [5]	1×	46
10. Methicillin-resistant Staphylococcus aureus pneumonia Asked in: Oct 2023 P-II Q4(b) [5]	1×	49
11. Mycoplasma pneumonia Asked in: Jun 2021 P-II Q2(b) [5]	1×	54
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PART 4

Pulmonary Infections

1. Approach to non-resolving / non-responding pneumonia

ASKED 2* · Intermediate answer

Asked in: Jun 2022 P-II Q8(b) [5] · Dec 2025 P-II Q3(b) [5]

Q: Define non-responding pneumonia and enumerate the causes. [5]

Q: Approach to a case with non-resolving pneumonia. [5]

Definition

- **Non-responding pneumonia:** pneumonia in which clinical improvement is not achieved on antibiotics, with persistent fever and symptoms.
- **Progressive pneumonia:** the second pattern of treatment failure, with clinical deterioration, even to respiratory failure or septic shock.
- Response is assessed after **72 hours** of antibiotics.
- Do not change therapy before 48 hours unless there is severe clinical deterioration or dramatic radiologic progression.
- Procalcitonin (PCT) falling after 3–4 days correlates with response.
- High initial PCT or CRP independently predicts inadequate response. PCT, CRP and IL-6 are useful markers for predicting it.
- **Non-resolving (slow-resolving) pneumonia:** radiographic clearing is delayed even though the patient may be clinically better. Use the same work-up.

Why it matters

- CAP mortality is **5–10%** in hospitalised patients and **20–50%** in those admitted to the ICU.
- Treatment failure signals a wrong diagnosis, a resistant or unusual organism, a complication, or host factors.
- Patients with undiagnosed TB or with unrecognised drug resistance remain infectious.

Causes

Infectious causes

- Specific infections account for about **40%** of non-responders in hospitalised CAP.
 - Commonest organisms: *S. pneumoniae*, *Legionella*, *P. aeruginosa*, *S. aureus*.
- Resistance to the empirical regimen.
 - *P. aeruginosa* is not covered by standard CAP therapy unless a fluoroquinolone is used. It causes about **10%** of non-responding CAP.
 - Resistant pneumococcus, MRSA, anaerobes.
- Unusual organisms needing different antibiotics: mycobacteria, *Nocardia*, anaerobes, fungi, *Pneumocystis jirovecii*, protozoa.
- Local or metastatic complications:
 - Empyema, one of the commonest complications, so tap any effusion.
 - Lung abscess; necrotising pneumonia.
 - Endocarditis, arthritis, pericarditis, meningitis, peritonitis. These are commoner with bacteraemic pneumonia.
- Bronchial obstruction by tumour, foreign body or teeth.
- Viral pneumonia with bacterial superinfection, especially influenza and RSV.

Noninfectious causes

- Noninfectious mimics account for about **22%** in CAP.
 - Pulmonary infarction (PE) and pulmonary haemorrhage.
 - Organising pneumonia and eosinophilic pneumonia.

- Hypersensitivity pneumonitis and drug-induced lung disease.
- Neoplasm, especially alveolar cell (lepidic) carcinoma, which can mimic pyogenic pneumonia on imaging.

Host and drug factors

- In about **30%** no specific cause is found despite adequate antibiotics.
 - This may reflect comorbidity or an exaggerated or diminished inflammatory response.
- Other contributors: immunodeficiency such as HIV, poor drug dosing, and poor drug absorption.

Table 1: Causes of non-responding pneumonia

Group	Examples	Clue
Resistant bacteria	<i>P. aeruginosa</i> , MRSA, resistant pneumococcus	Prior isolation, recent hospitalisation or parenteral antibiotics
Atypical or unusual	<i>Legionella</i> , TB, fungi, <i>Nocardia</i> , <i>Pneumocystis</i>	Exposure, travel, HIV, immunosuppression
Complications	Empyema, abscess, necrotising pneumonia	Effusion, cavitation, persistent sepsis
Obstruction	Tumour, foreign body	Lobar collapse, smoker
Noninfectious	PE, organising pneumonia, eosinophilic pneumonia, vasculitis, drug reaction, lung cancer	Eosinophilia, haemoptysis, migratory opacities

Approach

Immediate steps

- Assess severity and decide on transfer to a higher level of care (HDU or ICU).
- Check for sepsis or respiratory failure and give supportive care.
- Optimise the antibiotic regimen, including dose and route.

Focused evaluation

- Re-take the history for:
 - Travel, occupational or animal exposure.
 - Personal habits (alcohol, smoking, aspiration risk).
 - TB contact.
 - HIV risk.
 - Drugs taken.
- Re-examine for effusion, cardiac murmur, joints and meninges.
- Review all initial microbiology.
- Repeat blood cultures, sputum Gram stain/culture and AFB/GeneXpert, and urinary antigens.
- Send samples from non-respiratory sites.
- Pleural fluid, if present, for culture, direct fluorescent antibody and nucleic acid testing for likely pathogens.
- Check HIV status.
- Check PCT, CRP and IL-6 trends.

Imaging

- Chest radiograph for effusion, cavitation or new opacities.
- CT chest gives detail of parenchyma, pleura and mediastinum, and may suggest specific organisms or alternative diagnoses.
 - **Halo sign** nodules suggest aspergillosis or mucormycosis. Similar nodules occur in CMV, granulomatosis with polyangiitis, Kaposi sarcoma, and necrotic or haemorrhagic metastases.
 - Ground-glass interstitial opacities suggest *P. jirovecii*.
 - Nodules or masses, with or without cavitation, suggest *Nocardia*, TB or Q fever.
 - Diffuse mixed interstitial and alveolar opacities suggest viral infection or *M. pneumoniae*.
- CT pulmonary angiography to exclude PE.

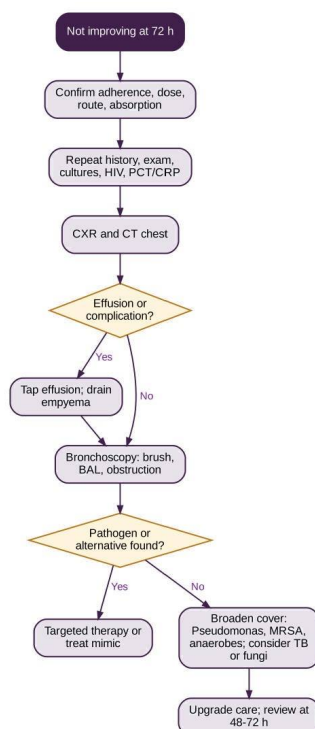
Table 46.5 Guidelines for Empirical Parenteral Inpatient Treatment of Immunocompetent Adults With Community-Acquired Pneumonia
MILD TO MODERATE DISEASE ATS/IDSA ¹⁰⁹ ■ Primary: ampicillin and sulbactam, cefotaxime, ceftriaxone, or ceftaroline with azithromycin or clarithromycin ■ Alternative: fluoroquinolone ^a alone or, if history of prior respiratory isolation of MRSA ^b or <i>Pseudomonas aeruginosa</i> , ^c treatment to cover these agents BTS ^{161,162} ■ Mild: oral amoxicillin. Alternatives parenteral amoxicillin or benzylpenicillin or clarithromycin ■ Moderate: oral amoxicillin and clarithromycin (can consider clarithromycin monotherapy if prior therapy with amoxicillin) ■ Alternative if unable to take oral medication: parenteral amoxicillin or benzylpenicillin plus clarithromycin (if intolerant of penicillin but able to take a cephalosporin parenteral second- or third-generation cephalosporin plus clarithromycin) ■ Alternative: if unable to take penicillin or macrolide, oral doxycycline, or if not able to take any of these, a respiratory fluoroquinolone ^d ERS/ESCMID ¹⁶³ ■ Aminopenicillin, aminopenicillin with β-lactamase inhibitor, penicillin, cefotaxime, ceftriaxone with or without macrolide ■ Respiratory fluoroquinolone alone ^e DRSPTWG ■ Primary: cefuroxime, cefotaxime, ceftriaxone, or ampicillin-sulbactam; macrolide ■ Alternative: fluoroquinolone ^f SEVERE DISEASE ATS/IDSA ¹⁰⁹ ■ Primary: Ampicillin and sulbactam, cefotaxime, ceftriaxone, or ceftaroline with azithromycin or clarithromycin ■ Alternative: broad-spectrum β-lactam as for primary with fluoroquinolone ^g or, if history of prior respiratory isolation or prior hospitalization with parenteral antimicrobials within 90 days in setting of locally validated risk factors for MRSA ^b or <i>P. aeruginosa</i> , ^c treatment to cover these agents BTS ^{161,162} ■ Primary: amoxicillin/clavulanate (or if penicillin intolerant cefuroxime, cefotaxime, or ceftriaxone) plus macrolide ERS/ESCMID ¹⁶³ ■ Cefotaxime or ceftriaxone plus macrolide or respiratory fluoroquinolone ■ Alternative: respiratory fluoroquinolone alone if no sepsis ■ Alternative if risk factors for <i>P. aeruginosa</i> : piperacillin/tazobactam, anti-pseudomonal cephalosporin (ceftazidime ^h or ceftipime) plus ciprofloxacin or plus macrolide and aminoglycoside ⁱ DRSPTWG ■ Primary: ceftriaxone or cefotaxime, macrolide; or ceftriaxone or cefotaxime, fluoroquinolone ^j ■ Alternative (with caution): fluoroquinolone. ^k
^a Antipneumococcal fluoroquinolones include levofloxacin 750 mg/day and moxifloxacin 400 mg/day. ^b Advanced macrolides are azithromycin and clarithromycin. ^c Ampicillin and sulbactam 1.5–3 g q6h, cefotaxime 1–2 g q8h, ceftriaxone 1–2 g/day, or ceftaroline 600 mg q12h and azithromycin 500 mg/day or 500 mg on day 1 and 250 mg once a day thereafter for mild disease) or clarithromycin 500 mg bid. ^d Anti-staphylococcal treatments include vancomycin (15 mg/kg q12h, adjust based on levels) or linezolid (600 mg q12h). ^e Antipseudomonal β-lactams include piperacillin-tazobactam (4.5 g q6h), ceftipime (2 g q8h), ceftazidime (2 g q8h), imipenem (500 mg q6h), meropenem (1 g q8h), or aztreonam (2 g q8h). ^f If ceftazidime used should be combined with penicillin to ensure coverage of pneumococci per ERS/ESCMID guideline. ^g Recommendation to double cover <i>P. aeruginosa</i> with both a β-lactam and either ciprofloxacin or an aminoglycoside per ERS/ESCMID guideline. ^h ATS/IDSA, American Thoracic Society/Infectious Diseases Society of America; BTS, British Thoracic Society; DRSPTWG, Drug-Resistant <i>Streptococcus pneumoniae</i> Therapeutic Working Group; ERS/ESCMID, European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases. ⁱ

Table 46.5 — Murray & Nadel 7e, pr.611. Table 46.5 Guidelines for Empirical Parenteral Inpatient Treatment of Immunocompetent Adults With Community-Acquired Pneumonia

Bronchoscopy

- Do it if not contraindicated, to look for obstruction and to sample the lower respiratory tract.
- Take a protected specimen brush and BAL in the same procedure.
 - Send for bacterial culture, direct fluorescent antibody staining and nucleic acid testing.
 - Yield of brush or BAL culture approaches **40%** despite prior antibiotics.
- In ventilated patients, a tracheal aspirate is useful.
- Gram stain of cytocentrifuged BAL fluid rapidly identifies intracellular organisms.
- The role of transbronchial biopsy is not established. It depends on the alternative diagnosis suspected.

Flowchart 1: Approach to non-responding pneumonia



Management

GUIDELINE

ATS/IDSA — Diagnosis and Treatment of Adults with CAP (Am J Respir Crit Care Med 2019;200:e45–e67), with the ATS 2025 incremental update (Am J Respir Crit Care Med 2025;212:24).

- Treat the cause found and de-escalate once susceptibilities are known.
- If no cause is found:
 - Consider empirical cover for resistant *S. pneumoniae*, *P. aeruginosa*, MRSA and anaerobes.
 - Choice depends on risk factors, severity and local resistance.
 - CA-MRSA regimens may include linezolid, or clindamycin plus vancomycin, guided by susceptibility.
 - Be alert for carbapenemase-producing *K. pneumoniae*.
- Consider fungal infection where endemic fungi are prevalent.
- Consider TB if there is a plausible exposure history.
 - Avoid fluoroquinolones when TB is possible, because as few as **10 days** can select fluoroquinolone-resistant TB.
- Drain empyema or abscess.
- Remove an obstructing lesion.
- Stop or avoid drugs that may be causing a drug reaction.
- Treat mimics specifically, for example anticoagulation for PE.
- The 2019 guideline removed the health care–associated pneumonia category. MRSA and *Pseudomonas* cover is reserved for patients with prior respiratory isolation, or recent hospitalisation with parenteral antibiotics plus locally validated risk factors.
- Switch from IV to oral when clinically stable (often 2–3 days). The minimum treatment duration is **5 days**.

Prevention

- Annual influenza vaccine.
- Pneumococcal vaccination.
- Smoking cessation.

PEARLS

- Assess response at **72 hours**, not earlier, unless the patient is severely deteriorating.
- Distinguish **non-responding** (no improvement) from **progressive** (deterioration) pneumonia.
- Specific infection explains about **40%** of non-responders. Noninfectious mimics explain about **22%**. About **30%** remain unexplained.
- Always tap any pleural effusion. Empyema is a frequent cause of failure.
- Think of TB, *Legionella*, *Pseudomonas*, MRSA and *Nocardia*, and test for HIV.
- A halo sign on CT suggests invasive aspergillosis or mucormycosis.
- Persistent or recurrent opacity in a smoker means bronchoscopy to exclude obstruction or lepidic carcinoma.
- Never add a single new drug to a failing regimen (a TB principle).
- Get a CT pulmonary angiogram if PE or infarct is suspected.

Sources

- Textbook: Murray & Nadel 7e — Ch 46 Community-Acquired Pneumonia, §Pneumonia (Adjustments in therapy; Nonresponding pneumonia) — pp. 610–611, 617–618
- Textbook: Murray & Nadel 7e — Ch 54 Tuberculosis: Treatment — p. 715
- [w] ATS/IDSA — Diagnosis and Treatment of Adults with CAP — 2019 — <https://academic.oup.com/ajrccm/article/200/7/e45/8496962>

- [w2] ATS — Diagnosis and Management of CAP, official clinical practice guideline update — 2025 — <https://academic.oup.com/ajrccm/article/212/1/24/8435770>

2. COVID-19 therapeutics – repurposed drugs, remdesivir, IL-6 and JAK inhibitors, monoclonal antibodies and convalescent plasma

ASKED 4* · Intermediate answer

Asked in: Jun 2020 P-IV Q6(b) [5] · Jun 2021 P-IV Q2(b) [5] · Jun 2021 P-IV Q5(b) [5] · Jun 2021 P-IV Q7(a) [5] · Jun 2021 P-IV Q7(b) [5] · Dec 2021 P-IV Q5(a) [5] · Dec 2022 P-IV Q8(b) [5]

Q: Enumerate Old and Re-purposed Drugs used or under evaluation for the treatment of COVID-19. [5]

Q: Casirivimab-Indevimab. [5]

Q: Baricitinib. [5]

Q: IL-6 inhibition in COVID-19. [5]

Q: Remdesivir. [5]

Q: Role of Monoclonal antibody treatment for COVID-19. [5]

Q: Convalescent plasma in the management of COVID-19. [5]

Mechanism and drug groups

- COVID-19 therapy targets two phases: **viral replication** (early) and **hyperinflammation** (later).
- Repurposed ("old") drugs were tested early in the pandemic because no specific antiviral existed.
- Groups:
 - Direct antivirals: remdesivir, lopinavir-ritonavir, ribavirin, interferons.
 - Anti-inflammatory and immunomodulatory drugs: dexamethasone and hydrocortisone, IL-6 inhibitors, baricitinib.
 - Passive immunotherapy: convalescent plasma, monoclonal antibodies, IVIG.
 - Adjuncts: extracorporeal cytokine adsorption.

GUIDELINE

WHO — Therapeutics and COVID-19: living guideline — 15th version, August 2025 (accessed as the current version; recommendations on hydroxychloroquine, lopinavir-ritonavir and ivermectin quoted from the 7th version, 7 Dec 2021).

IDSA — Guidelines on the Treatment and Management of Patients with COVID-19 — September 2022 version, plus the 2025 update on baricitinib versus tocilizumab.

Old and repurposed drugs (Jun 2020 Q6b)

- Coronavirus work (SARS and MERS) showed activity of HIV protease inhibitors, ribavirin, type I interferons, niclosamide and indomethacin in animal or in vitro experiments. None of these had undergone randomised trials.
- **SARS:** no antiviral showed benefit. High-dose steroids with ribavirin gave no clear benefit and toxicity was common.
- **MERS:** ribavirin with IFN-alfa-2a improved 14-day survival but not 28-day survival. Glucocorticoids and macrolides did not reduce mortality.
- **SARS-CoV-2:** a single-centre open-label trial of lopinavir-ritonavir showed no clinical benefit.
- WHO (7th version, Dec 2021) recommended:
 - **Strongly against** hydroxychloroquine.
 - **Strongly against** lopinavir-ritonavir.
 - Against ivermectin except within a clinical trial.
- Other agents under evaluation included convalescent plasma, monoclonal antibodies, IVIG and drugs interrupting inflammatory pathways.
- Device: CytoSorb adsorbs circulating inflammatory mediators and received FDA EUA on 10 April 2020. Efficacy data were preliminary.

Remdesivir (Jun 2021 Q7b)

- **Mechanism:** an intravenous nucleotide prodrug that binds viral RNA-dependent RNA polymerase and causes premature termination of RNA transcription.
- FDA emergency use authorisation was issued on 1 May 2020.
- **Wuhan trial:** a single-centre double-blind RCT with 237 patients, 158 of them on remdesivir. There was no difference in time to clinical improvement.
- **Larger trial (ACTT-1 type):** 1062 patients randomised 1:1 to remdesivir or placebo.
 - Time to recovery was shorter by about **5 days**.
 - In severe disease the illness was shortened by a median of **7 days**.
 - There were fewer deaths, with a larger effect in severe respiratory illness.
 - It reduced new oxygen or ventilation requirement and shortened ventilation or ECMO duration.
- **IDSA 2022:** suggests remdesivir over no antiviral in hospitalised patients with **severe** COVID-19 (conditional recommendation, moderate certainty).
- **Dose and duration:** not confirmed from the sources used, so refer to the product label.

Corticosteroids (the anchor of anti-inflammatory therapy)

- **RECOVERY:** open-label RCT with 2014 patients on **dexamethasone 6 mg daily** (oral or IV) versus 4321 on usual care.
 - Absolute reduction in 28-day mortality was **2.8%** overall.
 - The reduction was **2.9%** in patients on oxygen and **11.8%** in ventilated patients.
 - In patients on neither oxygen nor ventilation, mortality was 3.8% higher, but the confidence interval crossed 1.0.
- **WHO prospective meta-analysis:** 7 RCTs, 1703 patients.
 - Mortality was 33% with steroids versus 42% with placebo.
 - The odds ratio was **0.66** (95% CI 0.53–0.82).
 - Hydrocortisone and dexamethasone showed little difference.
- **Common approach:** hydrocortisone at least 150 mg/day in divided doses, or dexamethasone at least 6 mg daily, for at least **7 days**, in severe hypoxaemic patients.

IL-6 inhibition and baricitinib (Jun 2021 Q7a, Q5b)

- **IL-6 inhibitors** (tocilizumab) target the cytokine pathway driving hyperinflammation.
- **Baricitinib** is an oral Janus kinase inhibitor with an anti-inflammatory action.
- IDSA 2022 recommendation for baricitinib:
 - In severe COVID-19, suggests baricitinib **with corticosteroids** (conditional, moderate certainty).
 - Dose is **4 mg/day** (renally adjusted) for up to **14 days** or until discharge.
 - Greatest benefit is in patients on high-flow oxygen or non-invasive ventilation.
 - Limited data suggest a mortality benefit even in mechanically ventilated patients.
 - If a corticosteroid is contraindicated, suggests baricitinib **plus remdesivir** over remdesivir alone (conditional, low certainty).
- **IDSA 2025 update:**
 - In hospitalised adults on systemic glucocorticoids with **rapidly progressing severe or critical** COVID-19, suggests adding **either baricitinib or tocilizumab** (conditional, low certainty).
 - Baricitinib may reduce progression to mechanical ventilation compared with tocilizumab (RCT RR 0.88, 95% CI 0.65–1.19), but this cannot exclude no difference.

Monoclonal antibodies (Jun 2021 Q2b; Dec 2021 Q5a)

- **Casirivimab-indevimab** is a neutralising monoclonal antibody cocktail directed at the receptor-binding portion of the spike glycoprotein. Neutralising antibody is directed against this region.
- Textbook status: anti-SARS-CoV-2 monoclonal antibodies were "under investigation" for passive immunotherapy.

- Efficacy depends on variant spike mutations. For example, WHO updated its **strong recommendation against sotrovimab** in non-severe COVID-19 after evidence of reduced effectiveness (January 2023 update).
- The practical position is that monoclonal antibodies are useful only when the circulating variant is susceptible.

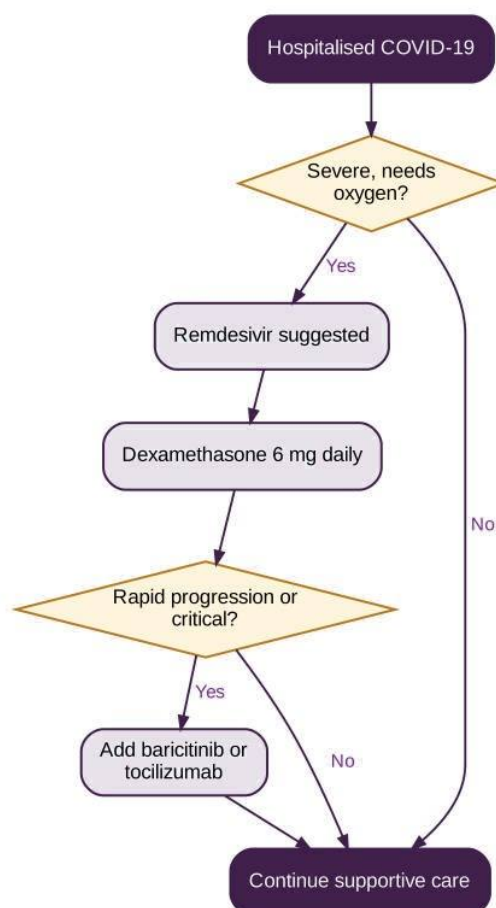
Convalescent plasma (Dec 2022 Q8b)

- **Rationale:** passive transfer of neutralising antibody from recovered donors.
- **SARS precedent:** an exploratory meta-analysis showed reduced mortality if given within **14 days** of illness.
- **WHO 7th version:** reviewed 16 RCTs in non-severe and in severe or critical illness.
- **IDSA 2022:** in ambulatory high-risk patients with no other treatment options, suggests FDA-qualified **high-titre** plasma within **8 days** of symptom onset (conditional).
- Earlier IDSA guidance (June 2020) limited plasma to clinical trials only.

Table 1: Summary of COVID-19 therapeutics

Agent	Role / stage	Key evidence	Guideline position
Dexamethasone 6 mg/day	Hypoxaemic and ventilated	RECOVERY: ARR 2.9% (O ₂), 11.8% (ventilated)	Standard of care
Remdesivir	Severe disease	Recovery shortened by about 5 days	IDSA: suggest in severe disease
Baricitinib 4 mg/day	Severe, on steroids	Most benefit on HFNO/NIV	IDSA: suggest with corticosteroids
Tocilizumab	Rapidly progressing severe or critical	Compared with baricitinib	IDSA 2025: either agent
Convalescent plasma	Ambulatory high-risk, early	SARS data within 14 days	IDSA: high-titre within 8 days
Hydroxychloroquine / lopinavir-ritonavir	None	No benefit	WHO: strong recommendation against

Flowchart 1: Immunomodulator selection in hospitalised COVID-19 (IDSA)



PEARLS

- Dexamethasone benefits patients needing oxygen or ventilation, and may harm those who need neither.
- RECOVERY ARR in ventilated patients was **11.8%**.
- Remdesivir shortens time to recovery and works best early in severe disease.
- The Wuhan remdesivir trial was negative on its primary end point.
- Baricitinib is given at **4 mg/day** for up to 14 days with steroids.
- IDSA 2025 accepts either baricitinib or tocilizumab as add-on to steroids.
- Hydroxychloroquine and lopinavir-ritonavir: WHO strongly recommends against.
- Monoclonal antibodies lose efficacy with spike variants, as with sotrovimab.
- Convalescent plasma is only suggested for high-titre use, within 8 days, in high-risk patients with no other options.
- Immunity to coronaviruses is short-lived, and reinfection rates are high.

Sources

- Textbook: Murray & Nadel 7e — Ch 46 Community-Acquired Pneumonia, §Treatment Failure › Less-Common Viral Pathogens — pp. 617.e22
- Textbook: Murray & Nadel 7e — Ch 46a COVID-19, §Treatment — pp. 631
- [w1] WHO — Therapeutics and COVID-19: living guideline, August 2025 (15th version) — 2025 — <https://www.who.int/publications/i/item/B09540>
- [w2] WHO — Therapeutics and COVID-19: living guideline, 7 December 2021 — 2021 — <https://www.who.int/docs/default-source/coronaviruse/2021.4-lg-therapeutics-and-covid-19-2021-12-07-en.pdf>
- [w3] IDSA — Guidelines on the Treatment and Management of Patients With COVID-19 (September 2022) — <https://academic.oup.com/cid/article/78/7/e250/6692369>
- [w4] IDSA — 2025 Clinical Practice Guideline Update: Baricitinib vs. Tocilizumab — 2025 — https://academic.oup.com/cid/article/82/Supplement_3/i18/8571316
- [w5] WHO — Therapeutics and COVID-19: living guideline, 13 January 2023 (PubMed 35917393) — <https://pubmed.ncbi.nlm.nih.gov/35917393>

3. COVID-19 vaccines – types, side effects, precaution dose, vaccine hesitancy and prevention strategies

ASKED 4* · Intermediate answer

Asked in: Dec 2020 P-IV Q8(b) [5] · Jun 2021 P-I Q5(a) [7] · Jun 2021 P-I Q5(b) [3] · Dec 2021 P-IV Q3(a) [5] · Apr 2023 P-IV Q10(b) [5]

Q: Vaccine in Covid-19. [5]

Q: Vaccination against COVID-19: types of vaccines and side effects. [7]

Q: Vaccine hesitancy. [3]

Q: Enumerate different strategies available for prevention against Corona virus. [5]

Q: Precautionary dose of Covid-19 vaccine. [5]

NOT IN TEXTBOOK

Searched in the supplied textbook pages for: COVID-19 vaccine, SARS-CoV-2 vaccination, precaution/booster dose, vaccine hesitancy, and prevention of coronavirus infection. The pages contain only a brief coronavirus section, which refers COVID-19 to Chapter 46a. They also contain the general outbreak infection-prevention principles of Chapter 59. The vaccine content below is therefore web-sourced, and the general prevention principles come from the textbook.

Definition and context

- **SARS-CoV-2** is an enveloped, positive-sense single-stranded RNA coronavirus.
- Its **spike (S) protein** mediates attachment and membrane fusion.
- Antibodies to spike are associated with protection, so spike is the main vaccine and therapeutic target.

- Vaccination is the central prevention measure. It works alongside isolation, personal protective equipment (PPE) and reporting.

Types of COVID-19 vaccines

- **Inactivated whole-virus**
 - Covaxin (BBV152) is grown in Vero cells and adjuvanted with an imidazoquinoline (Algel-IMDG).
 - WHO-listed schedule: 2 doses of 0.5 mL intramuscularly, 4 weeks apart.
- **Viral-vectored (adenovirus)**
 - Covishield is the Serum Institute of India product and uses the same technology as the AstraZeneca vaccine.
 - Janssen Ad26.COV2.S is a single-dose vectored vaccine.
- **mRNA vaccines**
 - Pfizer and Moderna are WHO-listed.
 - WHO accepts them, or the vectored vaccines, as the second dose after Covaxin.
- **Other vaccines in India**
 - ZyCoV-D, Covaxin, CorBEvax and Covovax received emergency use authorisation (EUA) for children.
 - Covaxin was the only option for ages 15–18 years at rollout.

Table 1: Indian schedule (National COVID-19 Vaccination Programme)

Vaccine	Primary schedule	Interval
Covishield	2 doses	12–16 weeks (84–112 days)
Covaxin	2 doses	4–6 weeks (28–42 days)

- Heterologous precaution dose with CorBEvax was allowed only after two doses of Covaxin or Covishield.

Side effects and safety

- Individuals with a history of **anaphylaxis to any vaccine component** should not receive the vaccine (WHO guidance for Covaxin).
- Adverse events following immunisation (AEFI) are monitored in India through the **Pharmacovigilance Programme of India (PvPI)**.
- Observational Indian data on the precautionary third dose found it reasonably safe.
- Vaccinated persons should be observed after the dose, and AEFI should be reported.

Precaution (booster) dose – India

- MoHFW called it a "precaution dose" and introduced it for healthcare workers (HCWs), frontline workers (FLWs) and people aged 60 years or more with comorbidities from **10 January 2022**.
 - The original interval was **9 months (39 weeks)** after the second dose.
 - For those aged 60 or more with comorbidities, it was given on doctor's advice.
- From **16 March 2022**, it was extended to all those above 60 years.
- From **10 April 2022**, it was offered to all those aged 18 years or more at private centres, after 9 months.
- From **6 July 2022**, the interval was cut to **6 months (26 weeks)** for all adults aged 18 years or more.
 - It is free at government centres.
- Early dosing was allowed for international travel, with a minimum of **90 days** after the second dose.
- Eligibility is recorded on Co-WIN, which sends an SMS when the dose is due.
- The precaution dose was to be the **same vaccine** as the primary series, or CorBEvax after Covaxin or Covishield.
- Uptake was low:
 - General-population coverage of the booster was reported at about **2.5%** by 6 June 2022.
- **WHO SAGE roadmap (March 2023; updated 10 November 2023)**
 - The terms "initial doses" and "re-vaccination" replace "primary series" and "booster".
 - The roadmap simplifies the schedule because most people have already been infected.

- A **monovalent Omicron-only vaccine** can be used for initial and booster doses.
- An extra dose **6–12 months** after the last dose is advised for the high-priority group. This group is older adults, younger adults with significant comorbidities, the immunocompromised, pregnant women and frontline HCWs.
- Boosters are not routinely recommended for medium- and low-risk groups.

Vaccine hesitancy

- **Definition:** delay in accepting, or refusal of, vaccination despite vaccine availability.
- Observed in India as a **low acceptance rate** of boosters compared with first and second doses.
- Younger age and delay in taking the first dose predicted delayed uptake of the precaution dose among HCWs.
- Contributing factors:
 - Concerns about safety and speed of development.
 - Emergency-use status of vaccines.
 - Perceived low risk after prior infection.
 - Misinformation.
- Countermeasures:
 - Transparent communication of AEFI data.
 - Co-WIN reminders and easy access.
 - Free doses at government centres.
 - Priority and counselling for HCWs.
 - WHO urges countries to improve coverage in high-priority groups.

Strategies for prevention of coronavirus infection

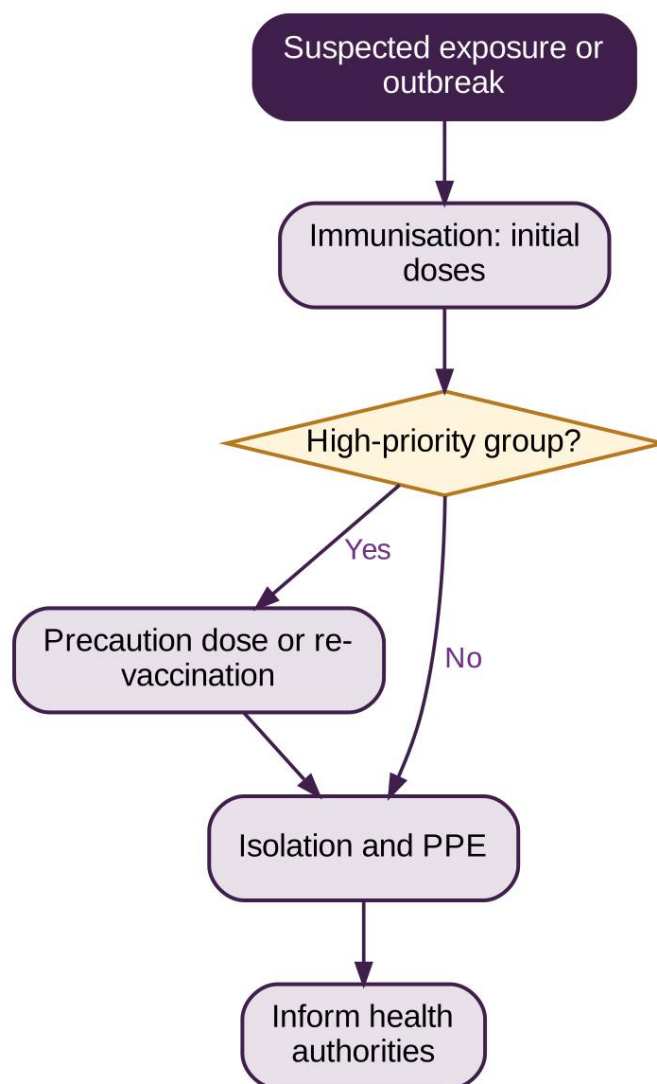
GUIDELINE

WHO — SAGE Roadmap on uses of COVID-19 vaccines in the context of Omicron and high population immunity — updated 10 November 2023.

MoHFW (India) — Guidelines for COVID-19 vaccination, precaution dose — January 2022, with the July 2022 interval revision.

- **Vaccination**
 - Primary doses, then precaution dose or re-vaccination for high-priority groups.
 - First responders and HCWs are priority groups during influenza and coronavirus pandemics.
- **Infection prevention and control**
 - Start as soon as a transmissible disease is suspected, even before confirmation.
 - Isolate the patient, and use PPE matched to the route of transmission (droplet, contact or airborne).
 - Involve the hospital infection-prevention team in all areas, including laboratories and radiology.
 - Protect staff and unaffected patients.
- **Reporting**
 - Inform local health authorities and follow notification rules for surveillance.
- Non-pharmacological public measures are masking, hand hygiene, distancing and ventilation. These are not covered in the sources used here.

Flowchart 1: Prevention strategy ladder



PEARLS

- India's **precaution dose** interval was cut from **9 months (39 weeks)** to **6 months (26 weeks)** on 6 July 2022.
- It was first given to HCWs, FLWs and people aged 60+ with comorbidities from **10 January 2022**.
- Covishield is spaced **12–16 weeks**, and Covaxin **4–6 weeks**.
- Covaxin is an **inactivated** vaccine, and Covishield is **vector-based** (ChAdOx1).
- WHO now uses "initial doses" and "re-vaccination", and recommends an extra dose at **6–12 months** for high-priority groups.
- Spike protein is the vaccine target, and antibodies to spike are linked to protection.
- Prior anaphylaxis to a vaccine component is the key contraindication.
- Start infection-control measures before diagnosis is confirmed.
- Hesitancy shows up as low booster uptake, so use counselling and easy access to counter it.

Sources

- Textbook: Murray & Nadel 7e — Ch 46 Community-Acquired Pneumonia, §Treatment Failure › Less-Common Viral Pathogens — pp. 617.e20 to 617.e20
- Textbook: Murray & Nadel 7e — Ch 59 Outbreaks, Pandemics, and Bioterrorism, §Other Syndromes / Management — pp. 800 to 800
- [w] WHO — Roadmap on uses of COVID-19 vaccines in the context of Omicron and high population immunity (updated 30 March 2023; latest update 10 November 2023) — <https://iris.who.int/server/api/core/bitstreams/113dda26-2938-4d3c-a0a1-0d3754e01803/content>

- [w2] WHO — Policy brief: COVID-19 vaccination — https://www.who.int/docs/default-source/coronaviruse/policy-briefs/policy-brief_covid-19_vaccination.pdf?download=true
- [w3] MoHFW India — Guidelines for COVID-19 vaccination of children 15–18 years and precaution dose to HCWs, FLWs and 60+ with comorbidities (January 2022) — <https://covid19dashboard.mohfw.gov.in/pdf/GuidelinesforCOVID19VaccinationofChildrenbetween15to18yearsandPrecautionDosestoHCWsFLWs&60populationwithcomorbidities.pdf>
- [w4] MoHFW India — FAQs on COVID-19 Vaccines and Vaccination Program — <https://covid19dashboard.mohfw.gov.in/pdf/FAQsCOVID19vaccinesvaccinationprogramWebsiteupload27Sep.pdf>
- [w5] WHO — The Bharat Biotech BBV152 COVAXIN vaccine: what you need to know — <https://www.who.int/news-room/feature-stories/detail/the-bharat-biotech-bbv152-covaxin-vaccine-against-covid-19-what-you-need-to-know>
- [w6] PubMed/PMC — Safety monitoring of precautionary third dose of COVID-19 vaccines in a district in Northern India — <https://pubmed.ncbi.nlm.nih.gov/38948581>
- [w7] PMC — Coverage of COVID-19 booster dose (precautionary) in the adult population: an online survey — <https://pmc.ncbi.nlm.nih.gov/articles/PMC9376214/>
- [w8] PMC — Time-to-event analysis of COVID-19 precautionary dose vaccination among healthcare workers (Co-WIN data) — <https://pmc.ncbi.nlm.nih.gov/articles/PMC12349814/>
- [w9] WHO — The Janssen Ad26.COV2.S COVID-19 vaccine: what you need to know — <https://www.who.int/news-room/feature-stories/detail/the-j-j-covid-19-vaccine-what-you-need-to-know>

4. COVID-19 – evaluation and management of adults: home, hospital and critical care

ASKED 3* · Intermediate answer

Asked in: Dec 2021 P-IV Q3(b) [5] · Dec 2022 P-IV Q6(b) [5] · Oct 2023 P-IV Q6(a) [5]

Q: Evaluation and management of COVID-19 case in adults. [5]

Q: Home and hospital management of COVID-19 disease. [5]

Q: Caring for the critically ill patient with COVID-19. [5]

Definition and why it matters

- **COVID-19** is the illness caused by SARS-CoV-2. It ranges from asymptomatic infection to pneumonia, ARDS and multi-organ failure.
- Silent hypoxaemia is a feature. Patients may be hypoxaemic without dyspnoea or accessory muscle use, so SpO₂ must be measured and not judged by symptoms.
- Prolonged respiratory failure is common. In critical COVID-19 the median duration of mechanical ventilation in survivors was **>2 weeks**.
- Inflammation, immunothrombosis and a hypoxaemic ARDS phenotype drive severe disease. Corticosteroids and thromboprophylaxis therefore matter.

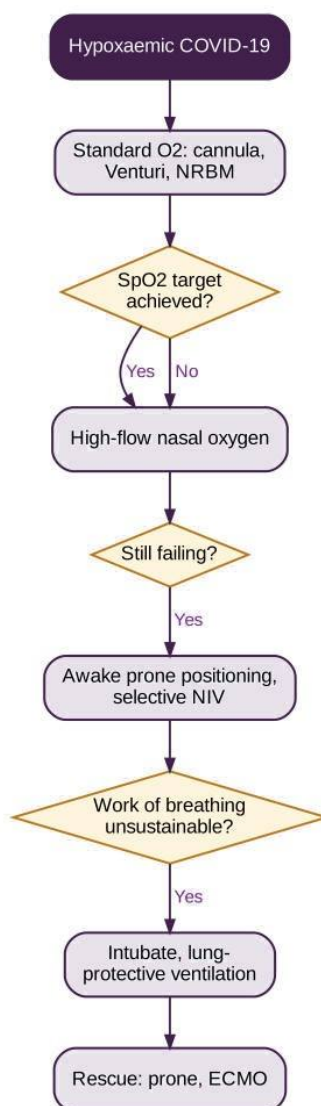
Evaluation

- Clinical severity grading is the first step. It decides the site of care: home, ward or ICU.
- The Indian protocol used **RR ≥24 and SpO₂ <94% on room air** as the defining parameters of moderate disease. Such patients are admitted for isolation and monitoring.
- Diagnosis is by real-time or conventional **RT-PCR**. Antibody tests are not recommended for diagnosing current infection.
- Baseline tests for admitted patients include a complete blood count with differential, absolute lymphocyte count, and renal and liver function tests.
- Look for secondary bacterial infection or sepsis. Sepsis in adults is life-threatening organ dysfunction from a dysregulated host response. Organ dysfunction signs are altered mentation, fast breathing, low SpO₂, low urine output, hypotension and raised lactate.
- Oxygenation impairment is graded by PaO₂/FiO₂:

- Mild ARDS: $200 < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$, with PEEP/CPAP $\geq 5 \text{ cmH}_2\text{O}$.
- Moderate ARDS: $100 < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$.

Table 1: Site of care by severity

Category	Setting	Core care
Mild / asymptomatic	Home isolation	Symptomatic care, SpO ₂ self-monitoring, early antiviral if high-risk
Moderate (RR ≥ 24 , SpO ₂ $< 94\%$)	Ward	Oxygen, monitoring, thromboprophylaxis
Severe / critical	HDU / ICU	Escalating oxygen support, steroids, lung-protective ventilation

Flowchart 1: Escalation of respiratory support in COVID-19 hypoxaemia

Management

GUIDELINE

MoHFW (India) — Clinical Guidance for Management of Adult COVID-19 Patients — updated 28 March 2023. WHO — Therapeutics and COVID-19 living guideline — version 13, January 2023. IDSA — 2025 focused update on antiviral treatment of mild–moderate COVID-19 in adults.

Home management (mild disease)

- Isolate at home with symptomatic care and monitoring for progression. Provide a follow-up mechanism.
- Check SpO₂ regularly. Escalate to hospital if breathlessness or low SpO₂ develops.

- **Corticosteroids are not recommended in non-severe disease.** WHO gives a conditional recommendation against them.
- Antivirals for patients at high risk of progression, started **within 5 days of symptom onset**:
 - **Nirmatrelvir/ritonavir**: 300 mg/100 mg every 12 h for 5 days if eGFR >60 mL/min. Use 150 mg/100 mg every 12 h for 5 days if eGFR 30–<60 mL/min.
 - Alternative: IV remdesivir for 3 days.
 - WHO gives a strong recommendation for nirmatrelvir-ritonavir in non-severe illness at highest risk of hospitalisation.
- Do not use repurposed drugs without evidence of benefit.

Hospital management (moderate–severe)

- Give oxygen for hypoxaemia even without dyspnoea. Targets are **SpO₂ ≥90%** in non-pregnant adults and 92–96% in pregnant patients. Start at 5 L/min and titrate.
- Watch for anaerobic metabolism (lactic acidosis) or incipient organ failure (altered mentation, myocardial injury). The SpO₂ target should be the value that avoids these.
- **Dexamethasone 6 mg daily**, orally or IV, is the standard dose. A common approach is dexamethasone ≥6 mg daily or hydrocortisone 150 mg/day in divided doses, for at least **7 days**, in severely ill hypoxaemic patients.
- The RECOVERY trial (dexamethasone 6 mg daily) showed:
 - 28-day mortality fell by an absolute **2.8%** overall.
 - The fall was **2.9%** in patients on oxygen and **11.8%** in ventilated patients.
 - There was no benefit, and a nonsignificant 3.8% higher mortality, in patients needing neither oxygen nor ventilation.
- The WHO prospective meta-analysis gave an odds ratio for death of **0.66** (95% CI 0.53–0.82). Mortality was 33% with steroids against 42% with placebo.
- Remdesivir is an IV nucleotide prodrug that inhibits viral RNA-dependent RNA polymerase.
 - In the ACTT-1 trial (1062 patients) it shortened time to recovery by about 5 days. The reduction was about 7 days in severe disease.
 - It may also reduce the risk of respiratory deterioration.
- WHO suggests **prophylactic-dose** heparin rather than therapeutic or intermediate dose in severe or critical disease (conditional).
- WHO recommends against statins and SGLT-2 inhibitors in severe or critical COVID-19 (strong). It suggests against metformin in acute management (conditional).
- Lopinavir-ritonavir showed no clinical benefit.
- Treat suspected secondary bacterial infection with antibiotics per local guidance.

Critical care

- **Oxygen devices**:
 - Standard cannulas, Venturi masks and non-rebreather masks suffice for many patients.
 - High-flow nasal oxygen gives higher flows and a higher effective FiO₂. It may lower work of breathing and oxygen consumption.
 - NIV is helpful only in selected cases, such as an imminently reversible cause. Use it cautiously because respiratory failure is prolonged.
 - HFNO and NIV may spread virus, so use them in areas with isolation, environmental precautions and PPE.
- **Awake prone positioning** may improve oxygenation. Observational data are mixed and the gains may not last.
- **Intubation**:
 - There are no firm criteria. Some experts favour early intubation and others advise caution. A small retrospective study found early intubation was not associated with lower mortality.
 - Assess whether work of breathing is too high to sustain, using serial examinations.
 - The most experienced clinician should intubate, using rapid sequence induction with neuromuscular blockade.
 - Keep a viral filter in the breathing circuit at all times.
- **Lung-protective ventilation**:

- Use tidal volume **6–8 mL/kg predicted body weight** (the Indian guidance and ARDS guidelines state 4–8 mL/kg), provided plateau pressure, driving pressure and mechanical power stay low.
- Keep plateau pressure **<30 cmH₂O**.
- Volume- or pressure-controlled modes are both acceptable. In pressure control, excessive patient effort can produce excessive tidal volumes.
- Respiratory mechanics are as heterogeneous as in non-COVID ARDS, so individualise settings, sedation, analgesia and neuromuscular blockade.
- **Prone ventilation** for at least **12 h/day** in severe ARDS (**PaO₂/FiO₂ <100 mmHg**).
- Rescue therapies (recruitment, high PEEP, inhaled pulmonary vasodilators, ECMO) have undefined roles. Consider ECMO in refractory hypoxaemia.
- Use conservative fluids once shock has been absent for 12 h. Follow the Surviving Sepsis bundle for sepsis or septic shock.
- Hold early goals-of-care and advance-directive discussions, because mortality is high with prolonged ventilation. Use video conferencing when visiting is restricted.

PEARLS

- Silent hypoxaemia occurs, so measure SpO₂ in every patient.
- Dexamethasone 6 mg daily for about 7–10 days helps only if the patient needs oxygen or ventilation. Steroids may harm patients who need neither.
- RECOVERY absolute mortality reduction was 2.8% overall and 11.8% in ventilated patients.
- Nirmatrelvir/ritonavir is for high-risk, non-severe patients within 5 days of symptom onset. Adjust the dose for eGFR.
- Tidal volume is by predicted body weight, with plateau pressure <30 cmH₂O. Prone positioning for ≥12 h/day if PaO₂/FiO₂ <100.
- Use NIV and HFNO cautiously and with airborne precautions.
- Thromboprophylaxis is at prophylactic, not therapeutic, heparin dose in severe disease.
- Do not use hydroxychloroquine, lopinavir-ritonavir or statins for treatment.

Sources

- Textbook: Murray & Nadel 7e — Ch 46 Community-Acquired Pneumonia (COVID-19), §Treatment — pp. 630–631
- Textbook: Murray & Nadel 7e — Ch 59 Outbreaks, Pandemics, and Bioterrorism, §Management › Supportive care — pp. 801–801
- [w1] WHO — Therapeutics and COVID-19: living guideline (v13) — 2023 — <https://www.ncbi.nlm.nih.gov/books/NBK582436/>
- [w2] WHO — Therapeutics and COVID-19: living guideline (IRIS) — <https://iris.who.int/server/api/core/bitstreams/23655773-e9d2-4eba-96d9-296d10bb9c61/content>
- [w3] IDSA — 2025 Guideline Update, antiviral treatment for mild to moderate COVID-19 in adults — 2025 — https://academic.oup.com/cid/article/82/Supplement_3/i1/8571315
- [w4] MoHFW India — Clinical Guidance for Management of Adult COVID-19 Patients (updated 28 March 2023) — <https://covid19dashboard.mohfw.gov.in/notification.html>
- [w5] MoHFW India — Clinical Management Protocol: COVID-19 — 2020 — <https://covid19dashboard.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19dated27062020.pdf>
- [w6] MoHFW India — Revised Guidelines on Clinical Management of COVID-19 — 2020 — <https://covid19dashboard.mohfw.gov.in/pdf/RevisedNationalClinicalManagementGuidelineforCOVID1931032020.pdf>

5. Community-acquired pneumonia – aetiology and severity assessment (CURB-65, PSI, ATS/IDSA criteria)

ASKED 2* · Intermediate answer

Asked in: Dec 2022 P-II Q1(a) [5] · Apr 2023 P-III Q10(a) [5]

Q: Aetiology and severity assessment of community acquired pneumonia. [5]

Q: Assessment of severity of community acquired pneumonia. [5]

Definition and importance

- **CAP** is an acute lung infection acquired outside hospital. It usually shows as fever, cough and a new radiographic opacity.
- Severity assessment decides the site of care: outpatient, ward or ICU.
- It also guides how broad the empirical antibiotics should be, and how intensive the monitoring.
- Delay in starting antibiotics of more than 4 to 8 hours is associated with longer stay and higher mortality.

Aetiology

- The pathogen is not identified in up to **60%** of patients, even with PCR-based diagnostics.
- **S. pneumoniae** and respiratory viruses are common in all settings.
- Up to **20%** of severe CAP is polymicrobial.

Table 46.1 Common Causes of Community-Acquired Pneumonia by Patient Location		
Outpatient	Hospitalized	ICU
MOST FREQUENT <i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> Respiratory viruses	<i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> Respiratory viruses	<i>Streptococcus pneumoniae</i> Viruses (e.g., influenza A virus)
OTHER ORGANISMS OFTEN ISOLATED <i>Chlamydia pneumoniae</i> <i>Coxiella burnetii</i> <i>Legionella</i> species <i>Haemophilus influenzae</i>	<i>Haemophilus influenzae</i> <i>Pseudomonas aeruginosa</i> (and enteric gram-negative bacilli) <i>Staphylococcus aureus</i> <i>Legionella</i> species Aspiration pneumonia	<i>Legionella</i> species <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i> (and enteric gram-negative bacilli)

ICU, intensive care unit.

Modified from references 4, 40, 42–45.

Table 46.1 — Murray & Nadel 7e, pr.602. Table 46.1 Common Causes of Community-Acquired Pneumonia by Patient Location

Table 1: Common causes of CAP by site of care

Setting	Most frequent	Other organisms often isolated
Outpatient	<i>S. pneumoniae</i> , <i>M. pneumoniae</i> , respiratory viruses	<i>C. pneumoniae</i> , <i>C. burnetii</i> , <i>Legionella</i> , <i>H. influenzae</i>
Hospitalised (ward)	<i>S. pneumoniae</i> , <i>M. pneumoniae</i> , respiratory viruses	<i>H. influenzae</i> , <i>Legionella</i> , aspiration pneumonia
ICU	<i>S. pneumoniae</i> , viruses (e.g. influenza A)	<i>Legionella</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> and enteric gram-negative bacilli

Viral causes

- During outbreaks, influenza accounts for more than **50%** of viral pneumonia in adults.
- Other viral causes are rhinovirus, human metapneumovirus, RSV, adenovirus, parainfluenza, coronaviruses (including SARS-CoV-2) and varicella.

Regional, host and seasonal factors

- Gram-negative bacilli are commoner in **Asia** and Southern Africa. **K. pneumoniae** is the most frequent, especially in ICU admissions.
- **P. aeruginosa** is uncommon without specific risk factors:
 - recent antibiotics
 - immunocompromise
 - bronchiectasis, cystic fibrosis or severe COPD

- **CA-MRSA** causes necrotising and haemorrhagic pneumonia.
- Influenza, *S. pneumoniae* and *H. influenzae* are commoner in **winter**. *Legionella* is commoner in summer and autumn.
- *Legionella* is often linked to a common environmental source in outbreaks.
- Age effects:
 - Children under 2 years: *S. pneumoniae* and RSV.
 - Older adults: more *H. influenzae*, group B streptococci, *Moraxella*, *Legionella*, gram-negatives and polymicrobial infection.
 - Over 80 years: more aspiration pneumonia and less *Legionella*.
- **Alcohol** increases aspiration and impairs immunity, especially in pneumococcal CAP.
- **Smoking** doubles the risk of CAP. It is associated with *S. pneumoniae*, *Legionella* and influenza.
- Pneumococcal conjugate vaccination reduces *S. pneumoniae* CAP, but non-vaccine serotypes may replace it.

Severity assessment

- There are two separate questions:
 - Does the patient need admission? (PSI, CURB-65)
 - Does the patient need ICU or high-level care? (ATS/IDSA criteria)
- Neither PSI nor CURB-65 is accurate for ICU need when there is no obvious indication. Obvious indications are mechanical ventilation or vasopressor need.
- Patients admitted to the ward and later moved to ICU have higher mortality than those admitted directly to ICU.

CURB-65 (BTS)

- Score **1 point** each for:
 - Confusion
 - Urea >7 mmol/L (BUN >20 mg/dL)
 - Respiratory rate ≥30/min
 - BP: systolic <90 or diastolic ≤60 mm Hg
 - 65: age ≥65 years
- Action by score:
 - 0–1: outpatient treatment.
 - 2: brief inpatient or supervised outpatient care.
 - ≥3: hospitalise. Consider ICU for a score of 4–5.
- Advantage: it is simple and bedside-applicable (CRB-65 omits urea).
- Limitation: its performance is variable in low- and middle-income countries, and it is of little use in sub-Saharan Africa.

Pneumonia Severity Index (PSI, Fine)

- It was derived in 14,199 patients and validated in 38,039.
- The score is age in years (minus 10 for women, plus 10 for nursing-home residents), plus points for the items below.
- It is heavily weighted by **age**. It is less useful at the extremes of age and is invalid in children.

Patient Characteristic	Points Assigned
DEMOGRAPHIC FACTORS	
Men	Age (yr)
Women	Age (yr) – 10
Nursing home residents	Age (yr) + 10
COMORBID ILLNESSES	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
PHYSICAL EXAMINATION FINDINGS	
Altered mental status	+20
Respiratory rate ≥30 breaths/min	+20
Systolic blood pressure <90 mm Hg	+20
Temperature <35°C or ≥40°C	+15
Pulse ≥125 beats/min	+10
LABORATORY FINDINGS	
pH <7.35	+30
BUN ≥20 mg/dL (≥10.7 mmol/L)	+20
Sodium <130 mEq/L	+20
Glucose ≥250 mg/dL (≥13.9 mmol/L)	+10
Hematocrit <30%	+10
PaO ₂ <60 mm Hg or O ₂ saturation <90%	+10
Pleural effusion	+10

A risk score is obtained by summing the patient's age in years (age – 10 for women) and the points for each applicable patient characteristic. Patients with a score <10 are candidates for outpatient treatment, whereas those with scores ≥10 warrant hospitalization. Proper management of patients with scores of 70 to 90 requires careful application of clinical judgment. BUN, Blood urea nitrogen; PaO₂, arterial oxygen pressure. Modified from Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243–250.

Table 46.3 — Murray & Nadel 7e, pr.609. Table 46.3 Pneumonia Severity Index Scoring System for Determining Risk of Complications in Patients with Community-Acquired Pneumonia

Table 2: PSI variables and points

Domain	Variable (points)
Comorbidity	Neoplasm +30; liver disease +20; CHF, cerebrovascular disease, renal disease +10 each
Examination	Altered mental status, RR ≥30, SBP <90 +20 each; temperature <35 or ≥40 °C +15; pulse ≥125 +10
Laboratory	pH <7.35 +30; BUN ≥30 mg/dL and Na <130 mEq/L +20 each; glucose ≥250 mg/dL, haematocrit <30%, PaO ₂ <60 mm Hg or SaO ₂ <90%, pleural effusion +10 each

- Action by score:
 - ≤70 (class I–II): outpatient treatment.
 - 71–90 (class III): brief hospitalisation may benefit.
 - >90 (class IV–V): inpatient care.
- Compared with CURB-65, PSI predicts short-term mortality better and classifies more patients as low risk.
- Limitation: neither score captures social and logistic issues. These include reliable oral intake and home support.
- PSI underestimates the need for admission in **pregnancy**.

ATS/IDSA severe CAP criteria

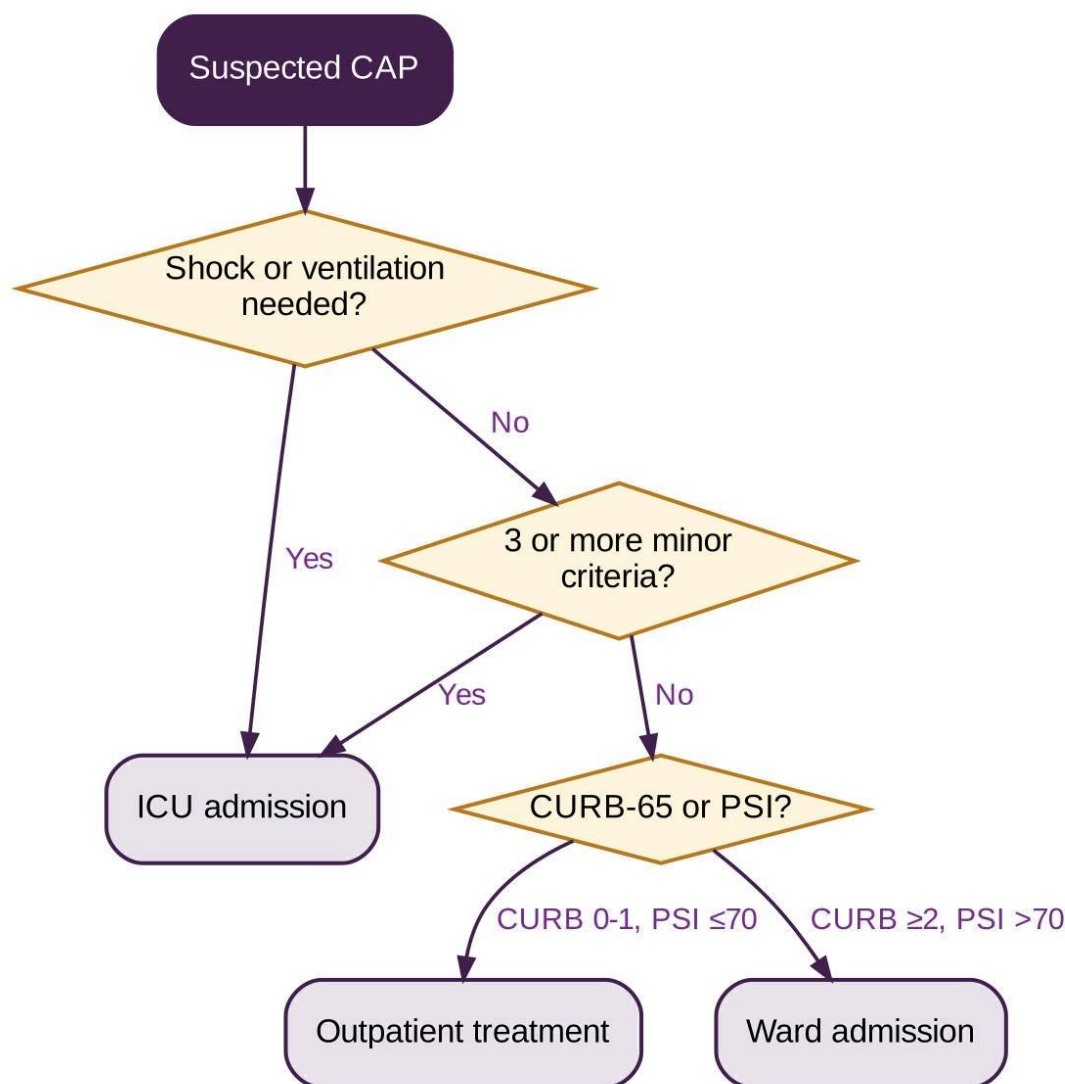
- **Severe CAP** is either one major criterion or three or more minor criteria.
- This definition is endorsed in the 2019 ATS/IDSA guideline and retained in the 2025 ATS update.
- For patients without a major criterion, the guideline suggests using the minor criteria with clinical judgement to guide the level of care.
- A meta-analysis found that one major or three minor criteria had a pooled sensitivity of 84% and specificity of 78% for ICU admission.

Table 3: ATS/IDSA severe CAP criteria

Major (either one)	Minor (three or more)
Septic shock needing vasopressors	RR ≥30/min
Respiratory failure needing mechanical ventilation	PaO ₂ /FiO ₂ ≤250
	Multilobar infiltrates
	Confusion/disorientation
	Uraemia (BUN ≥20 mg/dL)
	Leukopenia (WBC <4000/μL)
	Thrombocytopenia (platelets <100,000/μL)
	Hypothermia (core temperature <36 °C)
	Hypotension needing aggressive fluid resuscitation

- Other ICU-triage scores exist. They share risk factors and perform similarly. Their best use is to flag at-risk patients for extra monitoring.

Flowchart 1: Stepwise severity assessment and site of care



Other severity markers

- Hypoxaemia: $\text{SpO}_2 < 90\%$ or $\text{PaO}_2 < 60$ mm Hg.
- Bilateral or multilobar disease and a pleural effusion.
- Immunosuppression, including granulocytopenia ($< 500/\text{mm}^3$), which is linked to fulminant pneumonia.
- Comorbidity, and age > 65 years.

PEARLS

- CURB-65 is a 5-item, 1-point score. Admit at ≥ 2 and consider ICU at 4–5.
- PSI: outpatient ≤ 70 , class III 71–90, inpatient > 90 . It is age-dominated.
- Severe CAP = **1 major or ≥ 3 minor** ATS/IDSA criteria. The major criteria are vasopressors and mechanical ventilation.
- There are 9 minor criteria. Remember them as the CURB-65 elements plus $\text{PaO}_2/\text{FiO}_2 \leq 250$, multilobar infiltrates, leukopenia, thrombocytopenia and hypothermia.
- The pathogen is unidentified in up to 60% of CAP. *S. pneumoniae* is the commonest cause in every setting.
- Severe-CAP organisms: *S. pneumoniae*, *Legionella*, *S. aureus*, *P. aeruginosa*/gram-negatives and influenza.
- In Asia, *K. pneumoniae* is the leading gram-negative cause, especially in ICU.
- Severity scores predict mortality. They do not capture social factors, and PSI underestimates risk in pregnancy.

Sources

- Textbook: Murray & Nadel 7e — Ch 46 Community-Acquired Pneumonia, §Epidemiology — pp. 602–602

- Textbook: Murray & Nadel 7e — Ch 46 Community-Acquired Pneumonia, §Therapeutic Approach to Pneumonia — pp. 608–609
- Textbook: Murray & Nadel 7e — Ch 129 The Lungs in Obstetric and Gynecologic Diseases, §Bacterial Pneumonia — pp. 1803–1803
- [w1] ATS — Diagnosis and Management of Community-acquired Pneumonia: An Official ATS Clinical Practice Guideline (Am J Respir Crit Care Med) — 2025 — <https://academic.oup.com/ajrccm/article/212/1/24/8435770>
- [w2] ATS/IDSA — Diagnosis and Treatment of Adults with Community-acquired Pneumonia (Am J Respir Crit Care Med) — 2019 — <https://academic.oup.com/ajrccm/article/200/7/e45/8496962>
- [w3] ATS — Summary for clinicians: CAP guideline (Ann Am Thorac Soc) — 2025 — <https://academic.oup.com/annalsats/article/23/7/1001/8554088>

6. Community-acquired pneumonia – causative organisms, diagnostic work-up and treatment, including outpatient empiric antibiotics

ASKED 3* · Long answer

Asked in: Dec 2022 P-II Q3(b) [5] · May 2024 P-I Q6 [10] · Jun 2025 P-II Q10(b) [5]

Q: Management of CAP in out-patient setting. [5]

Q: Causative organisms, diagnostic work-up and principles of treatment of community acquired pneumonia. [10]

Q: Empiric antibiotic selection in adults outpatient of community-acquired pneumonia. [5]

Definition and importance

- **Community-acquired pneumonia (CAP)** is an acute infection of the lung parenchyma acquired outside hospital. It is usually bacterial or viral.
- Pneumonia is the infection most often linked with a poor outcome in profoundly neutropenic patients.
- Most patients are treated as outpatients, and the pathogen is rarely identified at presentation.
- Initial therapy is therefore **empirical**. It is guided by severity, comorbidity, recent antibiotics and local epidemiology.
- Rapid antibiotic start improves outcome.
- The old category of health-care-associated pneumonia has been removed from the North American HAP/VAP guideline. Such patients are usually infected with non-multidrug-resistant CAP pathogens.

Causative organisms

Typical bacteria

- *Streptococcus pneumoniae* is the commonest cause.
 - Penicillin resistance is due to altered penicillin-binding proteins, not β -lactamase.
 - Cefotaxime, ceftriaxone and cefepime retain activity against 75–95% of non-meningeal isolates.
 - Recent exposure to an antibiotic raises the chance of resistance to that class. Avoid agents used in the previous 90 days.
 - Asian data (2012–2017) showed 67% macrolide resistance in adult pneumococcal CAP or invasive disease.
- *Haemophilus influenzae* is important in COPD patients.
 - 20–50% of isolates produce β -lactamase.
 - Mortality is 2–7%, and up to 20% in bacteraemic elderly patients with comorbidity.
- *Moraxella catarrhalis* causes mild disease with lower-lobe opacities, mostly in COPD and the elderly.
- *Staphylococcus aureus* (including CA-MRSA), *Klebsiella pneumoniae* and other Enterobacteriaceae, and *P. aeruginosa* are the other bacterial causes. They are more likely in comorbid hosts and in nonresponders.

Atypical organisms

- *Legionella pneumophila* accounts for 2–6% of sporadic CAP and is one of the commonest causes of severe CAP.
 - It is acquired by inhaling contaminated aerosols from water systems, air-conditioning or whirlpool baths.
 - It is a facultative intracellular pathogen.

- *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are treated with doxycycline or a macrolide.
- *Coxiella burnetii* (Q fever) and *Chlamydophila psittaci* are treated with doxycycline.

Viral and endemic or regional organisms

- Influenza and RSV are common causes.
 - Bacterial superinfection is common in both. Look for it if the patient worsens.
- **Melioidosis** (*Burkholderia pseudomallei*) is endemic in Southeast Asia and northern Australia.
 - It can cause acute fulminant pneumonia or chronic upper-lobe cavitation that mimics tuberculosis.
 - It is not sensitive to the usual CAP antibiotics.
- **Tuberculosis** and endemic fungi must be considered in the right setting.
- In India, tuberculosis is the key mimic and co-diagnosis. Avoid fluoroquinolones when TB is possible, because as few as 10 days can select resistant *M. tuberculosis*.

Pathophysiology (brief)

- Organisms reach the lung by micro-aspiration of upper-airway flora or by inhalation of aerosols (*Legionella*).
- Most pathogens colonise the upper respiratory mucosa first. *Legionella* is the exception.
- *Legionella* infects alveolar macrophages and forms vacuoles that evade lysosomal fusion.
- Host defence defects raise risk. These include neutrophil dysfunction, immunosuppression, smoking, diabetes and chronic cardiopulmonary disease.

Clinical features

- Symptoms are fever, productive cough, dyspnoea and pleuritic chest pain. Signs are tachypnoea and consolidation.
- Elderly patients may present with confusion or prostration alone.
- Pneumococcal pneumonia usually responds clinically within **24–48 hours** of appropriate antibiotics.
- *Moraxella* pneumonia is mild, with productive cough and dyspnoea. High fever and pleuritic pain are uncommon.
- *Legionella* and melioidosis may present as severe pneumonia with sepsis.
- Severe disease shows RR ≥ 30 /min, systolic BP < 90 mmHg, altered mentation and hypoxaemia.

Diagnostic work-up

- **Severity assessment comes first.** It decides the site of care.
- Obtain **specimens for culture before antibiotics** in admitted patients.
- A brief delay for diagnostics is acceptable if the patient is not hypotensive. Delays of **>4–8 hours** are linked with longer stay and higher mortality.
- Outpatients usually need no microbiological work-up, because pathogens are rarely identified.

Table 1: Investigations in CAP

Test	Finding	Meaning
Chest radiograph	New infiltrate or consolidation	Confirms pneumonia. Pleural effusion adds points in PSI
Pulse oximetry or ABG	PaO ₂ < 60 mmHg or SpO ₂ $< 90\%$	Hypoxaemia. Pushes towards admission
Blood tests (urea, sodium, glucose, haematocrit, pH)	Abnormal values	Components of PSI
Sputum Gram stain and culture, blood culture	Predominant organism	Pathogen-directed therapy. Only screened sputum is useful (<i>Moraxella</i>)
Procalcitonin, CRP	Fall of PCT by day 3–4	Correlates with response. High initial PCT or CRP predicts poor response
Multiplex PCR	Pathogen detected	Increasingly used (e.g. <i>H. influenzae</i>)
Pleural fluid (thoracentesis)	Purulent or infected	Empyema. Must be sampled if effusion is present
Chest CT, bronchoscopy with BAL or biopsy	Cavity, mass, obstruction	For nonresolving disease

Table 46.3 Pneumonia Severity Index Scoring System for Determining Risk of Complications in Patients with Community-Acquired Pneumonia

Patient Characteristic	Points Assigned
DEMOGRAPHIC FACTORS	
Men	Age (yr)
Women	Age (yr) –10
Nursing home residents	Age (yr) +10
COMORBID ILLNESSES	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
PHYSICAL EXAMINATION FINDINGS	
Altered mental status	+20
Respiratory rate ≥ 30 breaths/min	+20
Systolic blood pressure < 90 mm Hg	+20
Temperature $< 35^{\circ}\text{C}$ or $\geq 40^{\circ}\text{C}$	+15
Pulse ≥ 125 beats/min	+10
LABORATORY FINDINGS	
pH < 7.35	+30
BUN ≥ 30 mg/dL (≥ 10.7 mmol/L)	+20
Sodium < 130 mEq/L	+20
Glucose ≥ 250 mg/dL (≥ 13.9 mmol/L)	+10
Hematocrit $< 30\%$	+10
PaO ₂ < 60 mm Hg or O ₂ saturation $< 90\%$	+10
Pleural effusion	+10

A risk score is obtained by summing the patient's age in years (age –10 for women) and the points for each applicable patient characteristic. Patients with a score < 70 are candidates for outpatient treatment, whereas those with scores > 90 warrant hospitalization. Proper management of patients with scores of 70 to 90 requires careful application of clinical judgment. BUN, blood urea nitrogen; PaO₂, arterial oxygen pressure. Modified from Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243–250.

Table 46.3 — Murray & Nadel 7e, pr.609. Table 46.3 Pneumonia Severity Index Scoring System for Determining Risk of Complications in Patients with Community-Acquired Pneumonia

Severity and site-of-care decision

- The **Pneumonia Severity Index (PSI)** is the score used.
 - The score is age in years (minus 10 for women) plus points for each applicable characteristic.
 - Examples: neoplastic disease +30, altered mental status +20, RR ≥ 30 /min +20, pH < 7.35 +30, urea ≥ 30 mg/dL +20.
 - **Score < 70** : candidate for outpatient treatment.
 - **Score 70–90**: needs clinical judgement.
 - **Score > 90** : hospitalise.
- The CRB-65 score has also been evaluated for admission decisions.

Principles of treatment

- Treat empirically and promptly.
- Choose the narrowest-spectrum agent that covers the likely pathogen, in line with antimicrobial stewardship.
- Consider these factors when choosing:
 - severity;
 - comorbidity and immunosuppression;
 - recent antibiotics;
 - local epidemiology and resistance.
- Guidelines rest on broad epidemiology, so local resistance patterns should shape the choice.
- Corticosteroids are not recommended for CAP or influenza pneumonia, except for refractory shock.
- Give antibiotics for bacterial superinfection in viral pneumonia. Specific antivirals are used for influenza.

Management

GUIDELINE

ATS — Diagnosis and Management of CAP: official ATS Clinical Practice Guideline — 2025 (updates the 2019 ATS/IDSA guideline; IDSA did not endorse it). Antibiotic selection follows the 2019 ATS/IDSA guideline, which the 2025 update does not replace.

Indian context: ICMR — Treatment Guidelines for Antimicrobial Use in Common Syndromes — 2019.

Outpatient CAP (the commonest exam version)

- **Site of care:** PSI <70 (or low CRB-65) and able to take oral therapy.
- **Healthy adult with no modifying factors:**
 - Amoxicillin 1 g every 8 h; or
 - doxycycline 100 mg every 12 h; or
 - an advanced macrolide only if local pneumococcal macrolide resistance is <25%.
 - Azithromycin 500 mg on day 1 then 250 mg daily; or
 - clarithromycin 500 mg every 8 h, or extended-release 1000 mg daily.
- **Adults with comorbidity** (chronic heart, lung, liver or kidney disease, diabetes, asplenia, alcoholism, malignancy):
 - a β -lactam **plus** a macrolide or doxycycline; or
 - a respiratory fluoroquinolone alone (levofloxacin or moxifloxacin).
 - The β -lactam is amoxicillin-clavulanate, cefpodoxime, cefprozil or cefuroxime. The dose is as in the dose table below.
 - A β -lactam/ β -lactamase inhibitor is preferred over erythromycin because of β -lactamase-producing *H. influenzae*.
 - Fluoroquinolone adverse effects are hepatotoxicity, QT prolongation, musculoskeletal and neurological events, and a tendency to promote *C. difficile* or MRSA.
- **Other guidelines** (outpatient):
 - BTS: amoxicillin first, with clarithromycin or doxycycline as alternatives.
 - ERS/ESCMID: amoxicillin or doxycycline, with a macrolide as an alternative if resistance is low.
- **India:** the ICMR 2019 syndrome guideline advises amoxicillin for mild disease.
 - It notes that pneumococcal resistance to amoxicillin is very low in India.
 - It also notes that pneumococcal resistance to macrolides and co-trimoxazole is widespread.
 - Macrolide monotherapy therefore needs caution locally.
- **Duration:** the textbook gives a minimum of 5 days, continued until clinical stability.
- **Follow-up:** reassess at 48–72 hours. Refer or admit if there is no improvement.

Table 2: Outpatient empirical regimens (ATS/IDSA 2019 as summarised in the textbook)

Group	Regimen	Dose
No comorbidity	Amoxicillin	1 g every 8 h
No comorbidity	Doxycycline	100 mg every 12 h
No comorbidity	Azithromycin (if resistance <25%)	500 mg day 1, then 250 mg daily
Comorbidity	Amoxicillin-clavulanate plus macrolide or doxycycline	500/125 mg every 8 h, or 875/125 mg every 12 h, or 2 g/125 mg every 12 h
Comorbidity	Levofloxacin or moxifloxacin	Alone, as monotherapy

Table 46.4 Guidelines for Empirical Oral Outpatient Treatment of Immunocompetent Adults With Community-Acquired Pneumonia**ATS/IDSA¹⁰⁹**

No modifying factors^a: amoxicillin,^b doxycycline or advanced macrolide if *S. pneumoniae* macrolide resistance <25%^{c,d}
 Comorbidities^a: β-lactam,^e macrolide^f or doxycycline,^d or fluoroquinolone^g alone

BTS^{161,162}

Primary: amoxicillin
 Alternatives: clarithromycin or doxycycline

ERS/ESCMID¹⁶³

Amoxicillin or doxycycline with macrolide as alternative if low levels of resistance

DRSPTWG

Primary: amoxicillin, amoxicillin-clavulanate, cefuroxime, doxycycline, macrolide (if low rate of resistance)
 Alternative: fluoroquinolone^h

^aAmerican Thoracic Society/Infectious Disease Society of America comorbidities (modifying factors) include chronic heart, lung, liver or kidney disease, diabetes, asplenia, alcoholism, and malignancy.

^bAmoxicillin 1 g q8h, doxycycline 100 mg q12h, azithromycin 500 mg on first day then 250 mg/day, clarithromycin 500 mg q8h, or clarithromycin extended release 1000 mg/day.

^cAdvanced macrolides are azithromycin and clarithromycin.

^dSecond-choice agent.

^eAmoxicillin-clavulanate (500 mg amoxicillin plus 125 mg clavulanate q8h, 875 mg amoxicillin plus 125 mg clavulanate q12h or 2 g amoxicillin plus 125 mg clavulanic acid q12h), cefpodoxime, cefprozil, or cefuroxime.

^fBecause of increasing macrolide resistance, erythromycin cannot be relied upon to ensure coverage of β-lactamase-producing *Haemophilus influenzae*. A combination of a β-lactam/β-lactamase inhibitor is preferred.

^gAntipneumococcal fluoroquinolones include levofloxacin, and moxifloxacin.

^hLevofloxacin or moxifloxacin.

ATS/IDSA, American Thoracic Society/Infectious Diseases Society of America; BTS, British Thoracic Society; DRSPTWG, Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group; ERS/ESCMID, European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases.

Table 46.4 — Murray & Nadel 7e, pr.610. **Table 46.4** Guidelines for Empirical Oral Outpatient Treatment of Immunocompetent Adults With Community-Acquired Pneumonia

Duration: 2025 update versus textbook

Table 3: Duration of therapy

Textbook · ATS/IDSA 2019	ATS · 2025 update
Minimum of 5 days, until clinically stable	For outpatients who reach clinical stability, suggests <5 days (minimum 3 days) rather than ≥5 days (conditional recommendation)

- The 2025 update makes this a conditional recommendation that needs individualisation.
- For adult outpatients **with comorbidities** and a positive test for a respiratory virus, it suggests empiric antibiotics because of concern about bacterial-viral coinfection.
- For adult outpatients **without comorbidities**, it suggests not prescribing empiric antibiotics.
- IDSA supports not prescribing for outpatients without comorbidities, but did not endorse the update as a whole.
- For exam answers, the practical line is amoxicillin or doxycycline for the healthy outpatient, with duration tailored to clinical stability.

Inpatient CAP (for completeness)

- **Mild to moderate disease:**
 - ampicillin-sulbactam, cefotaxime, ceftriaxone or ceftaroline **plus** azithromycin or clarithromycin; or
 - a respiratory fluoroquinolone alone.
- **Severe disease:**
 - a β-lactam plus macrolide, or a β-lactam plus fluoroquinolone.
 - Add cover for MRSA or *Pseudomonas* **only** with prior respiratory isolation, or with hospitalisation and parenteral antibiotics in the past 90 days plus locally validated risk factors.
- Observational data suggest combination therapy with a macrolide is linked with lower mortality in severe CAP, but not uniformly.
- Switch to oral therapy once the patient is clinically stable and absorbing. This is often by 2–3 days. No in-hospital observation is needed afterwards.

Table 46.5 Guidelines for Empirical Parenteral Inpatient Treatment of Immunocompetent Adults With Community-Acquired Pneumonia

MILD TO MODERATE DISEASE

ATS/IDSA¹⁰⁹

- Primary: ampicillin and sulbactam, cefotaxime, ceftriaxone, or ceftaroline with azithromycin or clarithromycin
- Alternative: fluoroquinolone^a alone or, if history of prior respiratory isolation of MRSA^b or *Pseudomonas aeruginosa*,^c treatment to cover these agents

BTS^{161,162}

- Mild: oral amoxicillin. Alternatives parenteral amoxicillin or benzylpenicillin or clarithromycin
- Moderate: oral amoxicillin and clarithromycin (can consider clarithromycin monotherapy if prior therapy with amoxicillin)
- Alternative if unable to take oral medication: parenteral amoxicillin or benzylpenicillin plus clarithromycin (if intolerant of penicillin but able to take a cephalosporin parenteral second- or third-generation cephalosporin plus clarithromycin)
- Alternative: if unable to take penicillin or macrolide, oral doxycycline, or if not able to take any of these, a respiratory fluoroquinolone^a

ERS/ESCMID¹⁶³

- Aminopenicillin, aminopenicillin with β -lactamase inhibitor, penicillin, cefotaxime, ceftriaxone with or without macrolide
- Respiratory fluoroquinolone alone^a

DRSPTWG

- Primary: cefuroxime, cefotaxime, ceftriaxone, or ampicillin-sulbactam; macrolide
- Alternative: fluoroquinolone^a

SEVERE DISEASE

ATS/IDSA¹⁰⁹

- Primary: Ampicillin and sulbactam, cefotaxime, ceftriaxone, or ceftaroline with azithromycin or clarithromycin
- Alternative: broad-spectrum β -lactam as for primary with fluoroquinolone^a or, if history of prior respiratory isolation or prior hospitalization with parenteral antimicrobials within 90 days in setting of locally validated risk factors for MRSA^b or *P. aeruginosa*,^c treatment to cover these agents

BTS^{161,162}

- Primary: amoxicillin/clavulanate (or if penicillin intolerant cefuroxime, cefotaxime, or ceftriaxone) plus macrolide

ERS/ESCMID¹⁶³

- Cefotaxime or ceftriaxone plus macrolide or respiratory fluoroquinolone
- Alternative: respiratory fluoroquinolone alone if no sepsis
- Alternative if risk factors for *P. aeruginosa*: piperacillin/tazobactam, anti-pseudomonal cephalosporin (ceftazidime^d or ceftipime) plus ciprofloxacin or plus macrolide and aminoglycoside^e

DRSPTWG

- Primary: ceftriaxone or cefotaxime, macrolide; or ceftriaxone or cefotaxime, fluoroquinolone^a
- Alternative (with caution): fluoroquinolone.^a

^aAntipseudomonal fluoroquinolones include levofloxacin 750 mg/day and moxifloxacin 400 mg/day.

^bAdvanced macrolides are azithromycin and clarithromycin.

^cAmpicillin and sulbactam 1.5–3 g q6h, cefotaxime 1–2 g q8h, ceftriaxone 1–2 g/day, or ceftaroline 600 mg q12h and azithromycin 500 mg/day or 500 mg on day 1 and 250 mg once a day thereafter for mild disease) or clarithromycin 500 mg bid.

^dAnti-staphylococcal treatments include vancomycin (15 mg/kg q12h, adjust based on levels) or linezolid (600 mg q12h).

^eAntipseudomonal β -lactams include piperacillin-tazobactam (4.5 g q6h), ceftipime (2 g q8h), ceftazidime (2 g q8h), imipenem (500 mg q6h), meropenem (1 g q8h), or aztreonam (2 g q8h).

^fIf ceftazidime used should be combined with penicillin to ensure coverage of pneumococci per ERS/ESCMID guideline.

^gRecommendation to double cover *P. aeruginosa* with both a β -lactam and either ciprofloxacin or an aminoglycoside per ERS/ESCMID guideline.

ATS/IDSA, American Thoracic Society/Infectious Diseases Society of America; BTS, British Thoracic Society; DRSPTWG, Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group; ERS/ESCMID, European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases.

Table 46.5 — Murray & Nadel 7e, pr.611. Table 46.5 Guidelines for Empirical Parenteral Inpatient Treatment of Immunocompetent Adults With Community-Acquired Pneumonia

Pathogen-directed therapy

- Penicillin-susceptible pneumococcus: penicillin G, amoxicillin or doxycycline.
- Legionella: azithromycin or levofloxacin or moxifloxacin.
- Atypical organisms: doxycycline or a macrolide.
- H. influenzae*: a β -lactam/ β -lactamase inhibitor.
- Influenza: oseltamivir.
- Melioidosis: ceftazidime or meropenem for the intensive phase. Meropenem is preferred in ICU, persistent bacteraemia and CNS disease. The continuation phase is TMP-SMX for 20 weeks.

Table 46.4 Agents for Specific Therapy of Selected Respiratory Pathogens

Type of Infection	Preferred Agent(s)	Alternative Agent(s)
COMMUNITY-ACQUIRED PNEUMONIA		
<i>Streptococcus pneumoniae</i>		
Penicillin-susceptible	Penicillin G, amoxicillin, doxycycline	Cephalosporin, macrolide ^a (MIC <2 g/mL), fluoroquinolone ^a
Penicillin-resistant	Agents identified using in vitro susceptibility tests, including cefotaxime, ceftriaxone, ceftaroline, vancomycin	Fluoroquinolone, ^a linezolid, clindamycin
<i>Mycoplasma pneumoniae</i>	Doxycycline, macrolide	Fluoroquinolone ^a
<i>Chlamydia pneumoniae</i>	Doxycycline, macrolide	Fluoroquinolone ^a
<i>Legionella</i>	Azithromycin, fluoroquinolone (levofloxacin or moxifloxacin)	Doxycycline
<i>Haemophilus influenzae</i>	β -lactam/ β -lactamase inhibitor, cephalosporin	Trimethoprim-sulfamethoxazole, azithromycin, doxycycline, fluoroquinolone ^a
<i>Moraxella catarrhalis</i>	β -lactam/ β -lactamase inhibitor, third-generation cephalosporin	Trimethoprim-sulfamethoxazole, azithromycin, doxycycline, fluoroquinolone ^a
<i>Neisseria meningitidis</i>	Third-generation cephalosporin, penicillin G	Chloramphenicol, fluoroquinolone ^a
<i>Streptococci</i> (other than <i>S. pneumoniae</i>)	Penicillin G, cephalosporins	Clindamycin (susceptibility should be confirmed), vancomycin
Anaerobes	β -lactam plus metronidazole, β -lactam/ β -lactamase inhibitor	Clindamycin, carbapenem
<i>Staphylococcus aureus</i>		
Methicillin-susceptible ^b	Oxacillin, nafcillin	Cephalosporins, vancomycin, clindamycin, fluoroquinolones ^a
Methicillin-resistant ^b	Vancomycin, ^c linezolid	Clindamycin, trimethoprim-sulfamethoxazole, fluoroquinolones, ^a and tetracyclines may also show activity (in vitro testing required)
<i>Klebsiella pneumoniae</i> and other Enterobacteriaceae (excluding <i>Enterobacter</i> sp)	Sensitive organism: third-generation cephalosporin, β -lactam/ β -lactamase inhibitor, carbapenem (all $\pm$ aminoglycoside) Extended-spectrum β -lactamase producing: carbapenems, fosfomycin (intravenous), tigecycline, colistin Carbapenemase-producing <i>Klebsiella</i> : ceftazidime-avibactam	
Influenza	Oseltamivir, zanamivir, peramivir, baloxivir	
Respiratory syncytial virus	Ribavirin	
LESS COMMON PATHOGENS		
<i>Nocardia</i>	Third-generation cephalosporin plus amikacin $\pm$ trimethoprim-sulfamethoxazole	Imipenem $\pm$ amikacin, third-generation cephalosporin, minocycline, tigecycline, linezolid, fluoroquinolones ^a
<i>Coxiella burnetii</i> (Q fever)	Doxycycline	Macrolides (clarithromycin or azithromycin), trimethoprim-sulfamethoxazole, fluoroquinolones
<i>Chlamydia psittaci</i> (psittacosis)	Doxycycline	Macrolide, chloramphenicol

^aAzithromycin (IV or PO) is the preferred macrolide; clarithromycin (PO) or erythromycin (IV or PO) may also be used.

^bLevofloxacin (IV or PO), gatifloxacin (IV or PO), moxifloxacin (IV or PO), or gemifloxacin (PO only) are preferred for *Streptococcus pneumoniae*. Ciprofloxacin has the best in vitro activity against *Pseudomonas aeruginosa*.

^cRifampin and gentamicin should be reserved for cases of bacteremic *Staphylococcus aureus* pneumonia, empyema formation, or lung abscesses. Activity of rifampin and gentamicin requires laboratory confirmation for methicillin-resistant *S. aureus*.

^dAntipseudomonal β -lactams include ceftazidime, ceftipime, imipenem, meropenem and piperacillin-tazobactam.

IV, intravenous; MIC, minimum inhibitory concentration; PO, by mouth.

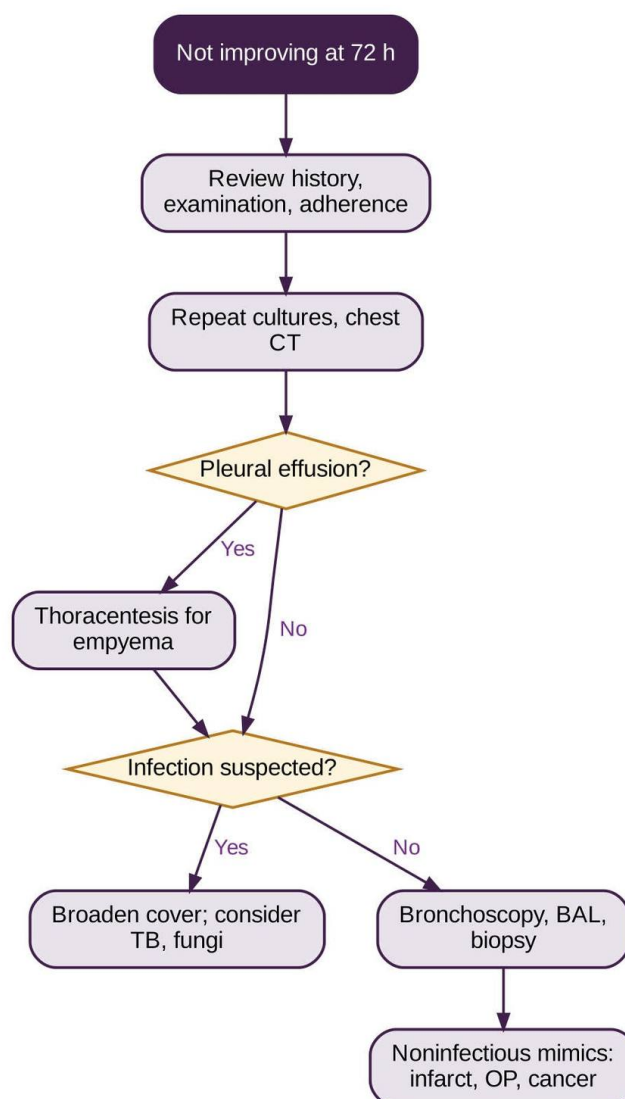
Updated from Bartlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for the management of community-acquired pneumonia in adults: Infectious Diseases Society of America. Clin Infect Dis. 2003;31:347–382.

eTable 46.4 — Murray & Nadel 7e, pr.610.e1. eTable 46.4 Agents for Specific Therapy of Selected Respiratory Pathogens

Nonresponding pneumonia

- Assess response at **72 hours**.
- Two patterns exist:
 - **progressive** pneumonia, with clinical deterioration;
 - **nonresponding** pneumonia, with persistent fever and symptoms.
- Infectious causes account for ~40% of nonresponders. The usual organisms are *S. pneumoniae*, *Legionella*, *P. aeruginosa* and *S. aureus*. About 22% of cases are noninfectious.
- About 30% have no cause found.

Flowchart 1: Approach to nonresponding CAP



- Noninfectious mimics include pulmonary infarction, pulmonary haemorrhage, organizing pneumonia, eosinophilic pneumonia, hypersensitivity pneumonitis, drug-induced lung disease and neoplasm.
- Other causes of failure are bronchial obstruction by tumour or foreign body, abscess and necrotizing pneumonia.
- Do not change therapy within 48 hours unless there is severe deterioration or dramatic radiological progression.

Complications and prognosis

- **Empyema** is the commonest complication. It has increased through serotype replacement in vaccinated populations.
- Other complications are septic shock, ARDS, abscess, necrotizing pneumonia and metastatic infection (endocarditis, arthritis, meningitis).
- Pneumococcal pneumonia remains a cause of septic shock and ARDS.

- Prognosis is worse with bacteraemia, comorbidity and advanced age.

Pearls

PEARLS

- Outpatient CAP in a healthy adult: **amoxicillin 1 g every 8 h** or **doxycycline 100 mg every 12 h**.
- Use a macrolide only if pneumococcal macrolide resistance is <25%. Indian pneumococcal macrolide resistance is widespread, so avoid macrolide monotherapy.
- With comorbidity, give a β -lactam/ β -lactamase inhibitor **plus** a macrolide or doxycycline, or a respiratory fluoroquinolone alone.
- Avoid fluoroquinolones when TB is possible. As few as 10 days can select resistant *M. tuberculosis*.
- **PSI <70** can be treated at home. A score **>90** needs admission.
- Culture before antibiotics in admitted patients. Delay of **>4–8 h** worsens outcome.
- Reassess at 72 hours. Think of empyema, *Pseudomonas*, TB, melioidosis and noninfectious mimics.
- Steroids are not recommended routinely. The ATS 2025 update suggests <5 days (minimum 3) of antibiotics in clinically stable outpatients.
- Legionella is acquired from water aerosols. It is a leading cause of severe CAP.

Sources

- Textbook: Murray & Nadel 7e — Ch 46 Community-Acquired Pneumonia, §Pneumonia › Correction of Host Abnormalities — pp. 609–610
- Textbook: Murray & Nadel 7e — Ch 46, §Pneumonia › Patients Who Are Stable or Improving — pp. 610.e1–611
- Textbook: Murray & Nadel 7e — Ch 46, §Pneumonia › Major Causes of Pneumonia — p. 613
- Textbook: Murray & Nadel 7e — Ch 46, §Pneumonia › Other Common Causes of Pneumonia — p. 617
- Textbook: Murray & Nadel 7e — Ch 46, §Treatment Failure › Less Common Causes of Pneumonia — p. 617.e13
- [w1] ATS — Diagnosis and Management of Community-acquired Pneumonia: An Official ATS Clinical Practice Guideline — 2025 — <https://academic.oup.com/ajrccm/article/212/1/24/8435770>
- [w2] IDSA — Position statement: why IDSA did not endorse the CAP guidelines 2025 update — 2025 — <https://academic.oup.com/ajrccm/article/212/5/1064/8494295>
- [w3] ICMR — Treatment Guidelines for Antimicrobial Use in Common Syndromes — 2019 — https://www.icmr.gov.in/icmrobject/custom_data/pdf/resource-guidelines/Treatment_Guidelines_2019_Final.pdf

7. Corticosteroids (glucocorticoids) in COVID-19

ASKED 2* · Intermediate answer

Asked in: Jun 2021 P-IV Q10(b) [5] · Dec 2022 P-IV Q8(a) [5]

Q: Corticosteroids in COVID-19. [5]

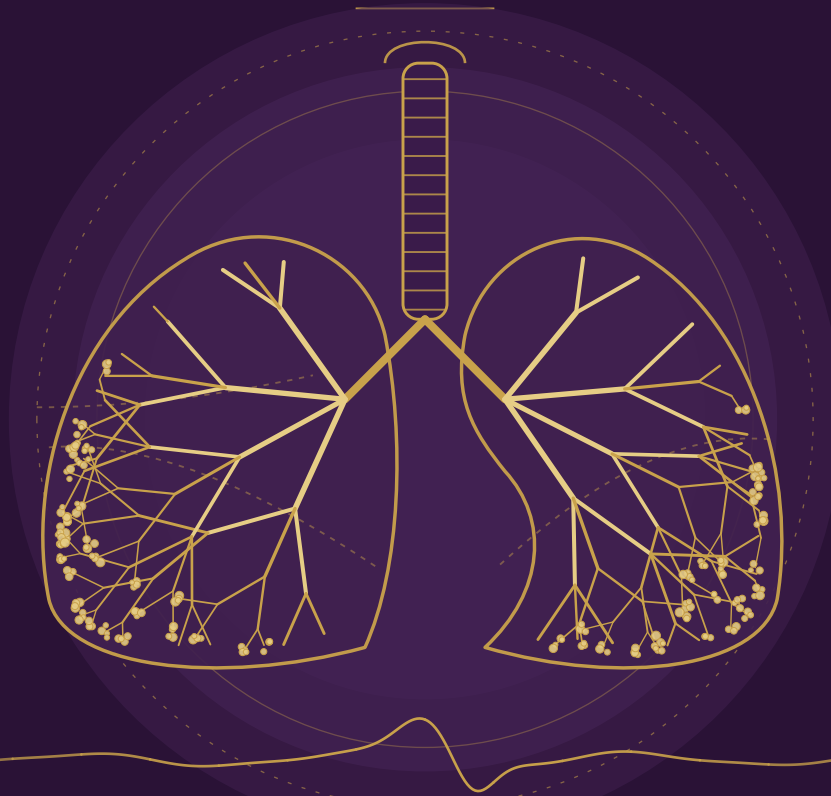
Q: Glucocorticoids in the management of COVID-19. [5]

Definition and rationale

- Systemic **corticosteroids** (glucocorticoids) are the one class of anti-inflammatory drug with proven mortality benefit in severe COVID-19.
- Rationale: severe COVID-19 is partly an inflammation-driven injury. The RECOVERY result supports a pathogenic role for inflammation.
- The host inflammatory phase usually follows the viral replication phase, at about 7 days after symptom onset.
- Related ARDS evidence also favours steroids: low-dose methylprednisolone and dexamethasone trials in non-COVID ARDS.



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Part 10 · Occupational and Environmental Lung Disease

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Answers are written from Murray & Nadel's Textbook of Respiratory Medicine (7th ed.), with printed page numbers cited in each answer, and from current guidelines found on official society and journal sites, cited [W#] and listed in the Web-Sourced Facts Register.

Updated till October 2026

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HOW TO USE

Each answer groups every year the question was asked and is written to the most demanding version. Badges show how often a topic was asked. Each answer ends with one Sources block: the Murray & Nadel 7e chapter and printed pages used, and the guideline/web sources (also listed in the register at the end). Section B lists this volume question by question; C lists high-yield topics.

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B • This volume, question by question

1. Driver mutations in NSCLC (EGFR, ALK, ROS1 and others) and their clinical implications	5×	12
Asked in: Dec 2020 P-I Q10(a) [5] · Jun 2022 P-II Q9(a) [5] · Dec 2022 P-IV Q3(b) [5] · May 2024 P-IV Q3(b) [5] · Dec 2025 P-IV Q3 [10]		
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3. Genetic susceptibility to lung cancer and mechanisms of genetic mutation	2×	23
Asked in: Jun 2021 P-I Q6(b) [5] · May 2024 P-I Q5(a) [5]		
4. Lung cancer screening – patient selection and implementation, and using screening CT for COPD	3×	27
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16. Small cell lung cancer – features, treatment and recent advances	3×	76
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PART 7

Lung Cancer and Thoracic Tumours

1. Driver mutations in NSCLC (EGFR, ALK, ROS1 and others) and their clinical implications

ASKED 5* · Long answer

Asked in: Dec 2020 P-I Q10(a) [5] · Jun 2022 P-II Q9(a) [5] · Dec 2022 P-IV Q3(b) [5] · May 2024 P-IV Q3(b) [5] · Dec 2025 P-IV Q3 [10]

Q: Mutations in lung cancer. [5]

Q: Briefly describe the various driver mutations for lung cancer. [5]

Q: ROS1 translocations in non small cell lung carcinoma and implications. [5]

Q: Briefly describes the mutations of clinical interest for non-small cell lung cancer. [5]

Q: Enlist the driver mutations responsible for tumour progression in non-small cell lung cancer. Mention limitation and toxicity of tyrosine kinase inhibitors in the management of non-small cell lung cancer. [10]

Definition and why it matters

- A **driver mutation** is a genetic alteration that gives a clone a selective growth advantage and drives tumour progression.
 - It may activate an oncogene or inactivate a tumour suppressor gene.
 - A **passenger mutation** is irrelevant to progression.
- Roughly **50% of non-squamous NSCLC** carry a known driver, though this varies with the population.
 - In the Lung Cancer Mutation Consortium, a driver was found in about **64%** of genotyped cases.
- Frequency differs by geography, environmental exposure and tobacco exposure.
- Targetable drivers change treatment and prognosis, so they must be tested for at diagnosis.
 - Targeted therapy is better tolerated and more effective than chemotherapy in selected patients.
- Immunotherapy (PD-1/PD-L1) is not a "targeted therapy" in the strict sense.
 - It modulates host immunity and does not block tumour signalling pathways.

Classification of drivers

- **Receptor tyrosine kinase (RTK) point mutations or deletions:** EGFR, HER2/ERBB2, MET exon 14 skipping.
- **Gene fusions or rearrangements:** ALK (usually EML4-ALK), ROS1, RET, NTRK.
- **Intracellular signalling kinase mutations:** KRAS (a GTPase), BRAF (V600E).
- **Co-operating and resistance pathways:** MET amplification, PIK3CA, TP53.
- In new diagnoses, the major drivers are mostly mutually exclusive.
- Small cell lung cancer (SCLC) has no targetable mutation to date.
 - It is defined by near-universal **Rb and p53** alterations.

Molecular background

- Carcinogens (PAHs in tobacco smoke and air pollution) are activated by phase I (CYP1A1) and phase II (glutathione S-transferase) enzymes and damage DNA.
- DNA damage with defective repair leads to genomic instability.
 - PARP is involved in base excision repair.
 - It is a synthetic-lethality target.
- Chronic inflammation (NF-κB, STAT3, IL-6) promotes cancer.
 - COPD is a lung cancer risk independent of smoking.
- Early in tumorigenesis, MHC-I antigen presentation falls.
 - HLA loss of heterozygosity is found in about **40%** of NSCLC and favours immune evasion.
- Intratumour heterogeneity follows a **branching ("trunk-branch") evolution** model.

- Known drivers sit on the trunk and arise early.
- Subclonal "branch" events drive progression and resistance.
- Chromosomal instability generates subclones and drug resistance.
- Adenocarcinoma in situ already carries the full genomic profile of invasive adenocarcinoma.

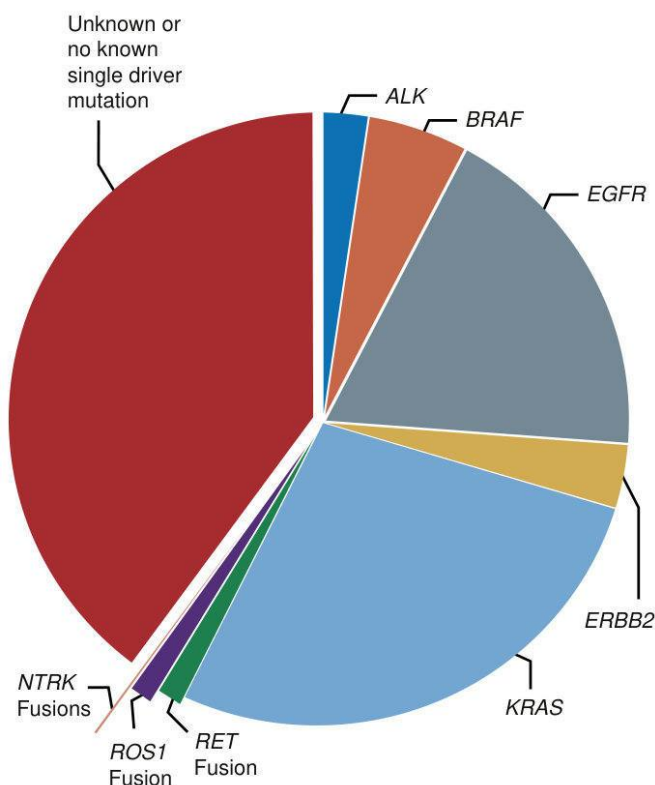


Figure 73.3 — Murray & Nadel 7e, pr.1012. Common and targetable mutations/fusions in non-small cell lung cancer (NSCLC). Relative percentage of the most common targetable mutations/fusions in NSCLC.¹³⁰ This is based on data available from the American Association for Cancer Research Genomics Evidence Neoplasia Information Exchange (GENIE) consortium. It is important to note that mutational frequency for different targets varies a great deal based on popul

Individual drivers

EGFR

- EGFR (ERBB1) is a receptor tyrosine kinase.
 - It signals through ERK, Akt and c-SRC.
 - Constitutive activation drives cyclin D1 and proliferation.
- It is mutated in **9–46%** of NSCLC, depending on geography and patient characteristics.
- The common sensitising mutations are **exon 19 deletions and L858R**.
- The phenotype is adenocarcinoma, never-smoker, female, East Asian.
- **HER2 (ERBB2)** is mutated in about 3% of NSCLC.
 - Trastuzumab is used with chemotherapy.
 - Ado-trastuzumab emtansine is an option, but responses are lower than in breast cancer.

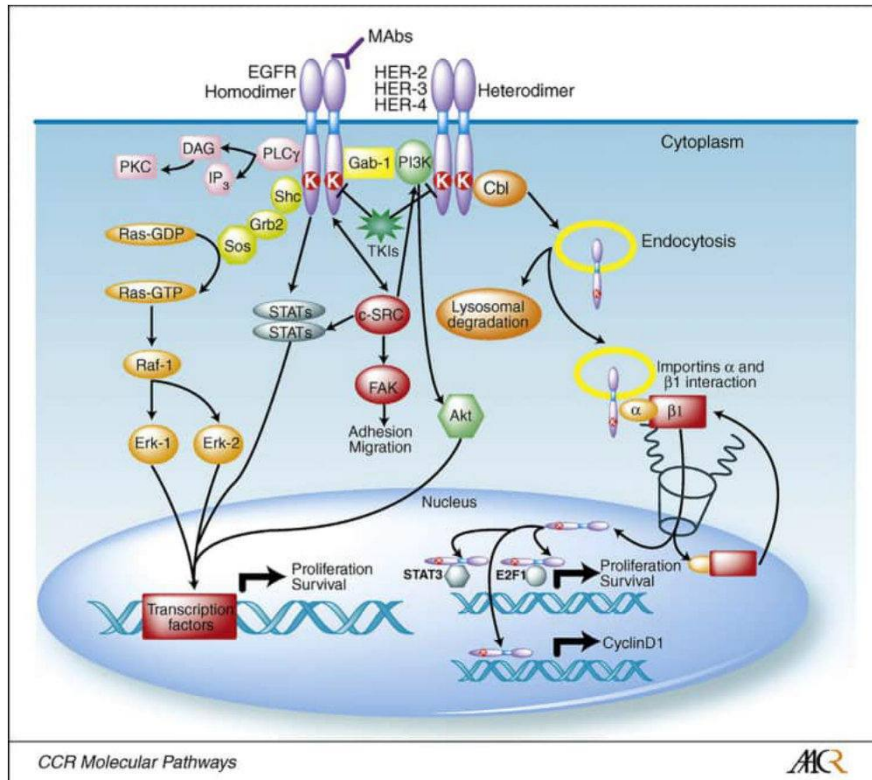


Figure 73.4 — Murray & Nadel 7e, pr.1013. Summary of Ras, EGFR, and HER2 signaling. Note the convergent signaling between Ras/KRAS, EGFR, and HER2 signaling pathways as well as downstream ERK and AKT conserved pathways. (From Scaltriti M, Baselga J. Epi-dermal growth factor receptor pathway: a model for targeted therapy. Clin Cancer Res. 2006;12[18]:5268–5272.)

ALK

- ALK fusions, most often **EML4-ALK**, are found in about **3–8%** of NSCLC.
 - They give constitutive kinase activation through ERK, PI3K, AKT, JAK-STAT, RAS and MEK.
- The typical patient is a young never-smoker with adenocarcinoma.
- There is a predilection for CNS metastases.

ROS1 (the topic of Dec 2022)

- ROS1 is a receptor tyrosine kinase with homology to ALK.
- ROS1 fusions account for **1–2%** of NSCLC drivers.
 - The fusion partners are more varied than for ALK.
- Crizotinib gives an overall response rate above **70%**.
 - Median overall survival is **51 months** (PROFILE 1001).
- Other agents are entrectinib, ceritinib and lorlatinib (second line).
 - Repotrectinib is a newer option.
- CNS metastases remain a long-term concern.
- **Implications:**
 - Test for it in adenocarcinoma, large cell carcinoma and NSCLC-NOS.
 - FISH is the standard method.
 - IHC is a screen and must be confirmed by a molecular method.
 - The prognosis is far better than for conventional NSCLC.

KRAS

- KRAS is mutated in about **11–30%** of lung cancers.
 - It is the most common mutation in adenocarcinoma.
- KRAS is a GTP/GDP molecular switch.
 - Mutations (codons **12, 13, 61**; most commonly **G12C**) block GTP hydrolysis.
 - This locks KRAS in the active state.

- It is associated with smoking.
- It has been a difficult target.
 - Sotorasib (AMG 510) and adagrasib (MRTX849) bind G12C.
- KRAS status is less informative than PD-L1 for predicting response to immunotherapy.

BRAF

- **V600E** is found in about 1–3.5% of NSCLC.
- BRAF is an intracellular kinase that signals through MEK and ERK.
- Dabrafenib plus trametinib is preferred over single-agent BRAF inhibition.
 - Median duration of response was about 10 months.

Other drivers

- **NTRK fusions:** 0.1–1% of NSCLC.
 - Larotrectinib and entrectinib are given regardless of tumour histology.
 - Testing needs RNA and DNA NGS.
- **RET fusions:** about 2%.
 - Selpercatinib and pralsetinib are used.
- **MET exon 14 skipping:** about 3–4%.
 - Capmatinib, tepotinib and crizotinib are used.
 - In GEOMETRY, the response rate was 68% first line.
 - MET overexpression or amplification is also a resistance pathway.
- **PIK3CA:** enriched in squamous cell carcinoma, with unclear prognostic importance.

Table 1: Targetable drivers in NSCLC and agents

Driver	Approximate frequency	Agents
EGFR (ex19del, L858R)	9–46%	Osimertinib, erlotinib, gefitinib, afatinib, dacomitinib
ALK fusion	3–8%	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
ROS1 fusion	1–2%	Crizotinib, entrectinib, repotrectinib, lorlatinib
BRAF V600E	1–3.5%	Dabrafenib + trametinib
NTRK fusion	0.1–1%	Larotrectinib, entrectinib
RET fusion	~2%	Selpercatinib, pralsetinib
MET ex14	3–4%	Capmatinib, tepotinib
HER2	2–3%	Trastuzumab-based agents, ado-trastuzumab emtansine
KRAS G12C	11–30% (KRAS overall)	Sotorasib, adagrasib

Table 73.3 NCCN Recommended Selected Targeted Therapies for Driver Mutation–Driven NSCLC		
Driver Genotype	Selected Targeted Therapies	
ALK fusions	Alectinib Brigatinib Ceritinib Crizotinib Lorlatinib (second-line therapy)	
BRAF	BRAF inhibitor Dabrafenib Vemurafenib	+ MEK inhibitor Trametinib Cobimetinib
EGFR	Osimertinib Erlotinib Afatinib Dacomitinib Gefitinib	
ERBB2	Ado-trastuzumab emtansine	
KRAS	AMG 510 (under investigation)	
NTRK fusions	Larotrectinib Entrectinib	
RET	Selpercatinib Pralsetinib	
ROS1 fusions	Crizotinib Entrectinib Ceritinib Lorlatinib (second-line therapy)	

NCCN: National Comprehensive Cancer Network; NSCLC: non-small cell lung

Table 73.3 — Murray & Nadel 7e, pr.1012. Table 73.3 NCCN Recommended Selected Targeted Therapies for Driver Mutation–Driven NSCLC

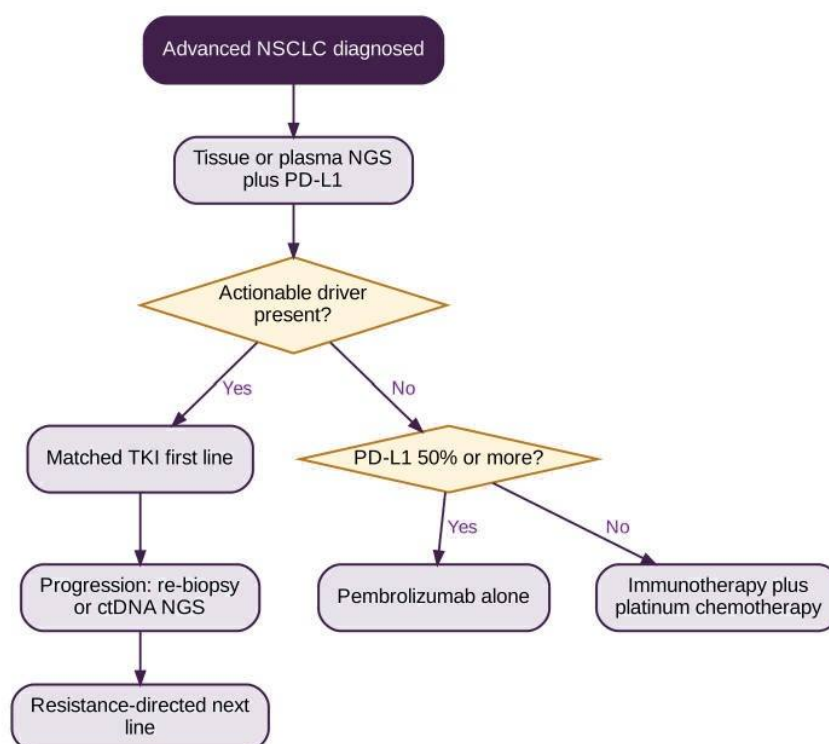
Table 77.2 Targeted Therapy for Metastatic NSCLC With Molecular Target			
Biomarker	First-Line Therapy	Second-Line Therapy	Promising Therapies
EGFR mutations	Erlotinib Gefitinib Afatinib Osimertinib	Osimertinib (after first- or second-generation TKI if T790M)	
ALK-fusion	Crizotinib Alectinib Ceritinib	Lorlatinib Brigatinib	
ROS1	Crizotinib Entrectanib		Repotrectinib
BRAF		Dabrafenib/trametinib	
RET-fusions			LOXO-292 BLU-667
MET exon 14 mutation		Crizotinib	Capmatinib Savolitinib Tepotinib
HER2 dysregulation			Trastuzumab* Ado-trastuzumab*
KRAS ^{G12C} mutation			AMG510 MRTX849

*Off-label use.

Table 77.2 — Murray & Nadel 7e, pr.1060. Table 77.2 Targeted Therapy for Metastatic NSCLC With Molecular Target

Testing

- Test for **EGFR, ALK and ROS1** in metastatic adenocarcinoma, large cell carcinoma and NSCLC-NOS.
- Consider EGFR and ALK testing in squamous or small cell cancer in never-smokers or young patients.
- Add HER2, MET, BRAF, KRAS and RET if the laboratory runs an NGS panel.
- **Panel NGS (DNA + RNA)** is preferred over single-gene testing.
 - It is more cost-effective and finds rare targets.
 - RNA sequencing is needed to detect fusions.
- Liquid biopsy (circulating tumour DNA) is an alternative when tissue is inadequate.
 - Sensitivity depends on disease burden and is poor in early disease.
- Repeat testing is needed at progression.
- **PD-L1 immunohistochemistry** is needed for all new NSCLC.
- Co-mutations such as TP53 may lower TKI efficacy.

Flowchart 1: Approach to molecular testing and first-line therapy in advanced NSCLC

Management

GUIDELINE

ESMO — Oncogene-addicted metastatic NSCLC Clinical Practice Guideline (2023) and its living-guideline update (2025).

Textbook framework: NCCN-based targeted therapy list in Murray & Nadel 7e (2022).

- **EGFR classical mutation:** a third-generation EGFR TKI is preferred first line, as monotherapy or in combination.
 - Osimertinib is the preferred agent (FLAURA).
 - Textbook figures: PFS **18.9 vs 10.2 months** against gefitinib or erlotinib, and duration of response 17.2 vs 8.5 months.
 - First- and second-generation TKIs are acceptable if osimertinib is unavailable.
 - Combinations with chemotherapy or anti-angiogenics are other options.
 - An Indian phase III trial supports gefitinib plus carboplatin-pemetrexed.
- **Uncommon EGFR mutations:** afatinib or osimertinib.
- **EGFR exon 20 insertion:** amivantamab plus carboplatin-pemetrexed first line.
- **ALK:** alectinib is the first-line TKI in the textbook.
 - Only **12%** progressed with CNS disease on alectinib, against **45%** on crizotinib.
 - Lorlatinib is used later.
- **ROS1:** crizotinib is the textbook standard; entrectinib is an alternative; repotrectinib is an additional first-line option.
- **BRAF V600E:** dabrafenib plus trametinib, or encorafenib plus binimetinib.
- **KRAS G12C:** sotorasib or adagrasib after progression on prior therapy.
- Treat even poor-performance-status patients if a driver is present.
 - Dramatic improvement is possible when the poor status is due to the cancer.
- Offer palliative care from diagnosis.

Table 2: Textbook 2022 vs current guideline emphasis

Textbook · NCCN list (2022)	ESMO living guideline (2025)
Erlotinib, gefitinib, afatinib or osimertinib first line	Third-generation TKI preferred first line
Crizotinib standard for ROS1	Repotrectinib added as a first-line option
KRAS G12C under investigation	Sotorasib or adagrasib after prior therapy

Limitations of TKIs

- Resistance is **inevitable**.
 - Most EGFR-mutant patients progress within **9–14 months** on first- or second-generation TKIs.
- EGFR resistance mechanisms:
 - **T790M** (about 50–60%).
 - C797S.
 - MET or HER2 amplification, and PIK3CA or KRAS alterations.
 - **Small cell transformation**, which has a dismal prognosis.
- ALK resistance comes mostly from secondary ALK kinase-domain mutations.
 - The pattern varies by mutation site.
 - Sequence the ALK inhibitors accordingly.
- The CNS is a **sanctuary site**.
 - CNS penetration is variable.
 - Crizotinib has negligible CNS penetration.
- Re-biopsy is often not feasible, so liquid biopsy is needed.
- Cost and access limit NGS use.
- A cure is not achieved.

- The 5-year survival with EGFR-TKI was 14.6%.
- Intratumour heterogeneity and chromosomal instability drive subclonal escape.

Toxicity of TKIs

- **First-generation EGFR TKIs (gefitinib, erlotinib):**
 - Rash, diarrhoea and GI upset.
 - Hand-foot syndrome.
 - These arise from wild-type EGFR inhibition.
- **Afatinib (second generation):** irreversible binding gives more frequent and significant toxicity, which limits its use.
- **Third-generation TKIs (osimertinib):** preferential binding of the mutant receptor gives a better toxicity profile.
- **BRAF inhibitors:** paradoxical MAPK activation in skin can cause cutaneous squamous cell carcinoma.
 - Adding a MEK inhibitor reduces this risk.
- Immune checkpoint inhibitors carry a higher risk of immune-related adverse events in patients with severe autoimmune disease, organ transplant or interstitial lung disease.

Prognosis

- Metastatic EGFR-mutant NSCLC: survival is usually **over 18 months**.
- With first-line third-generation TKI: PFS about 19 months and response about 80%.
- ALK: alectinib first line gives median PFS of **34 months**, and median survival may exceed 7 years with sequencing.

Recent advances

- Combination TKI regimens in the first line.
- Newer ALK, ROS1 and KRAS G12C inhibitors.
- Disease-agnostic approvals (NTRK).
- Single-cell and ctDNA monitoring.

PEARLS

- About **50%** of non-squamous NSCLC have a driver mutation.
- EGFR sensitising mutations are **ex19del and L858R**; T790M is the commonest first/second-generation resistance mechanism.
- ALK fusion is usually **EML4-ALK**; alectinib is the first-line TKI in the textbook.
- ROS1 fusion occurs in **1–2%**; crizotinib gives a response rate above 70% with **51-month** median survival.
- KRAS **G12C** is the most common KRAS mutation, and sotorasib targets it.
- **BRAF V600E** needs a BRAF inhibitor plus a MEK inhibitor.
- NTRK fusions are very rare but respond dramatically; they are found only by DNA and RNA NGS.
- Re-biopsy or liquid biopsy at progression is essential.
- Small cell transformation is a resistance mechanism with a poor prognosis.
- SCLC has no targetable driver; it shows near-universal p53 and Rb loss.

Sources

- Textbook: Murray & Nadel 7e — Ch 73 Lung Cancer: Molecular Biology and Targets, §Molecular Biology; §Clinically Relevant Molecular Targets — pp. 1005–1016
- Textbook: Murray & Nadel 7e — Ch 77 Lung Cancer: Treatment, §Stage IV Non–Small Cell Lung Cancer — pp. 1058–1061
- [w1] ESMO — Oncogene-addicted metastatic NSCLC Clinical Practice Guideline — 2023 — [https://www.annalsofoncology.org/article/S0923-7534\(22\)04781-0/fulltext](https://www.annalsofoncology.org/article/S0923-7534(22)04781-0/fulltext)
- [w2] ESMO — Updated treatment recommendations, oncogene-addicted mNSCLC living guideline — 2025 — [https://www.annalsofoncology.org/article/S0923-7534\(25\)00813-0/fulltext](https://www.annalsofoncology.org/article/S0923-7534(25)00813-0/fulltext)

- [w3] ESMO — Pan-Asian adapted guideline, oncogene-addicted mNSCLC — 2024 — <https://pmc.ncbi.nlm.nih.gov/articles/PMC11648200/>

2. Liquid biopsy tests in lung cancer

ASKED 3* · Intermediate answer

Asked in: Jun 2020 P-IV Q2(b) [5] · Dec 2020 P-IV Q4(a) [5] · Dec 2022 P-IV Q3(a) [5]

Q: Liquid biopsies tests for lung cancer patients. [5]

Q: Liquid biopsy for lung cancer. [5]

Q: Liquid biopsy tests for lung cancer patients. [5]

Liquid biopsy tests in lung cancer

Definition

- **Liquid biopsy** means molecular analysis of tumour-derived material in body fluid, usually blood, in place of or alongside tissue.
- Analytes include **circulating tumour DNA (ctDNA)**, circulating tumour cells (CTCs), exosomes, platelet RNA and circulating tumour RNA (ctRNA).
- **Plasma ctDNA** is the most widely studied and adopted analyte. It first entered practice for **EGFR mutation** detection in NSCLC.
- Other fluids can be used. Examples are pleural fluid supernatant or cells, and CSF in leptomeningeal disease.

Why it matters

- Targetable drivers are common. About **50% of non-squamous NSCLC** carries a known driver, so genotyping is needed in most advanced adenocarcinomas.
- The most common targetable driver is **EGFR**. It is found in 9–46% of cases, depending on geography and patient characteristics.
- Testing is needed at diagnosis and again at progression.
- Tissue is often scanty, inaccessible or heterogeneous, and results are slow. Plasma testing avoids these problems.
- **CNS disease is a sanctuary site**. ALK-positive disease in particular tends to spread to the CNS.

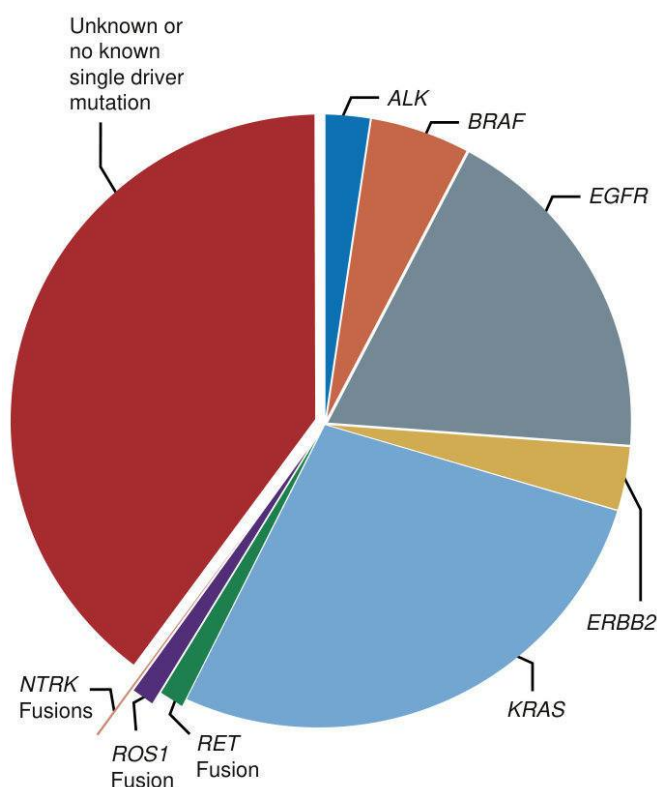


Figure 73.3 — Murray & Nadel 7e, pr.1012. Common and targetable mutations/fusions in non-small cell lung cancer (NSCLC). Relative percentage of the most common targetable mutations/fusions in NSCLC.¹³⁰ This is based on data available from the American Association for Cancer Research

Genomics Evidence Neoplasia Information Exchange (GENIE) consortium. It is important to note that mutational frequency for different targets varies a great deal based on popul

Table 73.3 NCCN Recommended Selected Targeted Therapies for Driver Mutation–Driven NSCLC		
Driver Genotype	Selected Targeted Therapies	
ALK fusions	Alectinib Brigatinib Ceritinib Crizotinib Lorlatinib (second-line therapy)	
BRAF	BRAF inhibitor Dabrafenib Vemurafenib	+ MEK inhibitor Trametinib Cobimetinib
EGFR	Osimertinib Erlotinib Afatinib Dacomitinib Gefitinib	
ERBB2	Ado-trastuzumab emtansine	
KRAS	AMG 510 (under investigation)	
NTRK fusions	Larotrectinib Entrectinib	
RET	Selpercatinib Pralsetinib	
ROS1 fusions	Crizotinib Entrectinib Ceritinib Lorlatinib (second-line therapy)	

NCCN. National Comprehensive Cancer Network. NSCLC non-small-cell lung

Table 73.3 — Murray & Nadel 7e, pr.1012. Table 73.3 NCCN Recommended Selected Targeted Therapies for Driver Mutation–Driven NSCLC

Principle

- Tumours shed DNA fragments into blood. Plasma is then sequenced or amplified to find tumour-specific alterations.
- Tumour-derived alleles are often **<1% of total cell-free DNA**. Sensitivity therefore depends on the assay and on avoiding contamination by normal DNA.
- Panel-based **NGS** tests many genes in one run. It can include RNA sequencing to detect fusions or rearrangements, mutations and copy-number changes.
- NGS is more cost-effective than single-gene testing. It also finds rare mutations and helps clinical-trial enrolment.

Sample collection and technique

- **Plasma is preferred over serum** for ctDNA extraction.
- Process EDTA tubes within about 2 hours. Special ctDNA preservative tubes allow up to 3 days.
- Centrifuge twice to remove cells and limit contamination by genomic DNA.
- Platforms used:
 - Real-time PCR (qPCR) and droplet digital PCR (ddPCR) detect known single hotspots.
 - Plasma-based NGS gives broad multigene profiling.

Types of liquid biopsy test

Table 1: Liquid biopsy analytes and uses in lung cancer

Analyte or fluid	Method	Main use
Plasma ctDNA	PCR, ddPCR, NGS	Genotyping, resistance, response, MRD
ctRNA	RNA sequencing	Fusions
CTCs	Enrichment and enumeration	Mainly research
Pleural fluid supernatant or cells	NGS, EGFR sequencing	Genotyping when cytology is poor
CSF	Sequencing	Leptomeningeal metastasis

- **Pleural fluid** can be tested on supernatant and cells together to increase yield.
- NGS on pleural fluid can detect markers even when few or no malignant cells are seen.

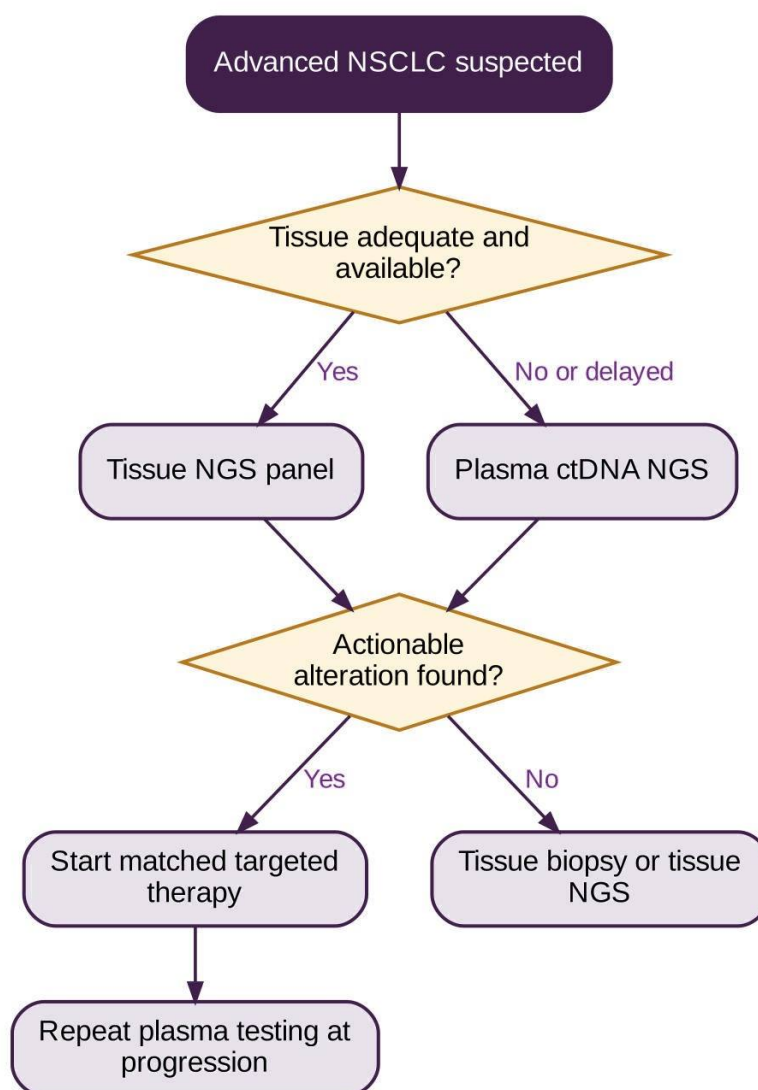
- Cell-free DNA from pleural fluid supernatant or blood can capture driver mutations in EGFR-mutant lung cancer.

Clinical applications

- **At diagnosis (advanced NSCLC):**
 - Plasma ctDNA is a valid genotyping tool that complements tissue.
 - IASLC suggests a "plasma first" approach when tissue is unavailable or turnaround time matters.
 - Plasma and tissue EGFR results are highly concordant. NGS also shows high concordance with tissue NGS.
- **At progression on EGFR TKI:**
 - Plasma genotyping looks for **T790M** and other resistance mechanisms.
 - Repeat testing avoids serial invasive biopsies.
- **Monitoring response:**
 - Falling ctDNA levels indicate response to targeted therapy.
- **Minimal residual disease (MRD):**
 - ctDNA can detect MRD where tissue cannot.
- **Beyond blood:**
 - Pleural fluid and CSF can be used for malignant effusion and leptomeningeal disease.

Interpretation

Flowchart 1: Using plasma genotyping in advanced NSCLC



- A **positive, actionable ctDNA result** is sufficient to start therapy.
- A **negative plasma result does not exclude** a driver. Tissue testing is recommended.

- If the plasma test fails to detect the sensitising EGFR mutation, it is "**non-informative**" and the false-negative chance is high.
- Plasma T790M testing may miss about **30% of cases**, so re-biopsy is warranted when plasma is negative.

Advantages and limitations

Table 2: Plasma (liquid) versus tissue genotyping

Feature	Liquid biopsy	Tissue biopsy
Invasiveness	Minimal, repeatable	Invasive, procedural risk
Turnaround	Faster (median 7–10 days in one cohort)	Slower
Heterogeneity	Can capture it	Sampling bias
Sensitivity	Lower (about 80%)	Reference standard
Concordance	>96% for EGFR, ALK, ROS1, BRAF in one cohort	Reference
Histology	Not provided	Provided (needed for diagnosis)

- Fusions (ALK, ROS1, RET) are harder to detect in plasma. They have variable fusion partners and breakpoints.
- Low tumour shedding gives false negatives. Early-stage disease and intrathoracic-only or CNS-only disease shed less.
- Sensitivity of PCR-based EGFR assays against tissue was as low as 43.1% in early studies.
- Clonal haematopoiesis can produce false-positive variants.
- Liquid biopsy does not replace tissue for **diagnosis and histological subtyping**.

Pitfalls

- Delayed processing releases normal DNA and dilutes the tumour fraction.
- Serum is unsuitable.
- A negative result in a patient who is not shedding is not reassuring.
- Test choice must match the question. Use ddPCR for known hotspots and NGS for broad profiling.

GUIDELINE

IASLC — Liquid Biopsy for Advanced NSCLC: Consensus Statement — 2021 (update of the 2018 statement). Found at.

PEARLS

- Plasma **ctDNA** is the most widely used liquid biopsy analyte. It was first applied to **EGFR** testing.
- A **positive** plasma result is actionable. A **negative** one needs **tissue confirmation**.
- Plasma T790M misses about **30%**, so re-biopsy if plasma is negative.
- IASLC supports a "plasma first" approach when tissue is unavailable or turnaround time matters.
- Use **plasma, not serum**. Process EDTA tubes within about 2 hours.
- Panel **NGS** is superior to single-gene testing. RNA sequencing detects fusions.
- The sanctuary CNS and malignant effusions can use CSF or pleural fluid.
- Liquid biopsy cannot replace tissue for histological diagnosis.

Sources

- Textbook: Murray & Nadel 7e — Ch 73 Lung Cancer: Molecular Biology and Targets, §Carcinoma — pp. 1012–1012
- Textbook: Murray & Nadel 7e — Ch 114 Pleural Malignancy, §Diagnosis — pp. 1579–1579
- [w1] IASLC — Liquid Biopsy for Advanced NSCLC: A Consensus Statement — 2021 — <https://www.sciencedirect.com/science/article/pii/S155608642102284X>
- [w2] IASLC — Liquid Biopsy for Advanced NSCLC: A Statement Paper — 2018 — <https://www.sciencedirect.com/science/article/pii/S1556086418306804>
- [w3] PMC — Clinical application of liquid biopsy genomic profiling in NSCLC: Asian perspectives — <https://pmc.ncbi.nlm.nih.gov/articles/PMC11863888>

- [w4] PMC — Liquid biopsy in NSCLC: current status and future outlook — <https://pmc.ncbi.nlm.nih.gov/articles/PMC8182706/>
- [w5] PMC — Integrating cfDNA analysis into clinical practice — <https://pmc.ncbi.nlm.nih.gov/articles/PMC9381753/>

3. Genetic susceptibility to lung cancer and mechanisms of genetic mutation

ASKED 2* · Intermediate answer

Asked in: Jun 2021 P-I Q6(b) [5] · May 2024 P-I Q5(a) [5]

Q: Genetic susceptibility to lung cancer. [5]

Q: What are the various mechanisms for genetic mutations of lung cancer. [5]

Definition

- **Genetic susceptibility** means inherited variation that changes an individual's lung cancer risk after exposure to carcinogens.
- Lung cancer arises from **somatic mutations**, which are acquired in airway epithelial cells. Germline variants modify who develops these mutations.
- Evidence for a genetic component:
 - About 85–90% of risk in Western countries is attributable to smoking.
 - Lung cancer develops in only about **15% of current smokers**, which implies differential susceptibility.
 - 10–15% of lung cancers arise in never-smokers.
 - Cancer aggregates in families after adjustment for each relative's smoking history.

Mechanisms of somatic mutation

Carcinogen-induced DNA damage

- Tobacco smoke contains about **3500 particulate constituents**, of which more than **70 are known carcinogens**.
- Polycyclic aromatic hydrocarbons (PAHs) and arylamines are activated by cytochrome P-450 enzymes (CYP1A1, CYP1A2, CYP3A4).
 - Benzo(a)pyrene is oxidised to an arene oxide, then a dihydrodiol, then a **diol epoxide**.
 - The diol epoxide forms a reactive carbocation.
 - This binds covalently to the exocyclic amino group of guanosine and forms a **DNA adduct**.
 - Adducts cause replication mismatches, altered promoter methylation and altered gene expression.
- Phase II enzymes (glutathione S-transferases) and conjugation (glucuronides, sulfates) detoxify carcinogens.
 - The balance between activation and detoxification, plus the efficiency of DNA repair, determines individual risk.
- Nicotine-specific nitrosamines are **NNK** and **NNN**.
 - NNK is converted to NNAL.
 - **CYP2A6** metabolises nicotine and NNAL, and its variation is strongly associated with lung cancer risk.
 - Nitrosamines are absent from cannabis smoke, which has no convincing link to lung cancer.
- PAH protein adducts raise reactive oxygen species, which damage DNA, lipids and proteins.
- Aryl hydrocarbon receptor-dependent and -independent pathways cause epigenetic alterations.

Genomic instability and genetic alterations

- Genomic instability is an early event and a hallmark of cancer.
- Alterations seen in at-risk airway epithelium include:
 - DNA adducts and DNA methylation
 - chromatin and chromosomal alterations
 - copy number gains and losses
 - point mutations
 - microsatellite expansion, a marker of faulty mismatch repair

- gene expression, proteomic and metabolic changes
- Sporadic cancers are not explained by DNA repair or mitotic checkpoint gene mutations. Carcinogens or oncogene-induced DNA damage are the more likely causes.
- Failure of repair, replication, chromosomal segregation or checkpoint control leads to chromosomal, microsatellite and nucleotide instability.
- Point mutations activate **oncogenes** or inactivate **tumour suppressor genes**.
 - **Driver** mutations give a selective advantage.
 - **Passenger** mutations are functionally irrelevant.
- **Branched (subclonal) evolution**: truncal mutations create the original clone, and later branches carry unique drivers and passengers.
- Metabolic reprogramming occurs early.
 - It involves glutamine uptake ("glutamine addiction").
 - It promotes epigenetic change and chromosomal instability.
- TCGA (2016) analysed 660 adenocarcinomas and 484 squamous cancers.
 - The mutation rate was **8.7 and 9.7 mutations per megabase**, respectively.
 - Six mutational signatures were found.
 - The commonest was **C to T transversions**, reflecting smoking.
 - Some tumours showed mismatch-repair or **APOBEC** signatures.

Table 1: Host and exposure patterns of common mutations

Feature	EGFR mutation	KRAS mutation
Sex	More common in women	More common in men
Ancestry	Asians	European descent
Smoking	Never-smokers	Smokers
Histology	Adenocarcinoma	Squamous histology (as stated in text)

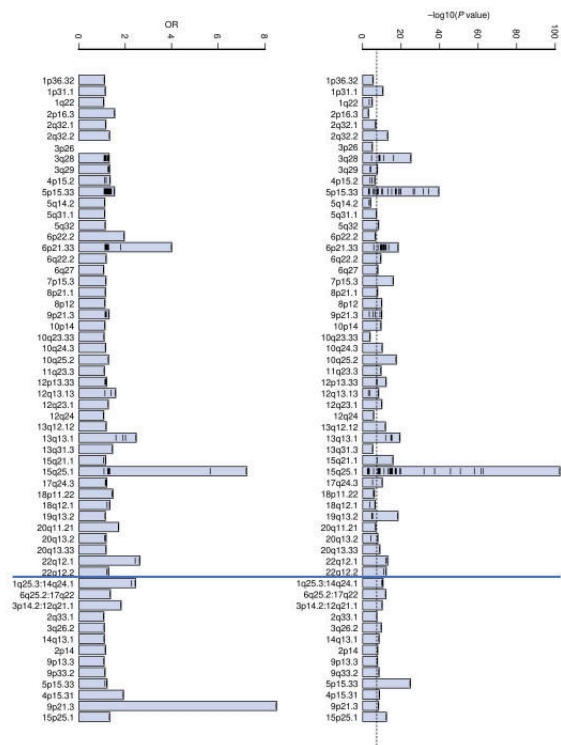
Inherited (germline) susceptibility

- **Chromosome 15q25 (nicotinic acetylcholine receptor subunit genes, CHRNA5)** affects both smoking behaviour and lung cancer risk.
 - The risk is about 1.8-fold in homozygotes.
- **6p21 (HLA region)** is largely associated with squamous cancer.
- **5p15**
 - *CLPTM1L* affects squamous cancer.
 - *hTERT* is more associated with adenocarcinoma.
- Other squamous loci: 12p13 (*RAD52*), 9p21 (*CDKN1B/ANRIL*), 2q32 and *TP63*.
- **BRCA2 K3326X** stop mutation (<1% of Europeans):
 - twofold overall risk
 - 2.5-fold risk of squamous cancer
 - twofold risk of small cell lung cancer
- *CHEK2* rare variant: protective.
- Asian GWAS: 3q28 (*TP63*), 13q12, 22q12, 10p14, 5q32, 20q13 and 17q24.3 (*BPTF*).
 - In never-smoking Asian women: 6p21, 5p15, 3q28, 10q25 and 6q22.
- Familial lung cancer: *LCORL*, a chromosome 6q locus, and *PARK2* mutation.
- High-penetrance syndromes, e.g. germline *TP53* (Li-Fraumeni).
 - Radiation exposure must be minimised in carriers.
- Xenobiotic-metabolising enzyme polymorphisms (CYP, GST) and DNA repair gene variants modify risk.
- Many risk loci act as expression quantitative trait loci, which implicates regulation of gene expression.

Table 73.1 Hallmarks of Cancer	
Established 2000 ¹	Added in 2011 ²
Sustained proliferation	Metabolic reprogramming
Evasion of tumor suppressors	Genomic instability
Invasion and metastasis	Tumor-promoting inflammation
Replicative immortality	Immune evasion
Angiogenesis	
Resisting apoptosis	

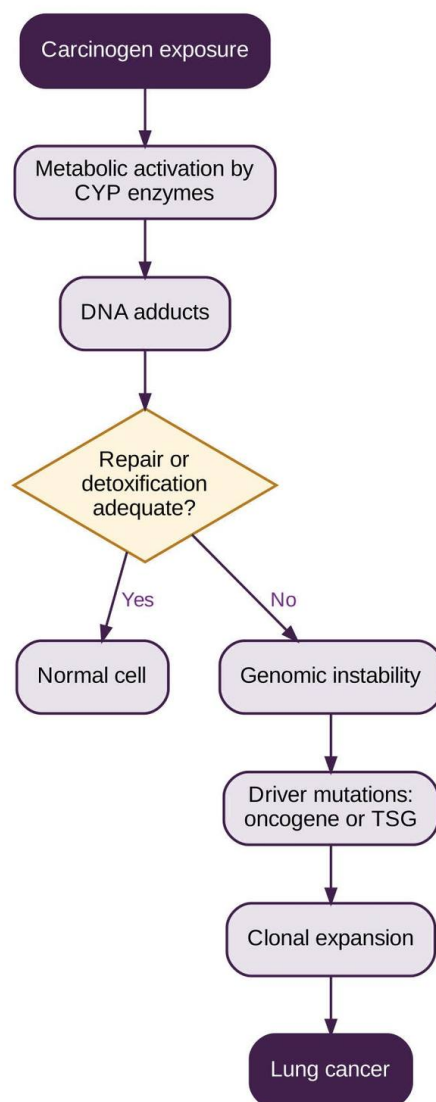
Table 73.1 — Murray & Nadel 7e, pr.1006. Table 73.1 Hallmarks of Cancer

eFIGURE IMAGE GALLERY



eFigure 74.1 — Murray & Nadel 7e, pr.1028.e1. Magnitude of genetic associations for 58 reported lung cancer susceptibility loci. The left and right panels show odds ratio (OR) and $-\log_{10}(P \text{ value})$, respectively. The top set of results were previously described by Bosse and Amos,¹⁸⁰ whereas results below the line are newly reported loci. Bars illustrate the smallest P values or the maximum OR reported per locus. Tick symbols inside bars are results of the indivi

Flowchart 1: From carcinogen to lung cancer in a susceptible host



Clinical relevance

- Genetic information may help select people for screening.
 - The text suggests that high-risk variants such as BRCA2 K3326X may justify screening, as a positive family history would.
- Tumour driver mutations (EGFR, KRAS) define molecular targets for therapy.

PEARLS

- Smoking causes about 85–90% of lung cancer risk, yet only about **15% of smokers** develop it.
- The commonest smoking signature is **C to T transversions**.
- 15q25 (CHRNA5)** links nicotine dependence and lung cancer risk.
- 6p21 (HLA)** is mainly associated with squamous cancer.
- 5p15 hTERT** is mainly associated with adenocarcinoma, and **CLPTM1L** with squamous cancer.
- BRCA2 K3326X** gives a 2.5-fold squamous cancer risk.
- CYP2A6** variation modifies nicotine and NNAL metabolism and lung cancer risk.
- EGFR mutations are common in women, Asians, never-smokers and adenocarcinoma. KRAS mutations are common in smokers.
- Genomic instability and metabolic reprogramming are early events in the at-risk epithelium.
- Driver** mutations confer a growth advantage, whereas **passenger** mutations do not.

Sources

- Textbook: Murray & Nadel 7e — Ch 73 Lung Cancer: Molecular Biology and Targets, §Molecular Biology — pp. 1005–1006
- Textbook: Murray & Nadel 7e — Ch 74 Lung Cancer: Epidemiology, §Smoking; §Genome-Wide Association Studies — pp. 1020–1021, 1027

4. Lung cancer screening – patient selection and implementation, and using screening CT for COPD

ASKED 3* · Intermediate answer

Asked in: Jun 2020 P-II Q8(a) [5] · Oct 2023 P-IV Q10(b) [5] · Jun 2025 P-IV Q10(a) [5]

Q: Screening for lung cancer. [5]

Q: Patient selection and implementation in lung cancer screening. [5]

Q: Leveraging lung cancer imaging for COPD screening. [5]

Definition and rationale

- **Screening** is the systematic examination of asymptomatic people to detect and treat disease early.
- Lung cancer fits screening criteria: it is common, has high mortality, and is more treatable when found early.
- Without screening, **75%** present with advanced disease. Their 5-year survival is **6–30%**, against about **60%** for localised disease.
- Aim: a favourable **stage shift** and lower lung cancer mortality.
- Chest radiograph and sputum cytology screening gave no mortality benefit. **PLCO** randomised 154,901 people aged 55–74 years to annual CXR or usual care and showed no benefit.

Evidence for LDCT

- **NLST** was the largest trial. It enrolled **53,454** people aged 55–74 years with ≥ 30 pack-years, current smokers or quit within 15 years.
- NLST compared annual LDCT for 3 years with annual CXR.
- NLST result: **20%** lower lung cancer mortality. All-cause mortality was 6.7% lower. The **number needed to screen was 320**.
- **NELSON** enrolled ages 50–75 years, ≥ 15 pack-years, current smokers or quit within 10 years.
 - Screening was at baseline, then 1, 3 and 5.5 years.
 - At 10 years the rate ratio for lung cancer death was **0.76**, a 24% reduction. Benefit was greater in women.
 - Volumetric work-up: growth was a volume increase of $\geq 25\%$. A nodule was negative if $< 50 \text{ mm}^3$, or if volume-doubling time was ≥ 400 days.
- Limits to generalisability:
 - NLST participants were younger, healthier and better educated (healthy-volunteer effect).
 - NLST was run in tertiary centres with expert multidisciplinary teams.
 - NLST surgical mortality was $< 1\%$, against 3–5% nationally.

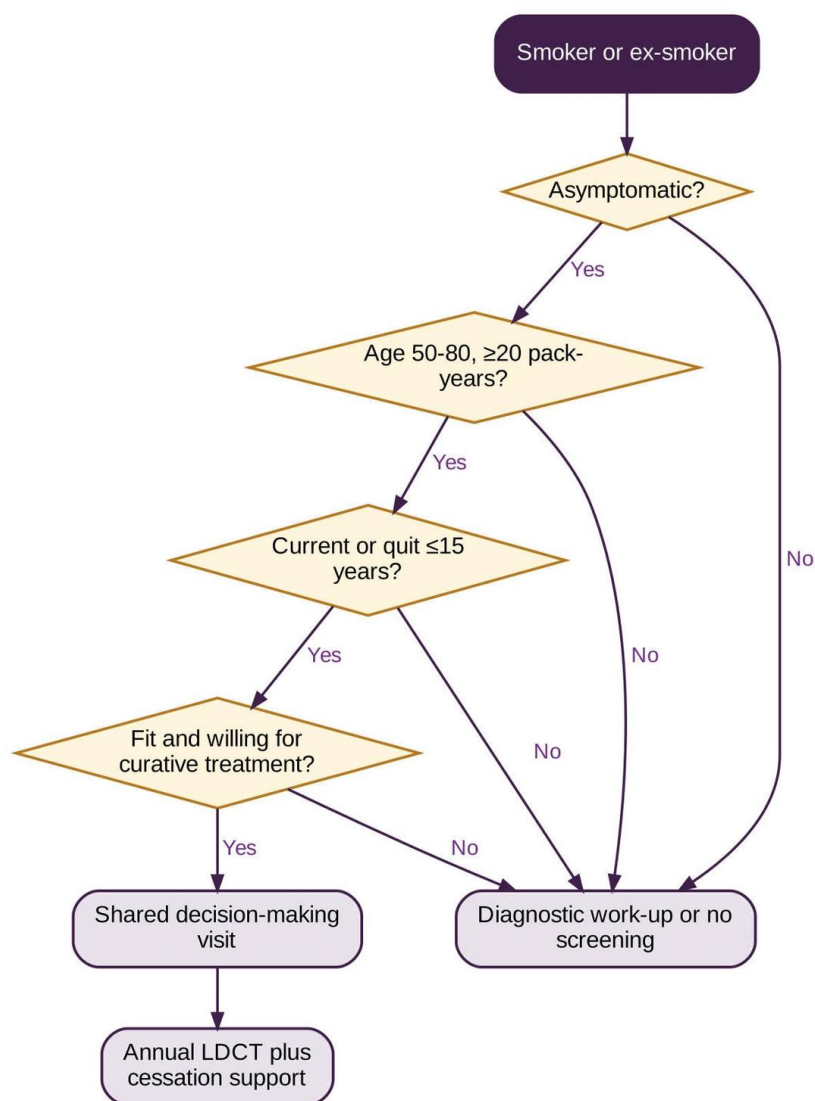
Patient selection

- Criteria must identify people whose mortality benefit outweighs harm.
- Screen only **asymptomatic** people. Symptomatic patients need diagnostic work-up.
- Exclude people whose comorbidity limits life expectancy, or who are unable or unwilling to have curative treatment.
- Stop screening once a person has been abstinent for 15 years, or develops a health problem that limits life expectancy or willingness for curative surgery.

Table 1: Eligibility criteria, textbook versus current guideline

Textbook · USPSTF 2013	Current · USPSTF 2021
Age 55–80 years	Age 50–80 years
≥30 pack-years	≥20 pack-years
Current smoker or quit ≤15 years	Current smoker or quit ≤15 years
Annual LDCT	Annual LDCT

- The 2021 update was based on a CISNET modelling study. It reduced disparity by sex, race and ethnicity.
- CMS (textbook version) used age 55–77 years.
- Risk-based selection:
 - **PLCOm2012** includes age, race, education, BMI, COPD, cancer history, family history and smoking status, intensity, duration and quit time.
 - It has better sensitivity and PPV than NLST/USPSTF criteria.
 - Benefits are fewer false positives and a lower number needed to screen.
 - NCCN adds a group aged ≥50 years with ≥20 pack-years plus a risk factor, with risk ≥1.3% over 6 years.
 - The 2018 CHEST guideline suggests 6-year risk ≥1.51% on PLCOm2012 as "high risk".
- People outside the criteria: screening is not recommended, because benefit is unproven and harms are more likely.

Flowchart 1: Eligibility for screening

Implementation

- Essential programme components:
 - Eligibility policy
 - Frequency and duration policy
 - Standard LDCT technique
 - Nodule definition
 - Structured reporting
 - Nodule management pathways
 - Smoking cessation
 - Education
 - Data collection

Table 75.1 Components Necessary for a High-Quality Lung Cancer Screening Program ⁵⁷
WHO IS OFFERED LUNG CANCER SCREENING Programs must confirm that a policy is in place about who will be offered screening that is in line with evidence-based guidelines.
HOW OFTEN, AND FOR HOW LONG, TO SCREEN Programs must confirm that there is a policy about the frequency and duration of screening that is in keeping with USPSTF recommendations.
HOW THE CT SCAN IS PERFORMED An LDCT scan should be performed based on the American College of Radiology and Society of Thoracic Radiology technical specifications.
LUNG NODULE IDENTIFICATION Programs should have a policy about the size and characteristics of a lung nodule to be used to label the test as positive.
STRUCTURED REPORTING A lung cancer screening program should use a structured reporting system, such as LungRADS, and collect data about compliance with the system.
LUNG NODULE MANAGEMENT ALGORITHMS Programs must have clinicians with expertise in the management of lung nodules and treatment of lung cancer. The program should have developed lung nodule care pathways with the ability to order additional testing and communicate results to the patient and/or provider. There should be a mechanism to track nodules and collect outcomes.
SMOKING CESSATION Programs must integrate smoking cessation services for active smokers.
PATIENT AND PROVIDER EDUCATION Programs are responsible for the oversight and supplementation of provider-based patient education.
DATA COLLECTION Programs must collect data related to each component of a lung cancer screening program, the outcomes of testing, as well as the cancers diagnosed, and report this data annually to an oversight body.

CT, computed tomography; LDCT, low-dose computed tomography; USPSTF, U.S. Preventive Services Task Force.

Table 75.1 — Murray & Nadel 7e, pr.1031. Table 75.1 Components Necessary for a High-Quality Lung Cancer Screening Program⁵⁷

- **Shared decision-making** visit before the scan, using decision aids.
- **LDCT technique:** CTDIvol ≤ 3 mGy, following ACR/STR technical specifications. LDCT uses about 8 mSv against 32 mSv for standard CT. Maximum intensity projection (slab about 10 mm) improves nodule detection.
- **Structured reporting** with **Lung-RADS**, which the textbook describes as the version 1.1 tool.
 - Category 0–4 is based on size, attenuation, morphology and time point.
 - **S modifier:** significant incidental non-lung-cancer findings.
 - **X modifier:** features that raise suspicion, such as spiculation, rapid growth or lymphadenopathy.
 - Positive solid nodule threshold is ≥ 6 mm (NLST used ≥ 4 mm). Nonsolid threshold is ≥ 30 mm.
 - Category 3 (solid 6 to <8 mm at baseline): about 1–2% malignancy risk, repeat LDCT at **6 months**.
 - Category 4B (growing nodule ≥ 8 mm): about 15% malignancy risk. Options are CT, PET or tissue sampling.
 - **Lung-RADS v2022** is the current ACR version. It adds criteria for atypical pulmonary cysts, juxtapleural nodules, infectious or inflammatory findings and airway nodules. It also introduces stepped management for categories 3 and 4A.

Category Descriptor	Lung-RADS Score	Findings	Management	Risk of Malignancy	Est. Population Prevalence
Probably Benign Probably benign finding(s) - short term follow up suggested; Includes nodules with a low likelihood of becoming a clinically active cancer	3	Solid nodule(s): ≥6 to < 8 mm (≥ 113 to < 268 mm ³) at baseline OR new 4 mm to < 6 mm (34 to < 113 mm ³)	6 month LDCT	1-2%	5%
		Part solid nodule(s) ≥ 6 mm total diameter (≥ 113 mm ³) with solid component < 6 mm (< 113 mm ³) OR new < 6 mm total diameter (< 113 mm ³)			
		Non solid nodule(s) (GGN) ≥ 30 mm (≥ 14137 mm ³) on baseline CT or new			

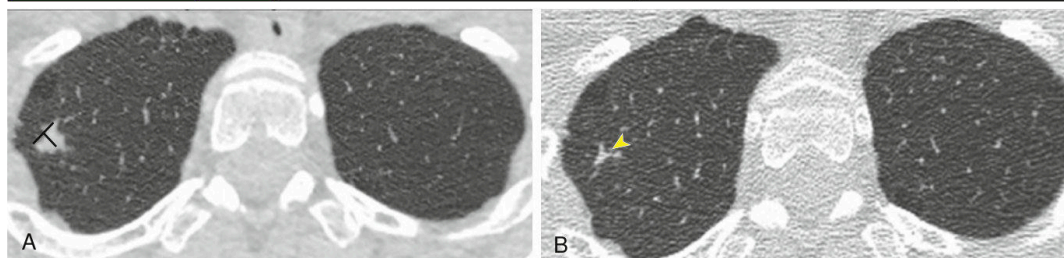


Figure 20.46 — Murray & Nadel 7e, pr.299.e26. Application of the Lung (CT) Screening Reporting and Data System (Lung-RADS) to low-dose computed tomography (LDCT) screen-ing results. (A) Axial chest CT image displayed in lung windows shows a right upper lobe nodule (note bidirectional measurement bars) measuring 8.3 mm × 6.3 mm, for an average bidirectional measurement of 7.3 mm, which, for a solid lesion at baseline LDCT, is consistent with Lung-RADS assessment

- Programme structure: centralised, decentralised or hybrid. A tracking system for nodules and an annual registry report to the oversight body are needed.
- **Smoking cessation** is integral.
 - 7 years of abstinence gave the same 20% mortality reduction as LDCT.
 - Combined with LDCT, mortality reduction was **38%**.
- Incidental findings are common, but <5% lead to an invasive procedure.

Using screening CT for COPD

- The screening scan is also a free chest CT of high-risk smokers, the group at highest risk of COPD.
- In NLST, emphysema was reported on LDCT in **30.7%** at baseline and 44.2% at any screen.
- Only **18%** of those with emphysema on baseline CT reported a COPD/emphysema history. This points to a large underdiagnosed group.
- Emphysema on LDCT raised respiratory disease mortality (HR **2.27**). Reticular opacities also raised it (HR 1.39).
- Practical use:
 - Report emphysema (extent and type) and fibrotic change as incidental findings, using the S modifier.
 - Use the finding to prompt confirmation of COPD and early treatment, and stronger cessation counselling.
 - Respiratory findings such as emphysema may also alert clinicians to coexisting interstitial disease.
- Limit: expert guidance does not currently recommend additional work-up of incidental emphysema or bronchial wall thickening, and no studies have defined how these findings correlate with moderate or severe COPD.
- Emphysema also complicates nodule assessment and surgical risk.

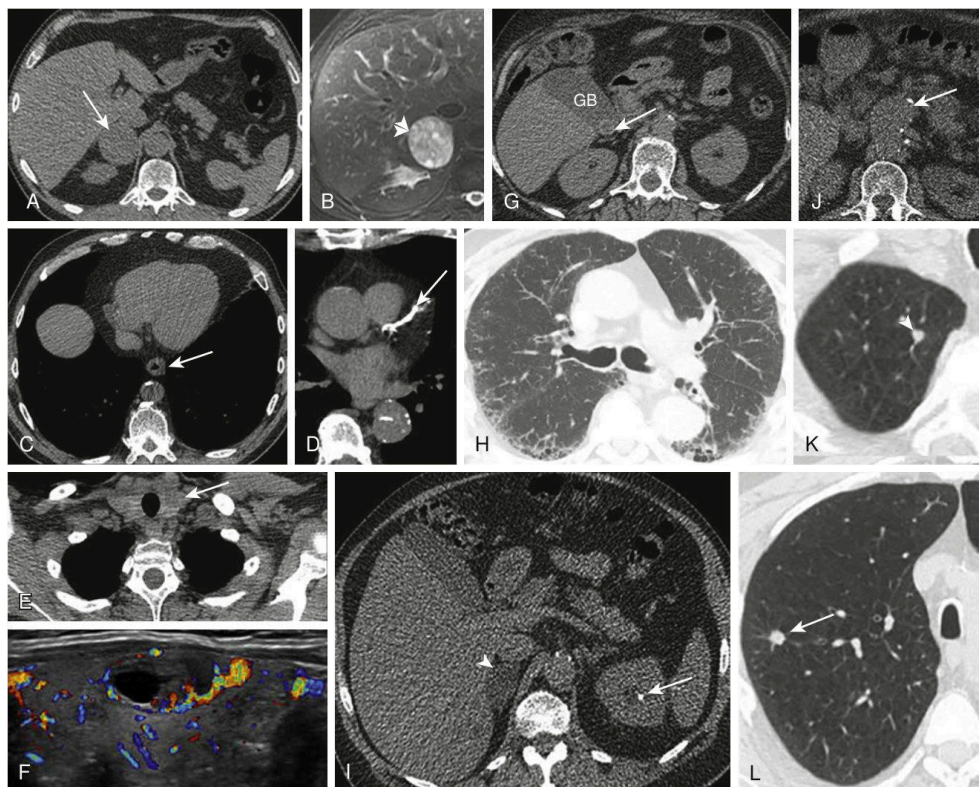


Figure 75.2 — Murray & Nadel 7e, pr.1034. Findings, many incidental, on low-dose lung cancer screening computed tomography. (A) Nonspecific right adrenal mass (arrow) found on low-dose lung cancer screening computed tomography (LDCT). (B) The right adrenal mass shows T2 hyperintensity on dedicated MRI (double arrowheads). Resection proved pheochromocytoma. (C) Axial LDCT shows nonspecific thickening of the distal esophagus (arrow). Upper endoscopy revealed r

Guideline

GUIDELINE

USPSTF — Lung Cancer Screening Recommendation — 2021 (eligibility); ACR — Lung-RADS v2022 (reporting and management).

Harms

- False positives, which are more frequent in low-risk groups.
- Unnecessary biopsy or surgery.
- Radiation exposure, cost, overdiagnosis and incidental findings.

PEARLS

- NLST: **20%** lower lung cancer mortality. NELSON: **24%** lower. NNS in NLST = **320**.
- Current USPSTF: **50–80 years**, **≥20 pack-years**, quit ≤15 years, annual LDCT.
- Lung-RADS positive threshold was raised from 4 mm to **6 mm** (solid) to cut false positives.
- Lung-RADS modifiers: **S** = incidental, **X** = increased suspicion.
- LDCT dose ≤**3 mGy** CTDIvol.
- Cessation plus LDCT gives **38%** mortality reduction.
- Emphysema on LDCT is common and often undiagnosed. It predicts respiratory mortality (HR 2.27).
- Screen only asymptomatic, fit people who are willing to have treatment.
- Shared decision-making and a nodule-tracking pathway are mandatory.

Sources

- Textbook: Murray & Nadel 7e — Ch 20 Thoracic Radiology: Noninvasive Diagnostic Imaging, §Techniques — pp. 283.e1; 299.e26

- Textbook: Murray & Nadel 7e — Ch 75 Lung Cancer: Screening — pp. 1029–1031; 1034; 1037
- [w1] USPSTF 2021 recommendation (summarised in PMC) — Comparing characteristics of individuals screened under 2021 vs 2013 USPSTF recommendations — <https://pmc.ncbi.nlm.nih.gov/articles/PMC11542990>
- [w2] CHEST — ACR Lung-RADS v2022: Assessment Categories and Management Recommendations — [https://journal.chestnet.org/article/S0012-3692\(23\)05673-8/fulltext](https://journal.chestnet.org/article/S0012-3692(23)05673-8/fulltext)
- [w3] CHEST (PMC) — Incidental Findings on Low-Dose CT Scan Lung Cancer Screenings and Deaths From Respiratory Diseases — <https://pmc.ncbi.nlm.nih.gov/articles/PMC9005861/>
- [w4] CHEST (PMC) — Does the Presence of Lung Incidental Findings on LDCT Lead to Additional Testing? — <https://pmc.ncbi.nlm.nih.gov/articles/PMC13418344/>

5. Electrolyte imbalance in small cell lung carcinoma

ASKED 1* · Intermediate answer

Asked in: Oct 2024 P-II Q3(a) [5]

Q: Electrolyte imbalance in small cell lung carcinoma. [5]

Electrolyte imbalance in small cell lung carcinoma

Definition and scope

- SCLC is a neuroendocrine tumour that makes ectopic hormones. These cause **paraneoplastic electrolyte disturbances**.
- **Hyponatraemia from SIADH** is the commonest and most examinable.
- **Hypokalaemic metabolic alkalosis** is due to ectopic ACTH (Cushing syndrome).
- **Hypercalcaemia of malignancy** is a further metabolic emergency in lung cancer.
- Treating the tumour with chemotherapy is the definitive correction for all of these.

Hyponatraemia: SIADH

- Only **10% of SCLC patients** have SIADH. SCLC accounts for about **75% of all SIADH**.
- Mechanism:
 - ADH (vasopressin) is made in the hypothalamus and acts on the renal collecting duct.
 - It moves water from the lumen into the medullary interstitium and concentrates the urine.
 - Here the tumour secretes it ectopically, so water is retained and the serum is diluted.
- Other causes of hyponatraemia in these patients (pulmonary infection, CNS disease, drugs) must be excluded.

Diagnostic criteria for SIADH

- Hyponatraemia with serum **hypo-osmolality** < 275 mOsm/kg.
- Inappropriately high **urine osmolality** > 200 mOsm/kg.
- **Urine sodium** > 20 mEq/L.
- Clinical **euvolaemia without oedema**.
- Normal renal, adrenal and thyroid function.
- Supportive findings: serum uric acid is usually low, and urine/serum osmolality ratio is often > 2.

Clinical features

- Severity depends on the **degree of hyponatraemia and the rapidity of fall**.
- Many patients are asymptomatic. In one large series only **27%** had symptoms despite a median sodium of **117 mEq/L**.
- Mild symptoms: anorexia, nausea, vomiting.
- Rapid onset (cerebral oedema): irritability, restlessness, personality change, confusion, coma, seizures and respiratory arrest.

Ectopic ACTH syndrome

- SCLC causes **75% of ectopic ACTH** cases. Only **1–2% of SCLC patients** develop Cushing syndrome.
- Other sources are carcinoid tumours, pheochromocytoma, neuroblastoma and medullary thyroid carcinoma.

- Because SCLC grows rapidly, patients present with **oedema, hypertension and muscle weakness** rather than classic moon facies or striae.
- Biochemistry: **hypokalaemic alkalosis** and hyperglycaemia are usually present.
- Best screening test: **24-hour urinary free cortisol**.
- Ectopic source is favoured by:
 - high cortisol with no suppression on high-dose dexamethasone;
 - plasma ACTH > **200 pg/mL (40 pmol/L)**, with no pituitary adenoma.
- Prognosis is worse, probably from opportunistic infection.

Hypercalcaemia

- Hypercalcaemia of malignancy needs hydration plus a potent antiresorptive agent, whatever the mechanism.
- Clinical clues: confusion, drowsiness, asthenia.

Table 1: Electrolyte disturbances in SCLC

Feature	SIADH	Ectopic ACTH	Hypercalcaemia of malignancy
Electrolyte change	Low Na ⁺	Low K ⁺ , alkalosis	High Ca ²⁺
Mechanism	Ectopic ADH	Ectopic ACTH, cortisol excess	Tumour-driven bone resorption
Key test	Urine osmolality > 200, urine Na ⁺ > 20	24-h urinary free cortisol, ACTH > 200 pg/mL	Albumin-corrected calcium
Acute treatment	Fluid restriction; 3% saline if severe	Enzyme inhibitors	IV fluids plus bisphosphonate
Definitive	Chemotherapy	Chemotherapy	Treat tumour

Differential diagnosis of hyponatraemia in SCLC

- Hypovolaemic hyponatraemia (vomiting, diuretics, adrenal insufficiency): the patient is clinically hypovolaemic.
- Hypervolaemic states (heart, liver, renal failure): oedema is present.
- Adrenal insufficiency (metastases, drugs) and hypothyroidism: renal, adrenal and thyroid function must be normal for SIADH.
- Drug-induced hyponatraemia and CNS disease.

Management of SIADH

GUIDELINE

European Society of Endocrinology / ESICM / ERA-EDTA — Clinical practice guideline on diagnosis and treatment of hyponatraemia — 2014 (Eur J Endocrinol 170:G1–47). Hypercalcaemia: Endocrine Society — Treatment of Hypercalcemia of Malignancy in Adults — 2023.

- Asymptomatic or minimally symptomatic:
 - **Fluid restriction 500–1000 mL/24 h** is the initial treatment.
 - If more is needed, oral **demeclocycline 900–1200 mg/day**. It induces nephrogenic diabetes insipidus.
 - Demeclocycline acts over hours to weeks, so it is not for emergencies. It is potentially nephrotoxic.
 - Vasopressin receptor antagonists: IV conivaptan is hospital-only. Oral agents are also approved.
- Severe symptoms (seizures, coma, severe confusion):
 - Give hypertonic **3% saline**.
 - The 2014 ESE guideline recommends **150 mL of 3% saline IV over 20 min**.
 - Recheck serum sodium after 20 min and repeat 150 mL for the next 20 min if needed.
 - If there is no improvement after a 5 mmol/L rise, continue 3% saline aiming for an additional 1 mmol/L per hour.
 - Stop when symptoms improve, and check sodium every 4 hours while infusing.
 - Consider weight-based dosing (2 mL/kg) when body composition is deviant.

- Overcorrection risk:
 - Faster correction causes **central pontine myelinolysis**: quadriplegia, pseudobulbar palsy, altered mentation, death.
 - Monitor sodium frequently.
- SIADH from SCLC:
 - Start **chemotherapy as soon as possible**. Hyponatraemia improves within a few weeks.
 - SIADH may recur on relapse.

Table 2: Textbook versus guideline for severe symptomatic hyponatraemia

Textbook · Murray & Nadel 7e	Guideline · ESE 2014
300 mL of 3% saline over 3–4 h with a loop diuretic	150 mL of 3% saline over 20 min, repeated once if needed
Saline without diuretic will not raise sodium	Recheck sodium after 20 min; target +5 mmol/L in first hour
Maximum correction 20 mEq/L/day	Stop when symptoms improve; check sodium every 4 h

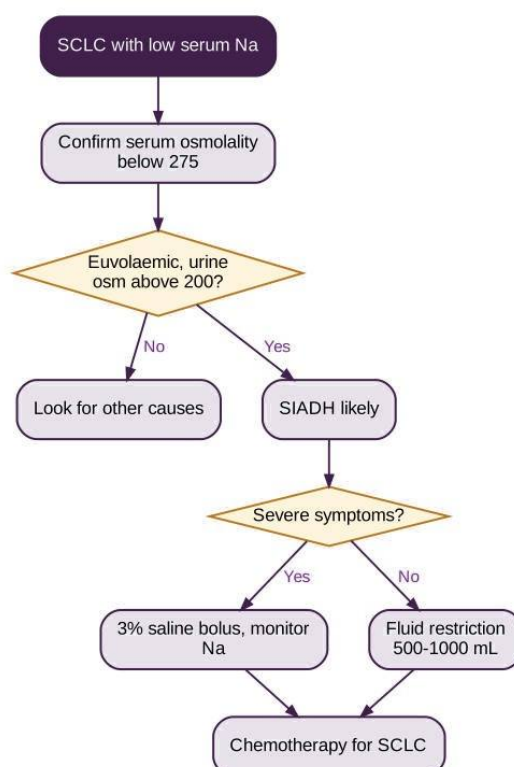
Management of ectopic ACTH

- Adrenal enzyme inhibitors, alone or in combination:
 - **Ketoconazole 400–1200 mg/day** orally.
 - **Metyrapone 250–750 mg three times daily**.
 - Control takes days to weeks and is variable.
 - Titrate to normal urinary free cortisol or morning plasma cortisol of 7–11 µg/mL.
- Watch for symptomatic hypoadrenalism. Some give replacement glucocorticoid.
- Give chemotherapy for the SCLC and watch for superimposed infection.
- Carcinoid or thymic sources are best treated by resection.

Management of hypercalcaemia (Endocrine Society 2023)

- Hydration plus a potent antiresorptive agent (IV bisphosphonate or denosumab).
- **Zoledronic acid 3–4 mg IV over 15–30 min**. Repeat after 7 days if needed, then every 3–4 weeks.
- **Pamidronate 60–90 mg IV over 2–24 h**. Repeat every 2–3 weeks.
- In renal insufficiency (creatinine clearance < 60 mL/min), use renally adjusted bisphosphonate dosing.
- Adverse effects: acute-phase reaction, hypocalcaemia, renal impairment, rarely osteonecrosis of the jaw.

Flowchart 1: Approach to hyponatraemia in SCLC



Complications and prognosis

- Cerebral oedema, seizures and respiratory arrest from untreated hyponatraemia.
- Osmotic demyelination from overcorrection.
- Opportunistic infection in ectopic ACTH. The textbook endocrine chapter lists *Cryptococcus*, *Aspergillus*, *Nocardia*, *Pneumocystis* and *M. tuberculosis*.
- Recurrence of the syndrome signals tumour relapse.

PEARLS

- SCLC is about **75% of SIADH**, but only **10%** of SCLC patients get SIADH.
- SIADH needs euvolaemia with **urine osmolality > 200** and **urine Na⁺ > 20 mEq/L**.
- Fluid restriction **500–1000 mL/day** is first-line for mild SIADH.
- **Demeclocycline 900–1200 mg/day** acts slowly and can be nephrotoxic.
- Overly rapid correction causes **central pontine myelinolysis**.
- Ectopic ACTH presents as oedema, hypertension, weakness and **hypokalaemic alkalosis**.
- **ACTH > 200 pg/mL** with no dexamethasone suppression points to ectopic ACTH.
- Screening test for Cushing syndrome is **24-h urinary free cortisol**.
- Ketoconazole and metyrapone control cortisol excess. Chemotherapy is definitive.
- Hypercalcaemia: IV hydration plus zoledronic acid 3–4 mg.

Sources

- Textbook: Murray & Nadel 7e — Ch 76 Lung Cancer: Diagnosis and Staging, §Paraneoplastic Syndromes (SIADH; Ectopic Corticotropin Syndrome) — pp. 1051.e4–1051.e4
- Textbook: Murray & Nadel 7e — Ch 128 Pulmonary Complications of Endocrine Diseases, §Adrenal Disorders (Cushing Syndrome) — pp. 1797–1798
- [w1] European Society of Endocrinology / ESICM / ERA-EDTA — Clinical practice guideline on diagnosis and treatment of hyponatraemia — 2014 — <https://academic.oup.com/ajendo/article/170/3/G1/6668028>
- [w2] Endocrine Society — Treatment of Hypercalcemia of Malignancy in Adults: Clinical Practice Guideline — 2023 — <https://academic.oup.com/jcem/article/108/3/507/6916871>

6. Factors affecting prognosis of NSCLC

ASKED 1* · Intermediate answer

Asked in: Dec 2022 P-II Q10(a) [5]

Q: Factors affecting prognosis of non-small cell lung carcinoma (NSCLC). [5]

Factors affecting prognosis of NSCLC

Definition and overview

- Prognosis in NSCLC is the expected survival and recurrence risk. It depends on **tumour factors, patient factors, treatment factors and care factors**.
- **Stage** is the single most important determinant. It portends prognosis and dictates treatment options.
- Stage alone is incomplete. Age, performance status, comorbidity, access and quality of care, choice of treatment and response to treatment also modify outcome.

Tumour factors

- **Anatomic stage (TNM)**: this is the strongest predictor.
 - It has three components: primary tumour (T), nodes (N) and distant metastasis (M).
 - The staging system is revised periodically as data and therapies change.
- **Tumour size**: each centimetre increase between 1 and 5 cm gives a clear fall in 5-year survival.
 - T1 and T2 are subdivided in 1-cm increments.

- T3 is >5 and ≤7 cm. T4 is >7 cm.
- Detailed size classification can change whether adjuvant chemotherapy is offered, because it moves a patient from stage I to stage II.
- **Nodal status:** N1/N2/N3 involvement worsens prognosis.
 - Under the 9th edition, N2 is split into **N2a** (single station) and **N2b** (multiple stations).
 - Multistation N2 disease has the worse outcome.
- **Metastatic status:** M1a is pleural or pericardial dissemination or a contralateral nodule. M1b is a single extrathoracic lesion. M1c is multiple lesions.
 - M1c is split into **M1c1** (multiple lesions in one organ system) and **M1c2** (multiple organ systems).
- **Multiple pulmonary lesions:** the pattern of disease changes the TNM assignment. The four patterns are second primary, separate tumour nodule, multifocal ground-glass/lepidic nodules, and diffuse pneumonic-type disease.
- **Histology and growth pattern:**
 - Adenocarcinoma patterns fall into three prognostic grades. **Grade 1** is lepidic (best). **Grade 2** is acinar and papillary. **Grade 3** is micropapillary and solid (worst).
 - In squamous carcinoma, keratinisation is associated with a better prognosis.
 - Large cell neuroendocrine histology has a survival curve overlapping SCLC, so its prognosis is worse than other NSCLC types.
 - Mixed histologies such as adenosquamous may carry a similar chance of targetable mutations as pure adenocarcinoma.
- **Molecular features:** personalised treatment should consider molecular analysis alongside histology. Targetable alterations allow targeted therapy and immunotherapy, which change outcome.
- **Special sites:** for superior sulcus tumours, poor prognostic factors are weight loss, vertebral body involvement and supraclavicular involvement. N1/N2 disease and incomplete resection also worsen outcome.

Table 1: 5-year survival by stage in the IASLC database (8th edition, patients diagnosed 1999–2010)

Stage	Clinical (%)	Pathologic (%)
IA1	92	90
IA2	83	85
IA3	77	80
IB	68	73
IIA	60	65
IIB	53	56
IIIA	36	41
IIIB	26	24
IIIC	13	12
IVA	10	–
IVB	0	–

Table 76.5 5-Year Survival (%) of Patients in the IASLC Database Diagnosed With NSCLC From 1999–2010

Type	IA1	IA2	IA3	IB	IIA	IIB	IIIA	IIIB	IIIC	IVA	IVB
Clinical	92	83	77	68	60	53	36	26	13	10	0
Pathologic	90	85	80	73	65	56	41	24	12	–	–

Average overall survival in the IASLC global database of patients receiving a diagnosis between 1999 and 2010.

IASLC, International Association for the Study of Lung Cancer; NSCLC, non-small cell lung cancer.

From Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT: The eighth edition lung cancer stage classification. *Chest*. 2017;151(1):193–203; with data from Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11(1):39–51.

Table 76.5 — Murray & Nadel 7e, pr.1044. Table 76.5 5-Year Survival (%) of Patients in the IASLC Database Diagnosed With NSCLC From 1999–2010

Staging edition and recent update

- The 8th edition was a worldwide standard from 1 January 2017.
 - Its database held about 95,000 patients treated between 1999 and 2010.
 - It moved T2 tumours >4–5 cm N0M0 from stage IB to **IIA**.

- The **9th edition** is based on a newer database of 124,581 patients from 25 countries. It is in use from January 2025.
 - The T component is unchanged.
 - N2 is split into N2a and N2b. M1c is split into M1c1 and M1c2.
 - T1N1 is downstaged from IIB to IIA. T1N2a is placed in stage IIB. T2bN2b is placed in stage IIIB.
 - A worse prognosis was shown for ypN disease (pathologic N after neoadjuvant therapy) than for pN disease.

Patient factors

- **Performance status** and **comorbidity** influence prognosis and fitness for treatment.
- **Age** is a prognostic factor.
- **Weight loss**: constitutional symptoms suggest metastatic disease.

Treatment and response factors

- **Resectability and completeness of resection**: incomplete resection has a worse prognosis.
- **Treatment choice**: surgery, chemoradiotherapy, targeted therapy or immunotherapy.
- **Metabolic response on FDG-PET/CT**:
 - In resectable disease treated with induction therapy, a model combining nodal involvement and primary tumour response separated good from poor prognosis. 5-year survival was **62%** versus **6%**.
 - In unresectable disease on radiotherapy, response at 2 weeks gave 2-year survival of **92%** in responders versus **33%** in non-responders (one study).
 - After completion of (chemo)radiotherapy, median survival was **31 months** in complete metabolic responders versus **11 months** in incomplete responders.
 - PET predicts survival better than baseline stage, CT response or performance status.
 - Salvage resection guided by abnormal FDG-PET gave median survival of 43 versus 12 months when guided by CT relapse.

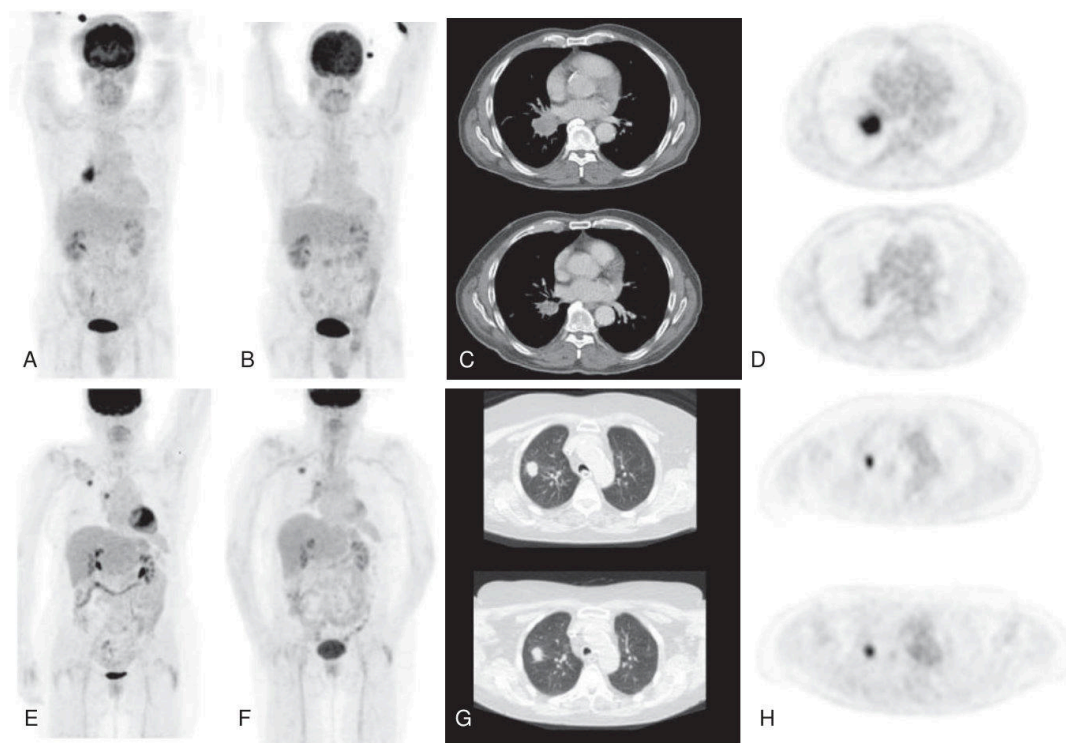


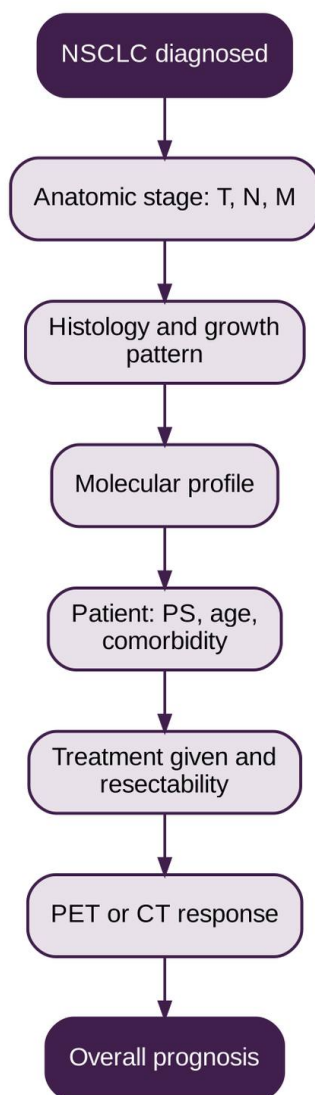
Figure 25.8 — Murray & Nadel 7e, pr.365. 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) after induction chemotherapy. Two

Care and diagnostic quality factors

- **Accuracy of staging**: clinical and pathologic TNM disagreed in **48%** of cases, mostly from clinical understaging.
- **Multimodality mediastinal staging** (CT ± PET ± invasive) was associated with a lower risk of death.
- **Guideline-concordant care** was associated with fewer complications.
- **Timeliness**: time to diagnosis and treatment often exceeds the recommended delay. Its link to outcome is variable.

- **Adequate tissue for molecular testing** is a quality indicator in advanced disease.

Flowchart 1: Framework for assessing NSCLC prognosis



PEARLS

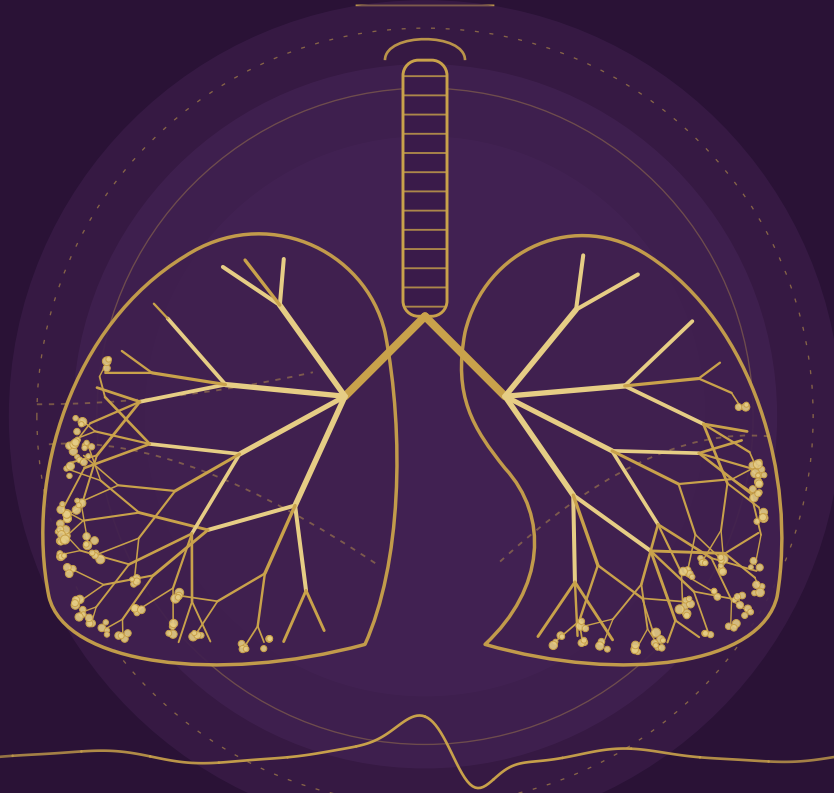
- **Stage** is the strongest prognostic factor in NSCLC. Remember the 5-year survival gradient from about 90% (IA1) to about 10% (IVA).
- The 9th edition TNM, in use from 2025, leaves T unchanged and splits **N2a/N2b** and **M1c1/M1c2**.
- Each 1-cm increase in tumour size from 1 to 5 cm worsens prognosis.
- Adenocarcinoma grade: lepidic (1) is best, acinar/papillary (2) is intermediate, micropapillary/solid (3) is worst.
- Keratinising squamous carcinoma does better than non-keratinising.
- Large cell neuroendocrine carcinoma behaves like SCLC.
- Metabolic response on PET (after induction therapy or after chemoradiotherapy) discriminates survival better than CT response or performance status.
- Clinical and pathologic stage disagree in about **48%** of patients, mainly from understaging.
- Superior sulcus tumours: weight loss, vertebral and supraclavicular involvement, N1/N2 disease and incomplete resection are poor factors.

Sources

- Textbook: Murray & Nadel 7e — Ch 25 Positron Emission Tomography, §Cell Lung Cancer › Response To Therapy — pp. 365–365



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Answers are written from Murray & Nadel's Textbook of Respiratory Medicine (7th ed.), with printed page numbers cited in each answer, and from current guidelines found on official society and journal sites, cited [W#] and listed in the Web-Sourced Facts Register.

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HOW TO USE

Each answer groups every year the question was asked and is written to the most demanding version. Badges show how often a topic was asked. Each answer ends with one Sources block: the Murray & Nadel 7e chapter and printed pages used, and the guideline/web sources (also listed in the register at the end). Section B lists this volume question by question; C lists high-yield topics.

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PART 11

Pleura and Mediastinum

1. Approach to pleural effusion – biochemical tests, transudates, and causes of recurrent non-malignant effusion

ASKED 4* · Long answer

Asked in: Apr 2023 P-II Q2 [10] · May 2024 P-II Q2(a) [5] · Dec 2025 P-I Q8(b) [5] · Dec 2025 P-II Q1(a) [5]

Q: Approach to moderate pleural effusion. [10]

Q: Enumerate various causes of recurrent non-malignant pleural effusion. [5]

Q: Biochemical tests for diagnostic evaluation of pleural effusion. [5]

Q: Transudative pleural effusion. [5]

Definition and scope

- **Pleural effusion** is abnormal fluid in the pleural space. It is a sign of disease in the pleura, lung or an extrapulmonary organ, not a diagnosis.
- A **moderate effusion** lies between a small effusion (blunted costophrenic angle) and a large one (opacifying two-thirds of the hemithorax). It is large enough to sample and usually causes symptoms.
- This answer covers four linked questions:
 - the stepwise approach to a moderate effusion
 - the biochemical tests
 - transudative effusions
 - causes of recurrent non-malignant effusion

Why it matters

- Increased opacity on a chest radiograph is often wrongly attributed to parenchymal disease when it is pleural fluid.
- **CHF and cirrhosis** cause almost all transudates.
- **Pneumonia, malignancy, pulmonary embolism (PE) and gastrointestinal disease** cause at least 90% of exudates.
- Up to **30%** of effusions have more than one cause, and CHF is the commonest contributor.
- About **30%** of exudates stay undiagnosed even after thorascopic biopsy. Of these, 10–15% later develop cancer, so follow-up is needed.

Immediate assessment

- Assess dyspnoea, hypoxaemia and haemodynamics first.
- Drain early if the patient is breathless. Removing fluid improves dyspnoea even in trapped lung, because chest wall and diaphragm mechanics improve.
 - In a prospective trial, **73%** improved after thoracentesis (median volume 1.7 L).
 - The benefit was greatest in those with abnormal baseline diaphragm movement.

Focused clinical evaluation

- Symptoms:
 - dyspnoea
 - cough, from lung distortion and volume loss
 - pleuritic pain, from inflammation, infection or malignant pleural involvement (mainly parietal pleural fibres)
- Signs:
 - **dullness to percussion** and **decreased tactile fremitus** are the most useful findings
 - decreased breath sounds
 - egophony at the upper fluid level
 - asymmetrical chest expansion or bulging intercostal spaces in large effusions

- Look for clues to the cause:
 - heart failure: orthopnoea, oedema, raised JVP, gallop
 - cirrhosis and ascites
 - nephrotic syndrome
 - hypothyroidism
 - yellow nails with lymphoedema
 - central lines or catheters
 - drug history
 - fever and pleuritic pain, which make CHF unlikely
- Bilateral effusions of unequal size, or a normal-sized heart, argue against CHF as the sole cause. In one series of bilateral effusions with a normal heart, only 4% were due to CHF.

Imaging

- Free fluid collects in the posterior costophrenic sulcus. A blunted posterior angle, or an obscured posterior diaphragm on the lateral film, calls for ultrasound.
- Ultrasound confirms fluid, estimates volume, guides the tap and shows septations.
 - Volume (mL) $\approx$ maximal pleural separation (mm) $\times$ 20. For example, 20 mm $\approx$ 400 mL.
 - Separation < **10 mm** is too small to tap.
- **CT** assesses pleural thickening, nodularity and parenchymal disease. In malignancy, nodular, circumferential, mediastinal or >1 cm parietal thickening is highly specific but not sensitive.
- Mediastinal position helps:
 - contralateral shift is expected with a large effusion
 - a midline mediastinum suggests ipsilateral lung collapse or a fixed mediastinum
 - shift towards the effusion suggests central bronchial obstruction or tumour infiltration, so the lung is unlikely to re-expand

Table 108.1 Differential Diagnoses of Pleural Effusions
TRANSUDATIVE PLEURAL EFFUSIONS
Congestive heart failure
Hepatic hydrothorax
Nephrotic syndrome
Peritoneal dialysis
Myxedema
Pericardial disease
Central venous occlusion
Pulmonary veno-occlusive disease
VERY LOW PROTEIN TRANSUDATES
Urinothorax
Subarachnoid-pleural fistula
Iatrogenic
EXUDATIVE PLEURAL EFFUSIONS
Neoplastic diseases (see Chapter 114)
• Metastatic disease
• Mesothelioma
• Primary effusion lymphoma
• Pyothorax-associated lymphoma
Infectious diseases (see Chapter 109)
• Pyogenic bacterial infections
• Tuberculosis
• Actinomycosis and nocardiosis
• Fungal infections
• Viral infections
• Parasitic infections
Pulmonary embolism
Abdominal diseases
• Esophageal perforation
• Pancreatic disease
• Intra-abdominal abscesses
• Postabdominal surgery
• Liver transplantation
• Bilious pleural effusion
Inflammatory diseases
• Rheumatoid pleuritis
• Lupus pleuritis
• Immunoglobulin G4-related disease
• Sarcoidosis
• Asbestos-related disease
• Uremia
• Post-cardiac injury syndrome
• Post-coronary artery bypass surgery
• Drug-induced pleural disease (see Chapter 99)
• Eosinophilic granulomatosis with polyangiitis
• Granulomatosis with polyangiitis
• Sjögren syndrome
• Acute eosinophilic pneumonia
Miscellaneous
• Lung transplantation
• Meigs syndrome
• Endometriosis
• Ovarian hyperstimulation syndrome
• Trapped lung (see Chapter 112)
• Yellow nail syndrome
• Misplaced catheters
Hemothorax (see Chapter 113)
Chylothorax (see Chapter 111)

Table 108.1 — Murray & Nadel 7e, pr.1499. Table 108.1 Differential Diagnoses of Pleural Effusions

Diagnostic thoracentesis

- Tap nearly every effusion with fluid > **10 mm** on decubitus film, ultrasound or CT.
- In obvious CHF, tapping can wait until the failure is treated. Tap without delay if there is:
 - fever
 - pleuritic pain
 - unilateral or unequal effusions
 - no cardiomegaly
- Safety:
 - A small-bore needle is safe even in coagulopathy, thrombocytopenia and ventilated patients.
 - Ultrasound guidance is recommended (BTS).
 - Pneumothorax risk is 2–6% in older series and 0.6% with routine ultrasound.
 - Avoid sites medial to the midclavicular line.
 - Routine post-procedure radiograph is unnecessary after an uncomplicated tap.

Biochemical tests on pleural fluid

Step 1: transudate or exudate

- Light's criteria: an **exudate** meets at least one of the following. A transudate meets none.
 - pleural fluid/serum protein > **0.50**
 - pleural fluid/serum LDH > **0.60**
 - pleural fluid LDH > **two-thirds of the upper normal limit for serum**
- Send only protein and LDH (with paired serum) if a transudate is likely. Add other tests if the fluid proves an exudate.
- Light's criteria misclassify up to **25%** of transudates as exudates, especially after diuresis.

Table 1: Biochemical and related tests on pleural fluid

Test	Finding	Meaning
Protein and LDH ratios (Light)	Any criterion met	Exudate
Serum – pleural protein	> 3.1 g/dL	Transudate despite borderline Light's result
Serum – pleural albumin	> 1.2 g/dL	Transudate
Pleural NT-proBNP	> 1500 pg/mL	Cardiac cause; better than BNP
Glucose (and pH)	Low	Metabolically active fluid: empyema, malignancy, rheumatoid
Creatinine (fluid > serum)	Elevated	Urinothorax (about 10% of other effusions also meet this)
β2-transferrin or beta-trace protein	Present	CSF leak (subarachnoid-pleural fistula)
Triglyceride and cholesterol	Lipid analysis of supernatant	Chylothorax vs pseudochylothorax
Amylase	Raised	Pancreatic disease or oesophageal rupture; salivary-origin in 10% of malignant effusions
ADA	Selected cases	TB
ANA, rheumatoid factor	Selected cases	Connective tissue disease
Haematocrit	> 50% of blood	Haemothorax

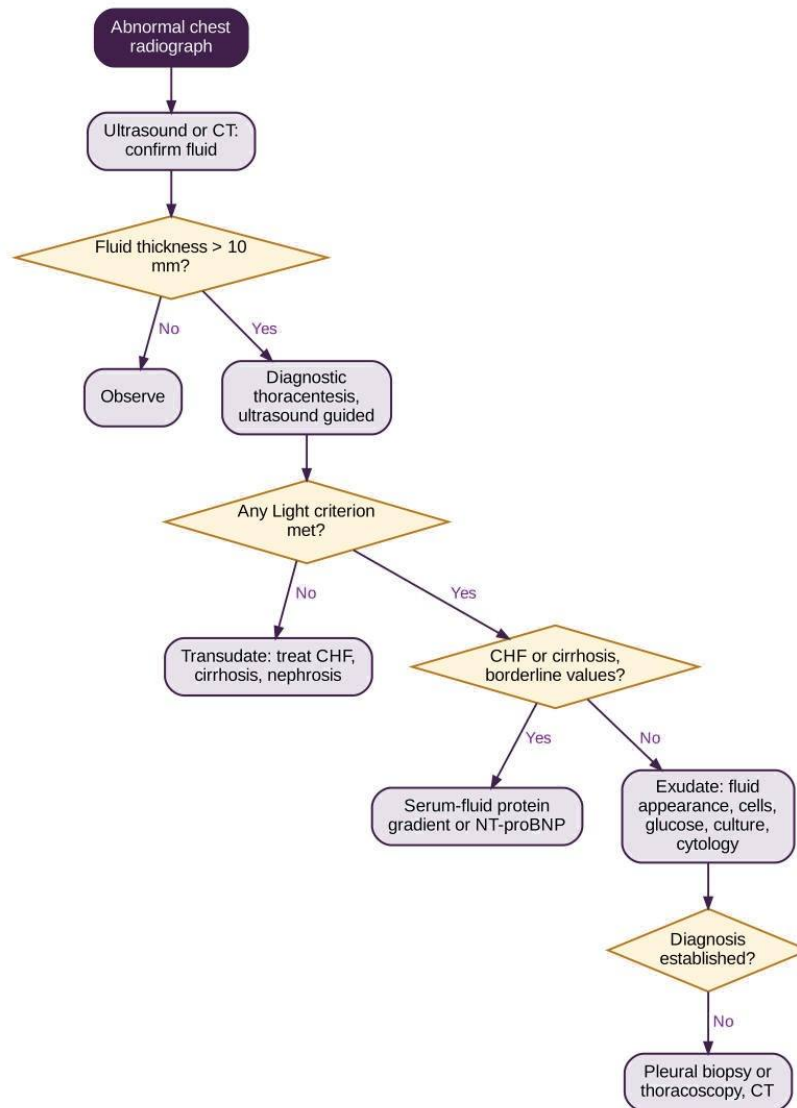
- Glucose is as useful as pH and easier and more reliable. Neither should select patients for pleurodesis.
- Do not order every test routinely in an undiagnosed exudate.
- Indeterminate values near the cut-offs suggest a mixed cause or an evolving process, such as after diuresis.

Step 2: gross appearance and cells

- **Putrid smell** suggests anaerobic infection. **Urine smell** suggests urinothorax.
- Bloody fluid: estimated haematocrit = RBC count ÷ 100,000.
 - > **50%** of blood haematocrit is haemothorax, so consider a chest tube.
 - < **1%** is not significant.

- 1–50% suggests malignancy, PE or trauma.
- Turbid fluid that clears on centrifugation is due to cells or debris. If turbidity persists, it is a chylothorax or pseudochylothorax.
 - Chylothorax: acute onset, thin pleura, no cholesterol crystals, high triglyceride.
 - Pseudochylothorax: chronic, thick pleura, cholesterol crystals.
- Also send:
 - differential cell count
 - Gram stain and culture (including mycobacterial)
 - cytology

Flowchart 1: Approach to a moderate pleural effusion



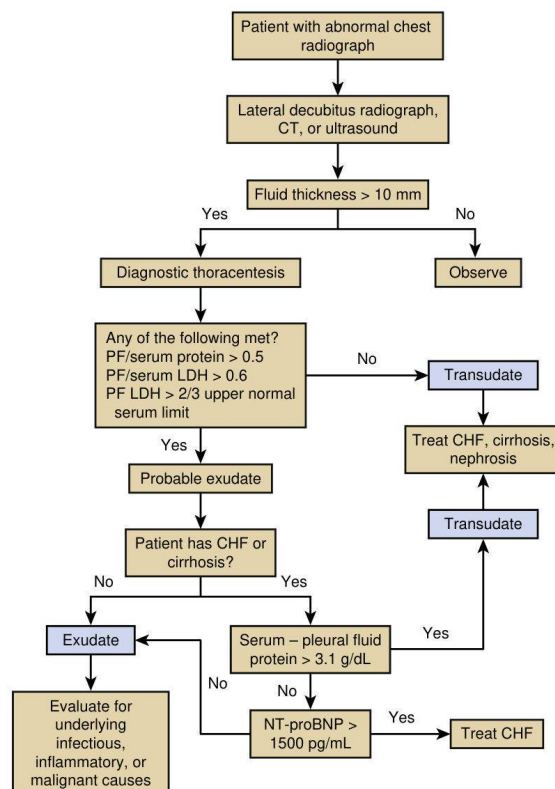


Figure 108.1 — Murray & Nadel 7e, pr.1501. Algorithm for distinguishing transudative from exudative pleural effusions. With the results of the initial thoracentesis, one can usually determine whether the effusion is an exudate or a transudate. If a transudate, the treatment can be directed to the likely causes—congestive heart failure (CHF), liver disease, or kidney disease. If the protein and lactate dehydrogenase (LDH) results are borderline exudative and

Transudative pleural effusion

Definition and mechanism

- A transudate is low-protein, low-LDH fluid (meets none of Light's criteria).
- It arises from systemic changes in hydrostatic or osmotic pressure.
- The pleural surfaces are usually normal. Disease is usually in the heart, liver or kidney, not the lung.

Causes

- Common causes:
 - congestive heart failure
 - hepatic hydrothorax
 - nephrotic syndrome
- Other causes:
 - peritoneal dialysis
 - myxoedema
 - pericardial disease
 - central venous occlusion
 - pulmonary veno-occlusive disease
 - right heart failure from pulmonary hypertension
- Very low protein transudates (**< 0.5 g/dL**) come from entry of CSF, urine, peritoneal dialysate or intravenous fluid into the pleural space:
 - urinothorax
 - subarachnoid-pleural fistula
 - iatrogenic (misplaced catheters)
- Malignancy can rarely cause a transudate through lymphatic obstruction, or alongside CHF. Cytology is rarely positive in these.

Congestive heart failure

- This is probably the commonest cause of effusion.
- Mechanism: interstitial lung oedema crosses a leaky visceral pleura into the pleural space.
- Typical picture:
 - bilateral effusions, larger on the right
 - cardiomegaly on chest radiograph
 - dyspnoea, orthopnoea, oedema, raised JVP
- Diuretics can raise protein and LDH ratios into the exudative range, usually only marginally.
 - Confirm a transudate with a serum–pleural protein gradient $> 3.1 \text{ g/dL}$, or albumin gradient $> 1.2 \text{ g/dL}$.
 - Alternatively, use pleural **NT-proBNP** $> 1500 \text{ pg/mL}$.
- Treat the heart failure with afterload reduction, diuretics and inotropes as needed.
- If effusions persist for more than a few days of treatment, tap.

Hepatic hydrothorax

- Mechanism: ascitic fluid passes through diaphragmatic defects such as blebs or fenestrations. Fluid moves until pleural pressure approaches peritoneal pressure.
- About **80%** are right-sided, 17% left-sided and 3% bilateral. It can appear suddenly and be massive.
- The diagnosis is clinical. Confirm with:
 - paracentesis and thoracentesis (both transudates)
 - intraperitoneal technetium-99m sulphur colloid scan if in doubt
- Pleural fluid protein is usually higher than ascitic protein but still $< 3.0 \text{ g/dL}$.
- Always tap. In one series of 60 patients, 30% had a diagnosis other than hepatic hydrothorax, including spontaneous bacterial pleuritis, TB and adenocarcinoma.

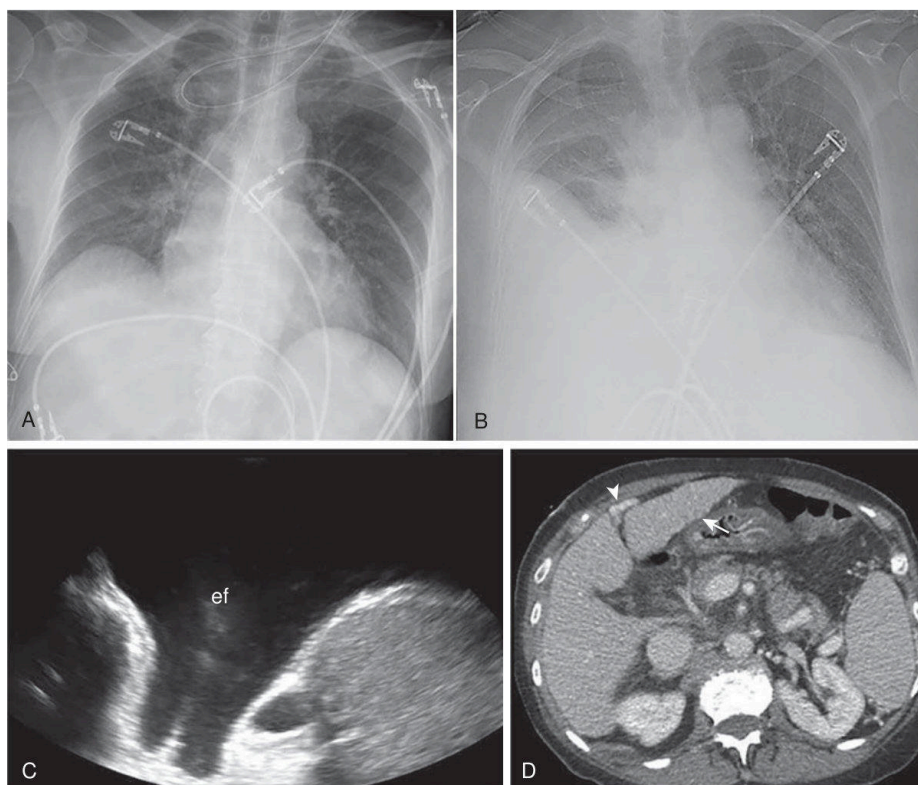


Figure 108.4 — Murray & Nadel 7e, pr.1511. Rapid development of hepatic hydrothorax. (A) Frontal chest radiograph shows an elevated right diaphragm but no other significant findings. (B) Frontal chest radiograph performed about 30 hours after A shows a new large right pleural effusion, shown to be a transudate. (C) Thoracic ultrasound performed for thoracentesis shows a large right pleural effusion (ef). (D) Axial enhanced computed tomography of the abdomen

Other transudative causes

- **Myxoedema:**
 - borderline fluid, often with a pericardial effusion

- treat with thyroid replacement
- **Pericardial disease:**
 - inflammatory pericardial disease tends to cause left-sided effusions
 - constrictive pericarditis causes right-sided or bilateral effusions
- **Central venous obstruction:**
 - suspect after central line placement or in haemodialysis patients with an ipsilateral fistula or arm swelling
 - the effusion is persistent and large, often left-sided
 - relieving the obstruction resolves it
- **Urin thorax:**
 - urine smell, fluid creatinine higher than serum
 - resolves when the obstruction is relieved
- **Subarachnoid-pleural fistula:**
 - headache or neurological symptoms
 - confirm with $\beta 2$ -transferrin or beta-trace protein
 - non-invasive positive pressure is used, with surgical repair if it fails
- **Misplaced catheter:**
 - suspect in anyone with a line and a rapidly developing effusion
 - remove the catheter immediately

Causes of recurrent non-malignant pleural effusion

- Recurrence needs a persistent driver of fluid formation or a failure of drainage or re-expansion.

Table 2: Recurrent non-malignant effusion

Group	Causes	Why it recurs
Transudative	CHF (including diuretic-resistant); hepatic hydrothorax; nephrotic syndrome; peritoneal dialysis; constrictive pericarditis; myxoedema; central venous occlusion; urin thorax or CSF fistula until the leak is fixed	Ongoing hydrostatic or oncotic driver, or a persistent fluid source
Mechanical	Trapped lung ; misplaced catheters	Fibrous visceral peel prevents re-expansion
Lymphatic	Yellow nail syndrome ; chylothorax	Lymphatic hypoplasia or leak; fluid recurs rapidly after tap
Inflammatory	Rheumatoid pleuritis; lupus pleuritis; IgG4-related disease; post-cardiac injury syndrome; uraemia; asbestos-related effusion; drug-induced; sarcoidosis	Chronic or relapsing pleural inflammation
Gynaecological	Meigs syndrome; endometriosis; ovarian hyperstimulation	Hormonal or ovarian source, recurring until treated
Infective	TB; empyema or residual collection	Incomplete treatment or loculation
Abdominal	Pancreatic disease; intra-abdominal abscess; amoebic liver abscess	Persistent source
Vascular	PE (recurrent)	Repeated emboli

Trapped lung

- A stable effusion that recurs after thoracentesis and resists diagnosis, with a past of pleural inflammation, uraemia, radiation, pancreatitis, connective tissue disease or surgery.
- Features:
 - usually asymptomatic or mildly breathless
 - fluid volume is constant from one study to the next
 - borderline exudate (protein ratio about 0.5, LDH ratio about 0.6)
 - on pleural manometry, pressure falls rapidly (> **14–15 cm H₂O per litre** removed)
- Management: observe if asymptomatic. Consider decortication in symptomatic patients, but it is major surgery and may not help if the lung is diseased.

Yellow nail syndrome

- Triad: yellow thickened nails, lymphoedema and pleural effusion. The three may appear years apart.
- Features:
 - effusion bilateral in about 50%, may be massive
 - lymphocytic exudate, with LDH low relative to protein
 - recurs rapidly after tap
- Management: no specific treatment. Pleurodesis is used for symptomatic effusions. Treating associated bronchiectasis or rhinosinusitis may help.

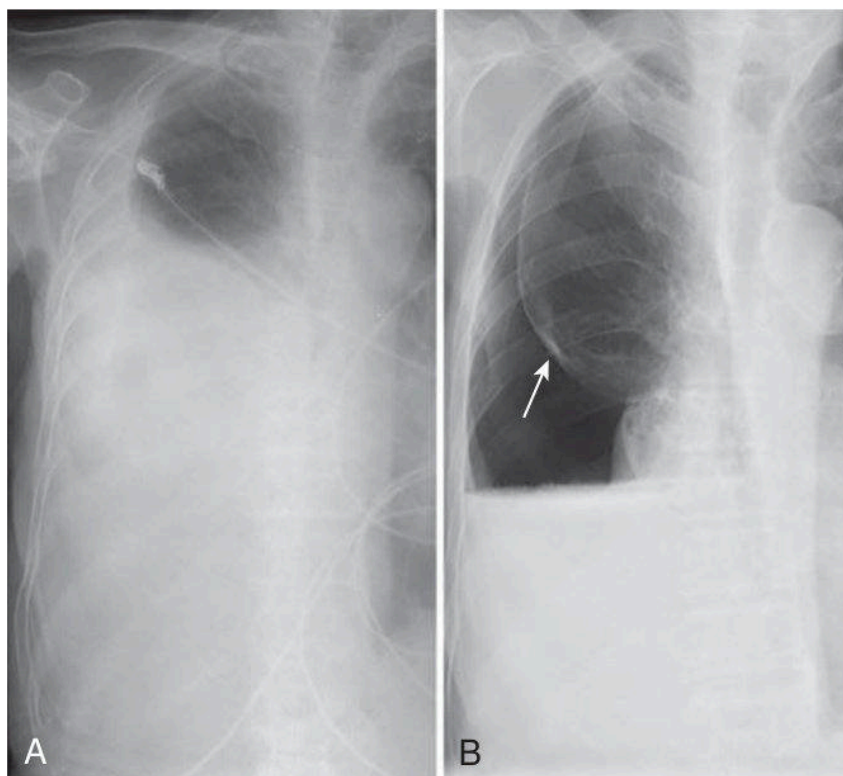


Figure 108.9 — Murray & Nadel 7e, pr.1522. Effusion with trapped lung. (A) Frontal chest radiograph shows a large right pleural effusion. (B) On a subsequent radiograph, the effusion has been partially drained, revealing the underlying lung with some visceral pleural thickening (arrow). The lung failed to reexpand despite negative intrapleural pressures. The intrapleural air likely entered the pleural space from the atmosphere along the drainage track. (Cou)

Gynaecological causes

- **Endometriosis:**
 - bloody or chocolate exudate, usually right-sided
 - hormonal therapy often fails and surgery may be needed
- **Ovarian hyperstimulation syndrome:**
 - presents within 2–3 weeks of hCG
 - neutrophilic exudate, usually right-sided
 - treat with volume restoration, electrolyte correction and VTE prophylaxis

Management by cause

GUIDELINE

BTS — Pleural Disease Guideline (Roberts ME et al., Thorax 2023;78 suppl 3) — 2023

- Use ultrasound guidance for pleural intervention.
- Interpret imaging with the clinical history and fluid characteristics.
- Consider pleural fluid NT-proBNP when heart failure is suspected, but do not use it alone, because multiple conditions can coexist.

- If the cause is unclear after fluid analysis, do a thorascopic or image-guided pleural biopsy, depending on local availability and clinical indication.
- Treat the underlying disease (a transudate is managed by treating the extrapleural disease):
 - heart failure: diuretics and afterload reduction
 - cirrhosis: manage ascites
 - hypothyroidism: thyroid replacement
 - urinary obstruction: relieve it
 - misplaced catheter: remove it
- Therapeutic tap relieves dyspnoea. Use pleurodesis or decortication only for persistent symptomatic recurrence.
- Apply the same principles to effusions in HIV/AIDS (diagnostic tap including mycobacterial and fungal cultures and ADA, then thoracoscopy if still undiagnosed). TB is the commonest cause in African series.

Prognosis

- Transudates resolve with control of the primary disease.
- Undiagnosed exudates need follow-up, because 10–15% later develop malignancy.

PEARLS

- A transudate meets none of Light's criteria: protein ratio ≤ 0.5 , LDH ratio ≤ 0.6 , fluid LDH $<$ two-thirds of the serum upper limit.
- Light's criteria misclassify up to 25% of transudates as exudates, especially after diuresis. A serum–pleural protein gradient > 3.1 g/dL or albumin gradient > 1.2 g/dL rescues them.
- Pleural NT-proBNP > 1500 pg/mL points to a cardiac cause. It is superior to BNP.
- CHF effusions are bilateral, larger on the right, with cardiomegaly. Tap if unilateral, febrile, painful or no cardiomegaly.
- Hepatic hydrothorax is right-sided in 80%. Pleural protein is < 3.0 g/dL.
- Very low protein transudates (< 0.5 g/dL) suggest urinothorax, CSF leak, dialysate or IV fluid.
- Pleural fluid haematocrit $> 50\%$ of blood means haemothorax.
- Think trapped lung when a stable effusion recurs after tap. Manometric pressure falls > 14 – 15 cm H₂O/L.
- Yellow nail syndrome gives lymphocytic exudates that recur rapidly after tap.
- Ultrasound volume estimate: separation in mm $\times 20$ mL. Separation < 10 mm is not safe to tap.

Sources

- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §Pleural Effusion, Separation of Exudates from Transudates, Differentiating Exudative Pleural Effusions — pp. 1499–1501
- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §Effusions (Congestive Heart Failure) — p. 1509
- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §Effusions (Hepatic hydrothorax) — p. 1511
- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §Myxedema, Pericardial Disease, Central Venous Obstruction, Very Low Protein Transudates — p. 1513
- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §Exudative Pleural Effusions › Miscellaneous — pp. 1522–1523
- Textbook: Murray & Nadel 7e — Ch 109 Pleural Infections, §Viral Infections, AIDS — p. 1537
- Textbook: Murray & Nadel 7e — Ch 114 Pleural Malignancy, §Pleural Fluid Analysis — p. 1577
- [w] British Thoracic Society — BTS Guideline for Pleural Disease (Roberts ME et al., Thorax 2023;78 suppl 3:1–42) — 2023 —
<https://www.brit-thoracic.org.uk/document-library/guidelines/pleural-disease/pleural-disease-full-supplement/>

2. Pleural aspiration and intercostal chest drain – indications, drain size, contraindications, complications, surgical emphysema and the non-functioning drain

ASKED 2* · Intermediate answer

Asked in: Oct 2024 P-IV Q2(b) [5] · Jun 2025 P-IV Q1(a) [5] · Jun 2025 P-IV Q1(b) [5] · Jun 2025 P-IV Q2(a) [5] · Jun 2025 P-IV Q2(b) [5]

Q: Indications and complications of ICD insertion in pleural effusion. [5]

Q: Relative contraindications and complications of pleural aspiration. [5]

Q: Indications of intercostal drain insertion and drain size. [5]

Q: Management of surgical (subcutaneous) emphysema following chest drain insertion. [5]

Q: Assessment of a non-functioning chest drain. [5]

Pleural aspiration and intercostal drain (ICD): overview

GUIDELINE

BTS — Clinical Statement on Pleural Procedures and Guideline for Pleural Disease — 2023 (Thorax; consult the BTS Guideline for Pleural Disease 2023 for the full text).

- **Diagnostic aspiration** is indicated in nearly every patient with free fluid measuring > **10 mm** on lateral decubitus film, ultrasound or CT.
 - Delay it only if the patient has obvious CHF and is afebrile, without pleuritic pain, and with effusions of comparable size on both sides.
- **Therapeutic aspiration** gives symptomatic relief in large effusions.
 - Drain slowly by manual syringe or gravity. Do not use vacuum bottles or wall suction.
 - Drain a maximum of about **1.5 L** per attempt.
 - Stop if chest tightness, pain or cough develops.
- Use ultrasound guidance routinely.

Relative contraindications to pleural aspiration

- Thoracentesis is safe with the small-bore needle, even with coagulopathy, thrombocytopenia or positive-pressure ventilation. These are therefore only relative cautions.
 - Correct or weigh the bleeding risk and use ultrasound.
- **Clopidogrel:** reports of haemorrhage are few. The Society of Interventional Radiology suggests withholding it for **5 days** when possible, but the risk of withdrawal must be balanced.
- Other relative cautions:
 - Small, loculated or minimal fluid with no safe ultrasound window.
 - Skin sepsis (for example cellulitis or herpes zoster) at the entry site.
 - An uncooperative patient.
 - Ventilated patients, where the risk of pneumothorax is higher.
 - Prior chest radiotherapy or multiple prior taps, which raise the pneumothorax risk.
 - Entry medial to the midclavicular line, because the intercostal bundle lies mid-space near the spine. Insert over the **upper border of the rib**.

Complications of aspiration

Table 1: Complications of pleural aspiration

Complication	Frequency / risk factors	Action
Pneumothorax	2–6% in older series; 0.6% with routine ultrasound. Risk rises with air aspiration, multiple passes, prior radiotherapy, vacuum bottles. About half need a drain.	Check lung sliding on ultrasound. Do a chest radiograph only if symptomatic or the tap was difficult.
Haemothorax or bleeding	1% in older series; 0.2% with ultrasound	Resuscitate and drain. Consider intercostal artery injury.
Re-expansion pulmonary oedema	0.01% in the ultrasound cohort	Stop the drainage, give supportive care.
Pain, cough, vasovagal reaction	Common, especially with large volumes	Stop and reassess.
Organ puncture, infection	Rare	Treat according to the organ and the infection.

Indications for ICD insertion in pleural effusion

- **Empyema or complicated parapneumonic effusion:** frank pus, positive Gram stain or culture, or pH < 7.2.
- **Malignant effusion** needing repeated drainage, or to allow pleurodesis (talc slurry).
- **Haemothorax:** trauma or iatrogenic.
- **Large symptomatic benign effusion** needing continuous drainage, or a patient who is ventilated with a large effusion.
- **Associated conditions needing a drain:**
 - Pneumothorax, including tension pneumothorax, secondary pneumothorax with a persistent air leak, or pneumothorax on positive-pressure ventilation.
 - Post-operative drainage, or oesophageal rupture with an effusion.
- **Avoid a drain in cirrhotic hydrothorax.** Ascitic fluid drains through the tube and causes protein depletion and collapse. Treat the ascites, and consider TIPS or an indwelling pleural catheter instead.

Drain size

- **Small-bore drains (< 14F)** suit most indications, including empyema.
 - Bore size has no effect on mortality, need for surgery or hospital stay. A bore > **14F** may cause more pain.
- **Large-bore drains** are considered in:
 - Unstable trauma and haemothorax with brisk bleeding or clots.
 - Large air leaks (secondary pneumothorax), ventilator barotrauma and bronchopleural fistula.
 - Thick, viscous fluid that fails small-bore drainage.
- Textbook line for trauma: a **14F** pigtail was not inferior to **32–40F** tubes for haemothorax. Historic teaching was ≥ **32F**.
- Talc slurry pleurodesis needs a drain of at least **12F**.
- **Site:** the "triangle of safety" (anterior border of latissimus dorsi, lateral border of pectoralis major, 4th–5th intercostal space).
 - Placement anywhere with suction gave equivalent haemothorax drainage.



Figure 113.4 — Murray & Nadel 7e, pr.1573. Triangle of safety. The triangle of safety is bordered by the pectoralis major muscle anteriorly, the latissimus dorsi muscle posteriorly, and the fourth to fifth intercostal space distally.

Complications of ICD insertion

Table 2: Complications of intercostal drain insertion

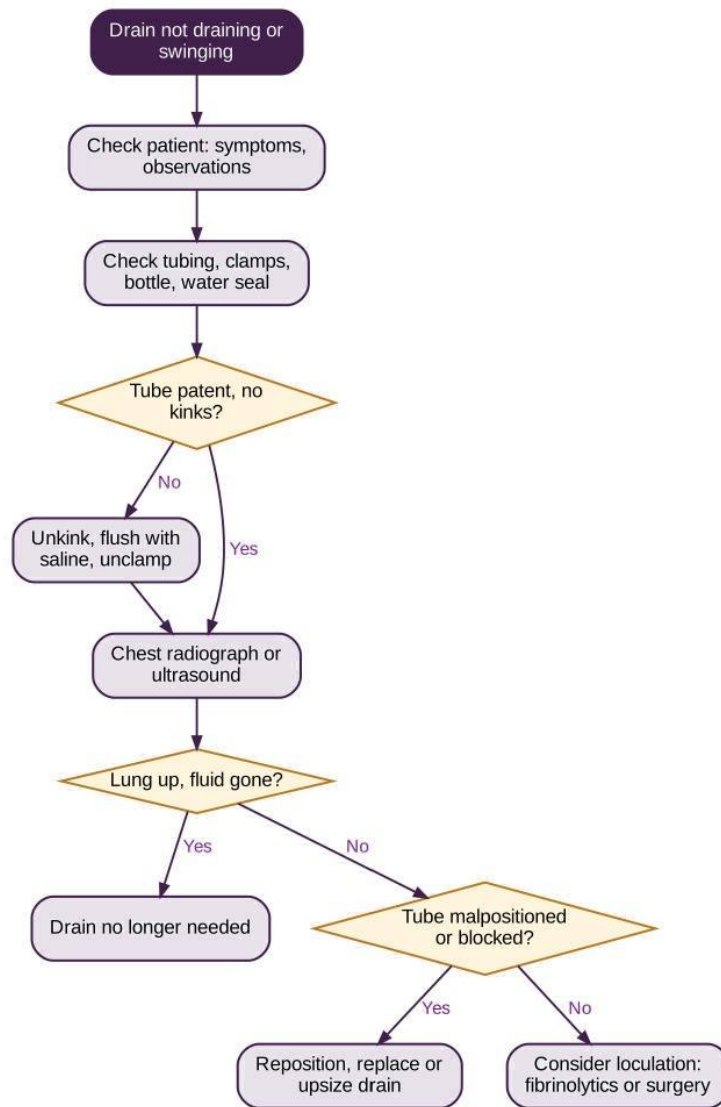
Complication	Timing	Recognition	Action
Haemorrhage (intercostal vessel)	Immediate	Bloody drainage, hypotension	Resuscitate. Surgical review or embolisation.
Organ injury (lung, liver, spleen, heart)	Immediate	Pain, abnormal drainage	Imaging. Remove or reposition the drain.
Wrong position	Immediate	No swing, poor drainage	Radiograph or CT, then reposition.
Re-expansion pulmonary oedema	Hours	Cough, dyspnoea	Clamp or slow drainage. Support.
Surgical emphysema	Early	Crepitus	See below.
Infection (empyema, cellulitis)	Days	Fever, purulent fluid	Antibiotics, drain care.
Blockage, kinking, dislodgement	Any	No drainage, no swing	See non-functioning drain below.
Pain, vasovagal reaction	Any		Analgesia. Smaller bore.
Persistent air leak	Late	Continuous bubbling	Suction, surgical review.

Surgical (subcutaneous) emphysema after drain insertion

- It is **common** and often of minimal clinical significance.
- Usually it settles once the lung re-expands and the leak is controlled.
- **Look for the cause:**
 - A blocked or kinked drain.
 - A tube too small for the air leak, or a drain side-hole lying subcutaneously.
 - A large bronchopleural leak, or tight sutures around the tube.
- **Management:**
 - Reassure the patient and mark the margins of the emphysema to monitor spread.
 - Check that the drain is patent, correctly placed (radiograph or CT) and unclamped.
 - If the emphysema is leaking around the tube, narrow the aperture with a simple interrupted suture. This also avoids wet dressings and chest wall cellulitis.
 - Consider a larger-bore drain or low-pressure suction if air is not escaping.
 - Give oxygen and analgesia.
 - Seek surgical or anaesthetic help for rapidly spreading emphysema.
- **Danger signs:** airway compromise or tension.
 - Rare emergency options include subcutaneous decompression incisions or infraclavicular "blow-hole" incisions.

Assessment of a non-functioning chest drain

Flowchart 1: Approach to a non-functioning drain



- **Clinical:** worsening dyspnoea, fever, emphysema or ongoing pain suggest a real problem.
- **Mechanical causes:**
 - Clamp left on, kinked or occluded tubing, a bottle above chest level, or a disconnected system.
 - Tube blocked by clot or fibrin, or a tube too small for thick fluid.
 - Suction not connected or not working.
- **Tube position:** side-holes outside the pleura, tube pulled out, or the tip against the lung or diaphragm.
- **Pleural causes:**
 - Loculated collections.
 - Trapped lung.
 - Fibrinous pleural infection.
- **Imaging** (ultrasound, chest radiograph or CT) checks the tube position and residual fluid.
- Absence of swing with a re-expanded lung and an empty pleural space means the drain has done its job.
- **Action:** flush with 20–30 mL of saline for a blocked tube. Reposition or replace it if malpositioned. Consider intrapleural fibrinolytics or surgical referral for residual infected collections.

PEARLS

- Diagnostic tap: do it for free fluid > **10 mm**. Light's criteria (protein ratio > **0.50**, LDH ratio > **0.60**) identify exudates.
- Ultrasound-guided thoracentesis gives a pneumothorax rate of about **0.6%**.
- Coagulopathy is not an absolute bar to aspiration. Use ultrasound.
- Drain ≤ **1.5 L** at one sitting. Avoid vacuum bottles.
- Use **small-bore (< 14F)** drains for most effusions and empyema. Use large-bore drains for trauma, haemothorax and large air leaks.
- Do not insert a drain for cirrhotic hydrothorax, because of protein loss.
- Place the drain over the **upper border of the rib**, in the triangle of safety.
- Surgical emphysema is usually benign. Check the drain is patent and position it correctly.
- A non-swinging drain needs a check of the tubing, a chest radiograph and ultrasound.

Sources

- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §Differential Diagnosis of Pleural Effusion — pp. 1500
- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §Effusions — pp. 1508
- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §Congestive Heart Failure / hepatic hydrothorax — pp. 1512
- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §Abdominal Diseases — pp. 1516
- Textbook: Murray & Nadel 7e — Ch 113 Hemothorax, §Management — pp. 1573
- [w1] British Thoracic Society — Clinical Statement on Pleural Procedures — 2023 — <https://www.brit-thoracic.org.uk/document-library/clinical-statements/pleural-procedures/bts-clinical-statement-on-pleural-procedures/>
- [w2] British Thoracic Society — Guideline for Pleural Disease — 2023 — <https://www.brit-thoracic.org.uk/document-library/guidelines/pleural-disease/bts-guideline-for-pleural-disease/>

3. Pleural biopsy – Abrams and Cope needles, technique and complications

ASKED 3* · Intermediate answer

Asked in: Dec 2021 P-IV Q8(b) [5] · Apr 2023 P-IV Q5(b) [5] · Oct 2023 P-IV Q4(b) [5]

Q: Pleural biopsy. [5]

Q: Complications of pleural biopsy. [5]

Q: Abraham and Cope's pleural biopsy needles. [5]

Pleural biopsy: Abrams and Cope needles, technique and complications

Definition and types

- Pleural biopsy means taking a tissue sample of the **parietal pleura** for histology and culture.
- **Closed (blind) needle biopsy** uses the **Cope needle** or the **Abrams needle**. It samples only a small, localised area of parietal pleura.
- **Image-guided biopsy** uses CT-guided or ultrasound-guided cutting needles. Ultrasound can also guide a closed biopsy or transthoracic needle aspiration.
- **Thoracoscopic biopsy** has two forms:
 - Medical thoracoscopy is done by a pulmonologist under local anaesthesia and conscious sedation.
 - Video-assisted thoracic surgery (VATS) is done by a thoracic surgeon under general anaesthesia with single-lung ventilation.
- Open pleural biopsy is a further option for an undiagnosed exudate.

Indications

- An **undiagnosed exudative effusion** after pleural fluid analysis and chest CT.

- Suspected **tuberculous pleuritis**. This is where needle biopsy is most useful.
- Suspected **malignant effusion** when the first diagnostic thoracentesis cytology is non-diagnostic.
- Pleural thickening or nodularity on CT. Image-guided biopsy is an excellent choice here.
- A small or loculated effusion, or pleural thickening without an effusion. CT-guided biopsy is the choice.
- Drug-susceptibility culture when drug-resistant TB is suspected.

Contraindications

- The textbook pages give no list.
- Relevant cautions from the complications are bleeding risk and no safe window or effusion.
- Image guidance is used to choose a safe site.

Abrams and Cope needles

- Both are used for blind or closed biopsy of the parietal pleura. This is useful mainly for malignant or tuberculous effusions.
- The procedure should be considered when one of these two diagnoses is suspected.
- The BTS comparison of closed biopsy with a core (cutting) needle versus an Abrams needle found a **higher diagnostic yield with the Abrams needle**.
- In randomised comparisons with thoracoscopy, thorascopic biopsy had a higher definitive diagnosis and diagnostic yield than blind closed biopsy.

Technique (outline)

- Obtain consent and review the CT and clinical picture.
- Use ultrasound or CT to choose the site.
- Give local anaesthesia, then take multiple parietal pleural specimens with the needle.
- Send some specimens for histology and some for **mycobacterial culture** when TB is suspected.
- Do a post-procedure check for pneumothorax and bleeding.

Diagnostic yield

Table 1: Yield of pleural biopsy methods

Method	Condition	Yield
Closed needle biopsy	Malignancy	40–60%
Pleural fluid cytology	Malignancy	58–69% (two series)
Closed needle biopsy	Malignancy in the same series	43–48%
Closed needle biopsy	TB, granulomas	50–80%
Closed biopsy, histology plus culture	TB	up to 92%
Abrams needle culture	TB (same 51 patients)	48%
Thoracoscopy culture	TB (same 51 patients)	76%
Closed pleural biopsy (randomised study)	Suspected malignant effusion, cytology negative	47%
Image-guided biopsy (same study)	Suspected malignant effusion, cytology negative	87%
Thoracoscopy	Malignancy	95% alone

- Fluid cytology samples cells shed from the whole pleura, so its yield is higher than that of a blind needle.
- Biopsy still adds some diagnoses when cytology is negative.
- **Granulomas on biopsy are virtually diagnostic of TB**. Caseation or acid-fast bacilli need not be shown.
- Rarely, fungal disease, sarcoidosis or rheumatoid pleuritis gives granulomatous pleuritis.
- Xpert MTB/RIF has higher sensitivity on pleural biopsy tissue than on pleural fluid.
- Needle biopsy is most valuable in TB for obtaining material for culture and drug-susceptibility testing.
- Sputum induction yields are similar to those of pleural biopsy culture (52% vs 62%).

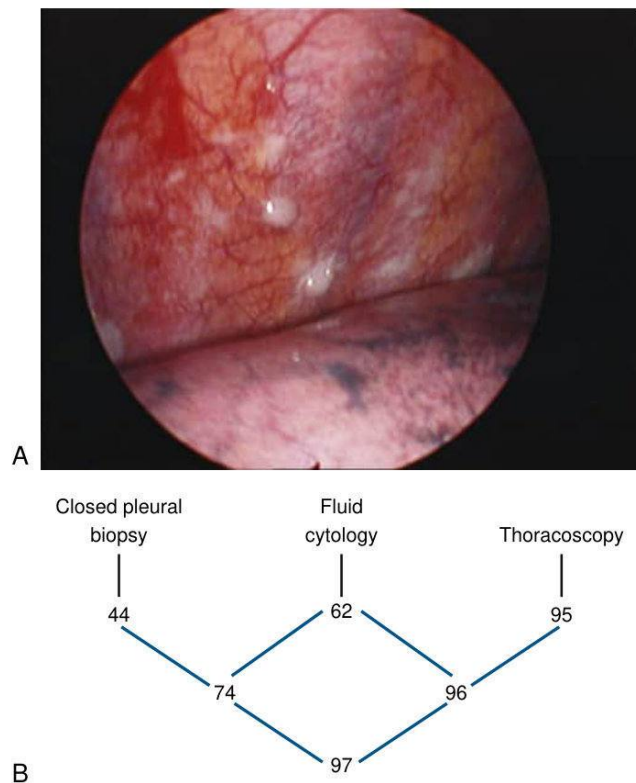


Figure 29.4 — Murray & Nadel 7e, pr.406. Thoracoscopy for diagnosis of malignancy. (A) View through the thoracoscope in a patient with a malignant pleural effusion due to breast cancer. Small whitish tumor nodules are present on the parietal (chest wall) pleura (top of photograph). The lung surface (bottom of photograph) demonstrates some anthracosis. (B) Sensitivity of different biopsy methods (cytologic and histologic results combined) for the diagnosis

Complications

Table 2: Complications of closed pleural needle biopsy

Complication	Timing	Recognition	Action
Pneumothorax	Immediate or early	Post-biopsy chest radiograph, dyspnoea	Chest tube needed in only about 1%
Haemothorax	Early	Bleeding from an intercostal artery or vein	Resuscitate and drain
Organ puncture (liver, spleen, kidney)	Immediate	Mistaken needle placement, haemorrhage	Treat haemorrhage
Non-diagnostic sample	At histology	Normal or nonspecific result	Repeat with image guidance or thoracoscopy

- Many pneumothoraces come from **air leaking through the needle**. They do not necessarily mean the lung was punctured.
- An older series reported **2 deaths from haemothorax in 227 biopsies**. Recent series report no significant haemothorax. Bleeding complications are rare overall.
- Nonspecific results are common. In one series, **68%** of adequate closed biopsies were nonspecific or normal.
- Of 143 patients with nonspecific results, 29 later had malignancy and 1 had TB. All 29 cancers were suggested clinically by weight loss, constitutional symptoms or a previous cancer.
- BTS statement: image-guided ultrasound biopsy had major complications in about **1%** and minor in about **2%**. Adverse events were 3% with ultrasound and 7% with CT.

Guideline position

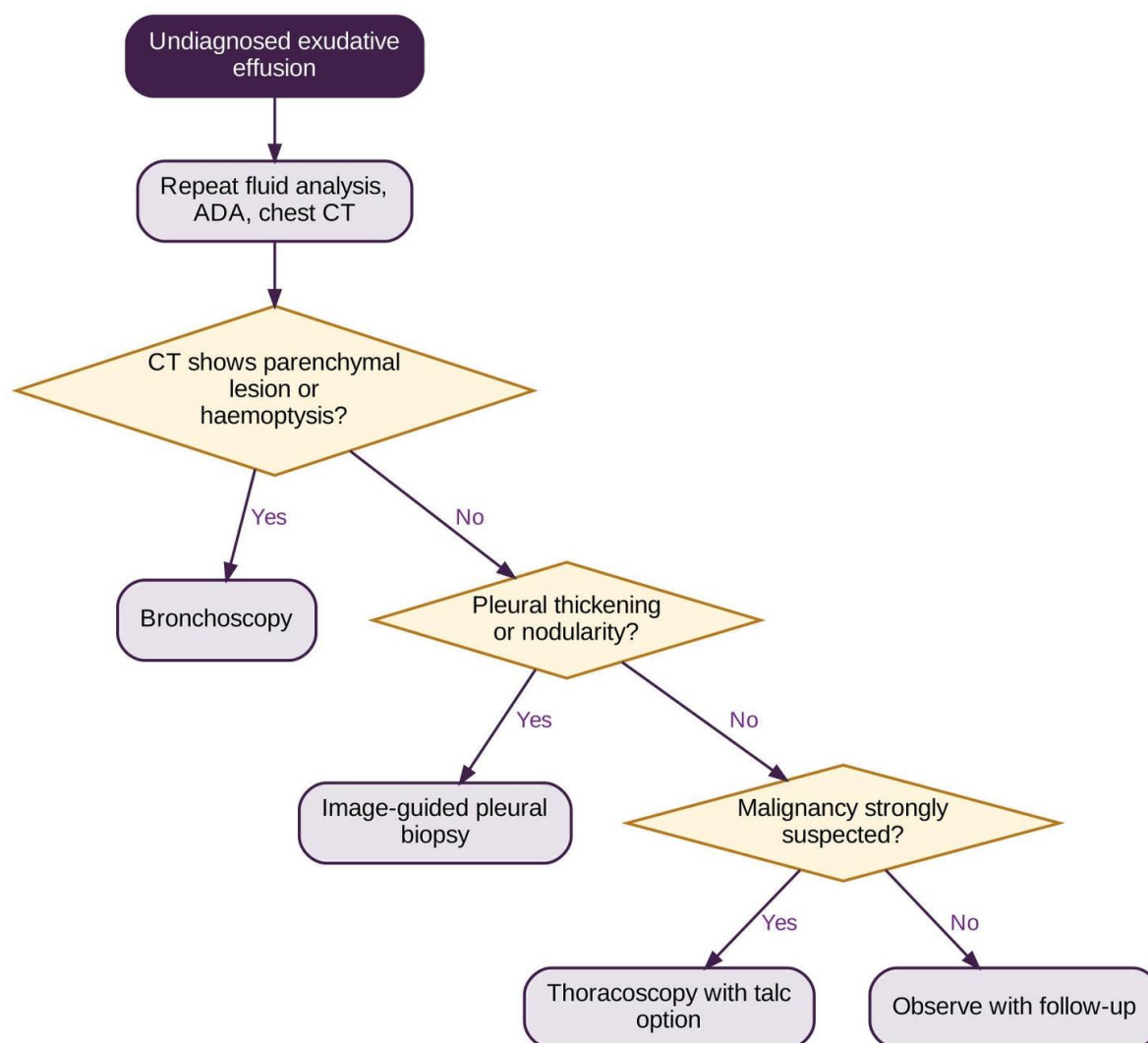
GUIDELINE

BTS — Guideline for Pleural Disease, with Clinical Statement on Pleural Procedures — 2023 (Thorax 2023;78 Suppl 3). Read on the BTS website.

- Thoracoscopic or image-guided pleural biopsy is recommended for undiagnosed pleural effusion. Choose by clinical indication and local availability, including the need to control pleural fluid.
- Blind pleural biopsy should be avoided.
- Image-guided biopsy gives a higher diagnostic yield than blind closed biopsy.
- CT-guided and ultrasound-guided biopsy do not differ in definitive diagnosis.
- Thoracoscopy gives a higher definitive diagnosis than image-guided closed biopsy.
- Image-guided thoracentesis should always be used.

Approach to an undiagnosed exudate

Flowchart 1: Invasive work-up of an undiagnosed exudate



- Three factors decide how vigorously to pursue a diagnosis:
 - The patient's symptoms and clinical course.
 - The trend of pleural fluid LDH over serial thoracenteses.
 - The patient's attitude.
- When an undiagnosed exudate resolves, PE and TB should still be excluded.

Thoracoscopy compared with closed biopsy

- Thoracoscopy sensitivity is about **91%**, specificity **100%** and negative predictive value about 92–93%.
- Its false-negative rate is about **15%** on follow-up.
- Talc pleurodesis can be done at the same sitting.
- It also gives hormone receptors and molecular targets, and allows staging.

PEARLS

- Closed needle biopsy (Abrams or Cope) is the best-known blind method. It is most useful in **TB**, less so in malignancy.
- Closed biopsy is positive in **40–60%** of malignant effusions. Cytology is usually higher at **58–69%**.
- **Granulomas** on pleural biopsy are virtually diagnostic of TB.
- Thoracoscopy culture for TB (76%) beats the Abrams needle (48%).
- The two major complications are **pneumothorax** (chest tube in about 1%) and **haemorrhage or haemothorax**. Organ puncture is a rare third.
- Image-guided biopsy (87%) beats blind biopsy (47%) when cytology is negative.
- BTS 2023 recommends image-guided or thoracoscopic biopsy and says blind biopsy should be avoided.
- Do CT before biopsy or bronchoscopy. Bronchoscopy is useful only with a parenchymal lesion or haemoptysis.
- Thoracoscopy has about a **15% false-negative rate**. Mesothelioma and lymphoma are the most often missed diagnoses.

Sources

- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §With Suspected Pleural Disease — pp. 1505.e1
- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §With Suspected Pleural Disease / Effusions — pp. 1507–1508
- Textbook: Murray & Nadel 7e — Ch 29 Thoracoscopy, §Medical Thoracoscopy — pp. 406
- [w1] BTS — Guideline for Pleural Disease — 2023 — <https://www.brit-thoracic.org.uk/document-library/guidelines/pleural-disease/bts-guideline-for-pleural-disease/>
- [w2] BTS — Clinical Statement on Pleural Procedures — 2023 — <https://www.brit-thoracic.org.uk/document-library/clinical-statements/pleural-procedures/bts-clinical-statement-on-pleural-procedures/>
- [w3] BTS — Online Appendix B6, pleural biopsy diagnostic accuracy — 2023 — <https://www.brit-thoracic.org.uk/document-library/guidelines/pleural-disease/online-appendix-b6-pleural-disease-pleural-effusion-pleural-biopsy-diagnostic-accuracy/>

4. Pleural effusions in the critically ill and at-bleeding-risk patients

ASKED 1* · Intermediate answer

Asked in: Oct 2023 P-IV Q10(a) [5]

Q: Pleural effusions in the critically ill and “At-Bleeding-Risk” population. [5]

Pleural effusions in the critically ill and at-bleeding-risk patients

Definition and scope

- Critically ill patients are those in ICU or HDU, often ventilated, septic or post-operative.
- "At-bleeding-risk" patients are those on anticoagulant or antiplatelet drugs, or with coagulopathy (raised INR), thrombocytopenia, liver disease or uraemia.
- The two groups overlap, and both need a safe diagnostic and therapeutic thoracentesis.

Causes and features in the critically ill

- **Post-abdominal surgery:**
 - About **50%** of patients develop an effusion in the first few days.
 - Incidence is higher after upper abdominal surgery, with postoperative atelectasis, or with free abdominal fluid at surgery.
 - An effusion within **72 hours** is probably from diaphragmatic irritation or transdiaphragmatic fluid movement.
 - An effusion appearing after **72 hours** is probably unrelated to surgery. Look for pulmonary embolism (PE), intra-abdominal abscess or hypervolaemia.
 - A significant effusion with fever needs diagnostic thoracentesis to exclude infection.

- **Intra-abdominal abscess:**
 - Subphrenic abscess gives an effusion in about **80%**, pancreatic abscess about 40%, splenic abscess about 30% and intrahepatic abscess about 20%.
 - The fluid is an exudate with predominantly polymorphs. The WBC count may exceed 50,000/ μ L, but pH stays above 7.20 and glucose above 60 mg/dL.
 - Suspect an abscess in an undiagnosed polymorph-rich exudate with a clear lung parenchyma. Get an abdominal CT.
 - Treat with drainage plus parenteral antibiotics.
- **Pancreatitis and pancreatic ascites:** the fluid has high amylase. Treat conservatively (nil by mouth, parenteral nutrition, octreotide), then endoscopic stenting if that fails.
- **Liver transplantation:**
 - About **68%** develop an effusion, mostly right-sided, from right hemidiaphragm irritation.
 - About 10% need therapeutic drainage.
 - It peaks by day 3 and resolves over weeks to months.
- **Bilious effusion:**
 - Suspect it after biliary obstruction or intervention.
 - A pleural-to-serum bilirubin ratio > **1.0** confirms it.
 - Treat by restoring biliary drainage.
- **Other important ICU causes:**
 - Parapneumonic effusion and empyema.
 - Heart failure and fluid overload.
 - PE.
 - Haemothorax.
 - Hypoalbuminaemia.
- **Missed effusions:**
 - Supine films under-detect fluid.
 - Effusions are easily missed behind lower-lobe consolidation.
 - Ultrasound is better than radiography after surgery.

Imaging in the critically ill

- **Chest radiograph** is only suggestive:
 - Blunting of the lateral costophrenic angle needs at least **175 mL** of fluid.
 - Some patients hold more than 500 mL without blunting.
 - Obscured posterior diaphragm or an elevated hemidiaphragm should raise suspicion.
- **Bedside ultrasound** is the preferred test:
 - It shows an echo-free space between the parietal and visceral pleura.
 - It needs no transport and no radiation, is quick, and guides drainage.
- **Contrast CT** is used when the diagnosis is unclear.
 - It separates empyema (lenticular, obtuse angle, split-pleura sign, uniform walls) from lung abscess.
 - Pleural thickening > 1 cm, nodularity and circumferential involvement suggest malignancy.
- **CTPA** is the first-line test for PE and is less affected by effusion than V/Q scanning.

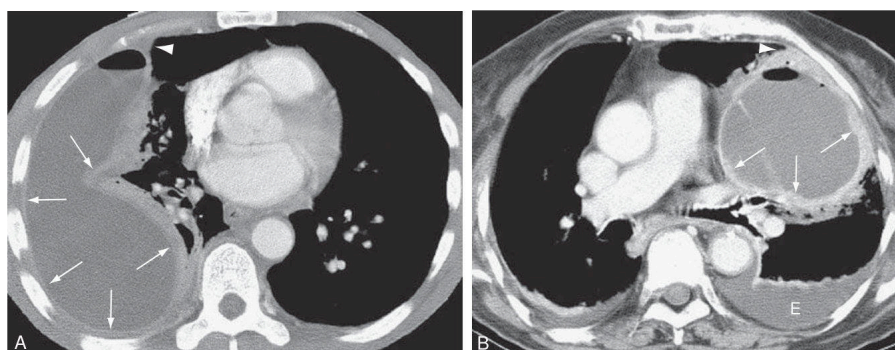


Figure 108.2 — Murray & Nadel 7e, pr.1506. Typical computed tomography (CT) features of a pleural empyema versus a lung abscess. (A) Axial CT through the lower thorax in a patient with fever and pleuritic chest pain shows features typical of empyema, including the formation of obtuse angles between the lesion and chest wall (arrowhead), a lenticular shape, a smooth internal surface (arrows), and mass effect on surrounding structures (note slight leftward shift)

- **Pleural manometry** has no established routine role. It is best used to diagnose trapped lung.
- **Cardiac and IVC ultrasound** for a coexisting effusion with shock:
 - Pericardial fluid lies anterior to the aorta in the PLAX view. Pleural or peritoneal fluid lies posterior.
 - An IVC less than 2 cm that collapses by 50% corresponds to a right atrial pressure of about 5 mmHg.
 - This relationship is lost with positive-pressure ventilation.



Figure 24.3 — Murray & Nadel 7e, pr.349. Images of the inferior vena cava. These images show (A) a small, nearly completely collapsed inferior vena cava compared with (B) a large, dilated inferior vena cava. (C) Application of M-mode imaging just distal to the hepatic vein to visualize inferior vena cava diameter over time and identify maximum (arrows) and minimum (arrowheads) inferior vena cava diameter. The appearance of the inferior vena cava reflects r

Pleural fluid tests useful in this setting

- Cell count and differential.
- pH, glucose and LDH.
- Gram stain and culture, aerobic and anaerobic.
- Amylase and bilirubin, according to the suspected cause.
- Adenosine deaminase (ADA) is a poor guide in the critically ill, because a falsely low ADA can occur in elderly or critically ill patients.

Management and bleeding-risk strategy

GUIDELINE

British Thoracic Society — Guideline for Pleural Disease and Clinical Statement on Pleural Procedures — 2023

Indian reference: ICS/NCCP Pleural Effusion Guidelines, Section 1 (Lung India) — 2024

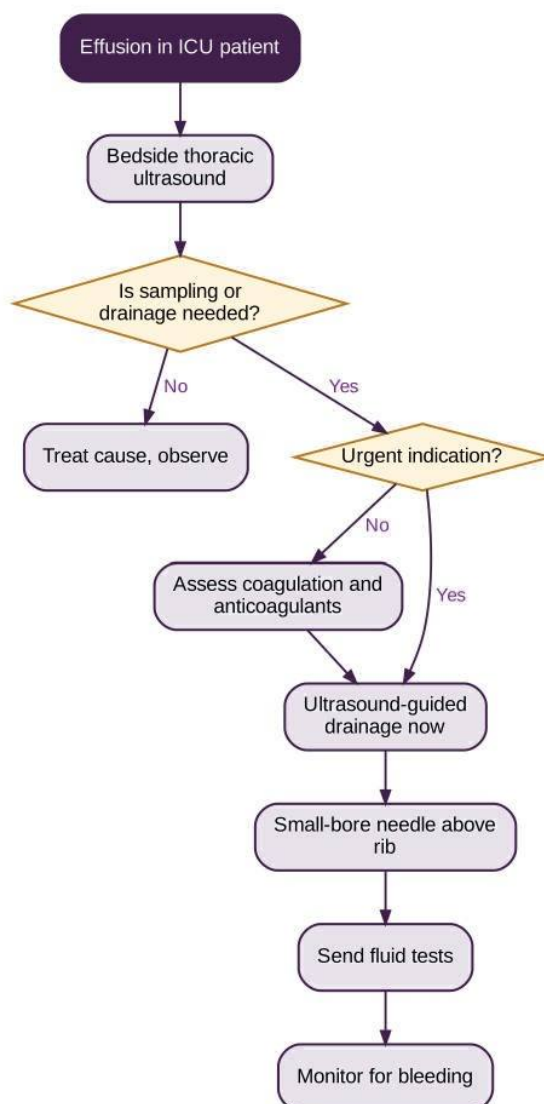
- **Ultrasound guidance:**
 - It is mandatory before pleural fluid procedures, except in emergencies.
 - Perform the procedure in the same position and immediately after marking.
 - Image guidance lowers pneumothorax risk (38 vs 50 per 1000).
 - Use it for small effusions and for patients with anticoagulation or comorbidity.
- **Technique to lower bleeding:**
 - Insert the needle directly above a rib, to avoid the neurovascular bundle.
 - Use small-bore needles.
 - Color Doppler can map the intercostal artery.
- **Bleeding risk with ultrasound guidance:**
 - Bleeding after aspiration is uncommon, at about 3 per 1000, with no difference between guided and unguided procedures.
 - Haemorrhagic complications are rare, and correcting platelets or INR beforehand is unlikely to help (ICS/NCCP 2024).
 - A meta-analysis of 18 studies (5,134 procedures) in uncorrected coagulopathy found pooled major bleeding of 0 (95% CI 0–1%).
 - Iatrogenic intrapleural haemorrhage is rare but life-threatening.

- **Coagulation threshold:** the older BTS 2010 advice was to avoid non-urgent aspiration or drain insertion if INR > 1.5, and this is cited in the ICS/NCCP document.
- **Mechanical ventilation** may raise the likelihood of complications. Use ultrasound and a careful approach.
- **Treatment by cause:**
 - Treat empyema or complicated parapneumonic effusion with antibiotics and drainage.
 - Treat intra-abdominal sepsis by draining the abscess.
 - Treat heart failure with diuretics.
 - Treat haemothorax by drainage.
- **Drain vs aspiration:** drain only when needed, such as for infection or symptomatic large effusions. Avoid routine drains in transudates.

Table 1: Practical approach to the at-bleeding-risk patient

Issue	Approach
Anticoagulation	Assess urgency, apply the local INR threshold, and use ultrasound
Thrombocytopenia or coagulopathy	Use ultrasound-guided small-bore access, and weigh urgency against risk
Urgent need (respiratory failure, sepsis)	Proceed under ultrasound, as correction should not delay drainage
Site	Directly above a rib, at the marked site, immediately after scanning
Aftercare	Monitor for haemothorax and haemodynamic change

Flowchart 1: Effusion in a critically ill, at-bleeding-risk patient



Complications

- Haemothorax or intercostal artery injury.
- Pneumothorax.
- Re-expansion pulmonary oedema.
- Infection.

PEARLS

- **Ultrasound guidance** is mandatory for pleural procedures, except in emergencies.
- **Post-abdominal surgery** effusions occur in about **50%**, and an effusion after **72 hours** is probably not surgical.
- Suspect an **abdominal abscess** in a polymorph-rich exudate with a clear lung. Get a CT abdomen.
- A pleural-to-serum **bilirubin ratio** > **1.0** indicates a bilious effusion.
- In ventilated patients the **IVC–right atrial pressure relationship fails**.
- Bleeding after thoracentesis is rare, at about **3 per 1000**, and coagulopathy alone is a weak predictor when ultrasound is used.
- Always aspirate **above the rib**.
- A low **ADA** does not exclude TB in the critically ill or elderly.

Sources

- Textbook: Murray & Nadel 7e — Ch 24 Ultrasonography: Advanced Applications and Procedures, §Right Atrial Pressure — pp. 349–349
- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §Other Diagnostic Tests For Pleural Fluid / Radiographic Tests — pp. 1505–1506
- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §Exudative Pleural Effusions › Abdominal Diseases — pp. 1517–1518
- [w1] British Thoracic Society — Clinical Statement on Pleural Procedures — 2023 — <https://www.brit-thoracic.org.uk/document-library/clinical-statements/pleural-procedures/bts-clinical-statement-on-pleural-procedures/>
- [w2] British Thoracic Society — Guideline for Pleural Disease — 2023 — <https://www.brit-thoracic.org.uk/document-library/guidelines/pleural-disease/bts-guideline-for-pleural-disease/>
- [w3] Lung India — Pleural effusion guidelines from ICS and NCCP, Section 1 — 2024 — https://journals.lww.com/lungindia/fulltext/2024/05000/pleural_effusion_guidelines_from_ics_and_nccp.16.aspx
- [w4] CHEST — Safety of Thoracentesis and Tube Thoracostomy in Patients With Uncorrected Coagulopathy (systematic review and meta-analysis) — [https://journal.chestnet.org/article/S0012-3692\(21\)00761-3/abstract](https://journal.chestnet.org/article/S0012-3692(21)00761-3/abstract)

5. Pleural ultrasonography in pleural effusion

ASKED 2* · Intermediate answer

Asked in: Oct 2024 P-IV Q10(a) [5] · Jun 2025 P-IV Q4(a) [5]

Q: Pleural ultrasonography. [5]

Q: Ultrasonography in pleural effusion. [5]

Principle

- Ultrasound uses reflected sound; fluid transmits sound well, so simple pleural fluid appears **anechoic (black)**.
- Aerated lung reflects sound, so it is not seen directly. Solid structures give bright hyperechoic edges with acoustic shadowing.
- Acoustic enhancement lies behind low-impedance structures such as cysts and vessels.
- B-mode (2D) is the commonest mode.
- M-mode samples one line over time. It is used for pleural, diaphragmatic and vessel wall movement.
- Colour Doppler detects flow and motion.

Table 23.1 Point-of-Care Ultrasound Terminology		
Term	Definition	Clinical Application
PHYSICS OF ULTRASOUND		
Echogenicity	Interpretation of returning sound wave energy by the ultrasound machine that results from differences in tissue impedance, attenuation, reflection, and scatter of sound waves	Tissues are described as isoechoic when similar in intensity or brightness, hyperechoic when brighter than reference, hypoechoic when dimmer, and anechoic when black
Frequency	The physical property of sound waves indicating the time elapsed between wave peaks passing a specific point	Higher frequency, shorter wavelength waves attenuate more quickly in body tissues, so are best for imaging structures close to the skin surface
Focal zone	A property of the beam emitted from the transducer where it is most narrow	Lateral resolution, or the ability to distinguish objects side by side, is best for any transducer within its focal zone
Acoustic impedance	Property of a tissue that influences sound wave propagation, including transmission, reflection of waves, and energy loss over distance	Physical basis for visualizing distinct tissues with ultrasound
Acoustic enhancement	Region of increased echogenicity immediately distal to a tissue with low acoustic impedance relative to surrounding tissues, such as a cyst or blood vessel	May facilitate identification of vessels and cysts compared to soft-tissue masses or nodules, such as lymph nodes
Acoustic shadowing	Region of hypoechoic or anechoic signal immediately distal to a tissue with very high impedance relative to surrounding tissues, such as a bone	Allows identification of bones, calcifications, and certain stones
TRANSDUCER NOMENCLATURE		
Linear transducer	Transducer in which crystals are activated in a sequential, linear fashion along the length of the array. Narrow rectangular footprint	Best for examining static structures throughout the field, or motion within a single vertical line from the transducer
Phased-array transducer	Transducer in which crystals are activated in a simultaneous, sweeping fashion through the field of view	Ideal for detecting motion across an entire field of view, such as in echocardiography
Convex/curvilinear transducer	Transducer in which crystals are activated in a linear fashion but with a curved footprint; usually lower frequency for imaging deeper structures	Creates a wider field of view than linear transducer, used for imaging the abdomen or, less common, the thorax
Transducer indicator	Marker on the ultrasound screen and on the transducer that allows for orientation of image direction	Standard orientation in lung ultrasound is cephalad left on the ultrasound screen
MODES		
B-mode or two-dimensional	"Brightness" mode, or two-dimensional imaging, wherein pixel intensity corresponds to the strength of the returning sound wave energy	The most commonly used modality in point-of-care ultrasound
M-mode	"Motion" mode of imaging, wherein a signal intensity along a single line within the transducer beam is evaluated over time	Often used to detect and measure movement of structures, such as the pleura, diaphragm, vessel walls, or heart structures
KNOBILITY		
Depth	Distance from the transducer; shallow structures appear at the top of the ultrasound screen; deeper structures appear lower	Depth is often adjusted so that the region of interest is in the middle of the screen; in procedural ultrasound, depth may be set to maximize the operative field of view for needle passage
Far field/near field	Region distal (far) or proximal (near) to the focal zone within the ultrasound beam, a property of the transducer	Lateral resolution, or the ability to distinguish objects side by side, is poorer for any transducer outside its focal zone
Gain	Factor by which all signals received from the transducer are multiplied as to make an image appear brighter or darker	Makes the image brighter or darker
Time gain compensation	Application of increasing gain inversely proportional to the timing of signal return to the transducer so as to compensate for sound wave attenuation due to distance traveled through the tissues	Used to make a tissue appear homogeneous through the depth of the image, whereas would otherwise appear darker at increasing depth due to ultrasound attenuation

Table 23.1 — Murray & Nadel 7e, pr.332. Table 23.1 Point-of-Care Ultrasound Terminology

Technique and quality criteria

- Patient position: upright is best, because volume estimates are more accurate upright.
- Orientation: cephalad is to the left of the screen.
- Probes:
 - Convex or curvilinear: wider field and deeper view, used for the thorax and abdomen.
 - Phased-array: detects motion across the field.
 - High-frequency linear: pleura and chest wall near the skin, and Doppler of the intercostal space.
- Higher frequency gives better resolution but poorer penetration.
- Adjust depth, gain and focal zone so the effusion is mid-screen.
- Confirm that the anechoic space lies **above the diaphragm**. This distinguishes effusion from ascites.

Normal and abnormal sonographic findings

- Normal pleura is a thin hyperechoic line.
- With normal lung, the aerated lung descends with respiration and obscures liver or spleen. This is the **curtain sign**.
- With effusion, a central echo-free space separates the parietal pleura echoes from the visceral pleura and lung.
- The lung floats or flutters in the fluid. Visceral pleural movement gives the **sinusoid sign** on M-mode.
- Pleural thickening is a focal lesion > **3 mm** from either pleural surface.
 - It is typically hypoechoic and can mimic fluid.
 - Fluid transmits respiratory and cardiac motion, but thickening does not, so Doppler flow helps to separate them.

Uses in pleural effusion

- Detection: more sensitive than chest radiograph, less sensitive than CT.
- Volume: estimated by multiplying the distance between pleural surfaces by a constant.
- Characterisation: ultrasound is superior to CT for internal structure.
 - Anechoic: simple fluid.
 - Echogenic material or septations: complex exudate. Loculation may need a different management approach.
 - Pleural thickening > **3 mm** suggests an exudate.

- Loculated effusion: confirmed by ultrasound or CT. On radiograph it is D-shaped without air bronchograms.
- Guidance for thoracentesis or pleural biopsy:
 - It improves success and safety.
 - It gives continuous guidance for biopsy.
 - It is quick, cheap, bedside and free of ionising radiation.
- Pneumothorax exclusion after the procedure: lung sliding at the uppermost chest excludes it.

Ultrasound-guided thoracentesis

- Static guidance: mark the site just before the procedure, with the patient in the same position.
 - Note the skin-to-fluid depth and the fluid depth.
- Dynamic guidance: real-time needle tracking.
 - It is needed for very small or loculated effusions.
 - It should be done by experienced operators.
- Site selection:
 - Maximise the fluid depth.
 - Avoid lung and other structures.
 - Pass the needle over the top of a rib to avoid the neurovascular bundle.
 - Note the downward lung excursion and upward diaphragm excursion in respiration.
- Minimum fluid depth: BTS suggests **10 mm**. Some authors suggest **20 mm**.
- Colour Doppler locates the intercostal artery and aberrant vessels, and may reduce bleeding. POCUS rules out such a vessel with sensitivity **0.86** compared with CT.
- Reported complication rates with routine ultrasound use (9320 procedures): pneumothorax **0.6%**, bleeding **0.2%**, re-expansion pulmonary oedema **0.01%**.

Table 1: Ultrasound appearance and interpretation

Appearance	Interpretation
Anechoic, no septa	Simple effusion, often transudate or early exudate
Echogenic material or septations	Complex exudate, possible loculation
Pleural thickening > 3 mm	Suggests exudate, possible malignancy
Sinusoid sign on M-mode	Effusion present, free-flowing
Anechoic space below the diaphragm	Ascites, not effusion

Related pneumothorax algorithm

Flowchart 1: Ultrasound evaluation of suspected pneumothorax

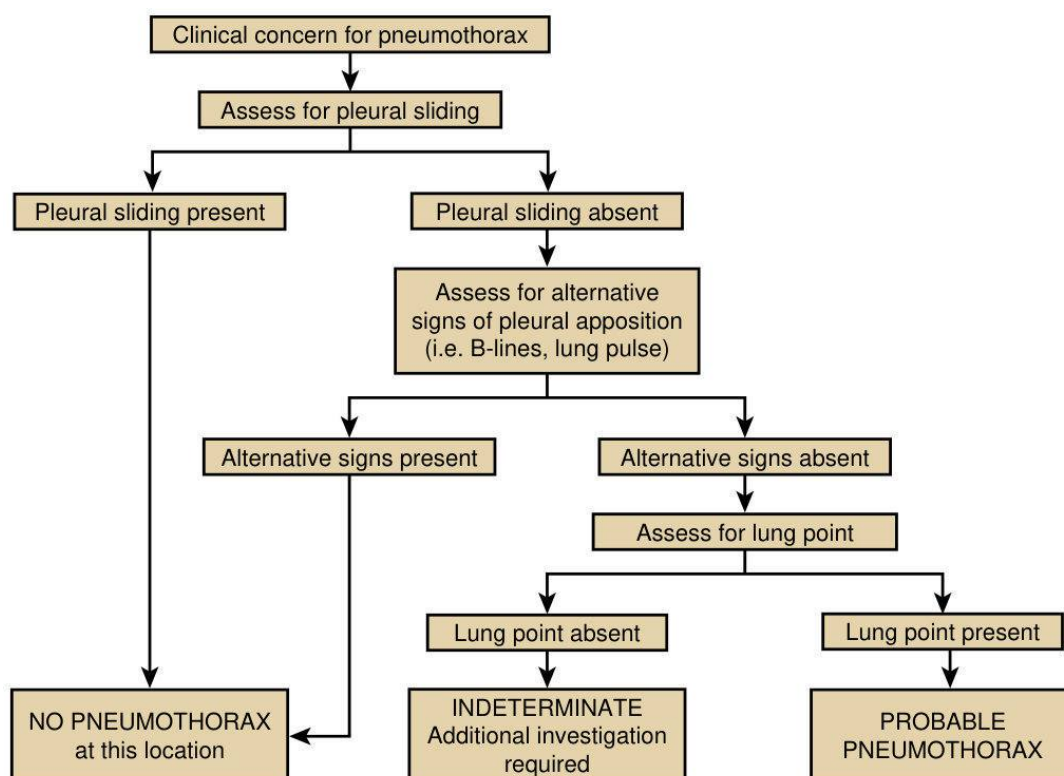
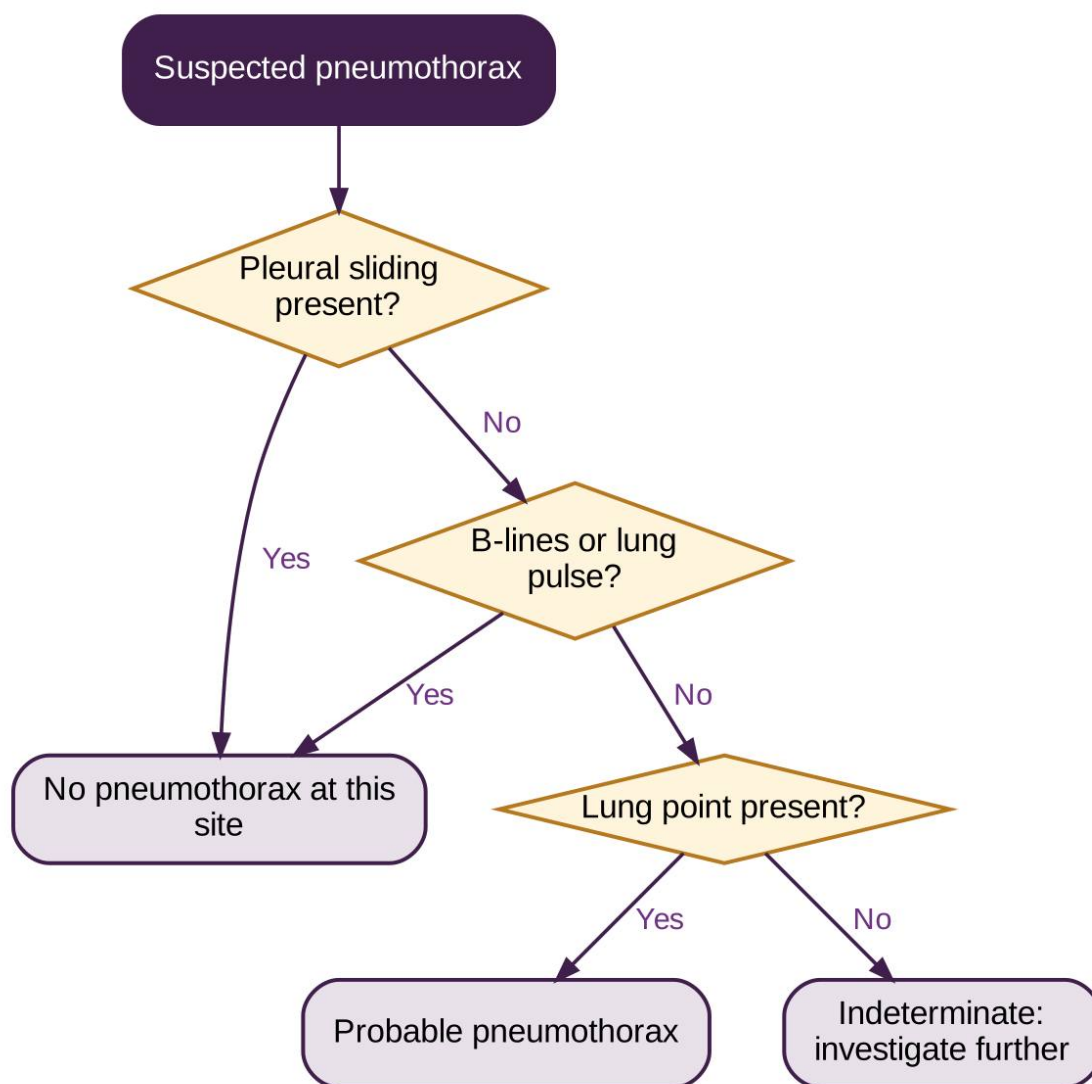


Figure 23.10 — Murray & Nadel 7e, pr.338. Sample algorithm for evaluation of suspected pneumothorax using ultrasound. The presence of pleural sliding rules out this diagnosis at the scanned location, but its absence is not confirmatory of that diagnosis. When pleural sliding is absent, one can look

for alternative findings to suggest pleural apposition, such as B-lines or a lung pulse. Absent these, finding a lung point is highly suggestive of a pneumo-thor

Pitfalls

- Thickened pleura can be mistaken for fluid, so use Doppler.
- Small effusions can be missed, and CT is more sensitive.
- Ascites can be mistaken for effusion if the diaphragm is not identified.
- Volume estimates are less accurate when the patient is supine.
- Absent sliding does not by itself confirm pneumothorax.

PEARLS

- Ultrasound is more sensitive than chest radiograph but less sensitive than CT for effusion.
- Simple fluid is **anechoic**. Septations suggest a complex exudate or loculation.
- The **curtain sign** is normal. The **sinusoid sign** indicates effusion.
- Pleural thickening **> 3 mm** suggests an exudate.
- Confirm that the fluid lies above the diaphragm to avoid mistaking ascites for effusion.
- Ultrasound guidance improves the safety of thoracentesis.
- BTS minimum fluid depth for thoracentesis is **10 mm**.
- Colour Doppler maps the intercostal artery and reduces bleeding risk.
- Ultrasound is better at excluding than diagnosing pneumothorax.

Sources

- Textbook: Murray & Nadel 7e — Ch 23 Ultrasonography: Principles and Basic Thoracic and Vascular Imaging, §Physics of Ultrasound; Thoracic Ultrasound — pp. 332–338
- Textbook: Murray & Nadel 7e — Ch 108 Pleural Effusion, §Differential Diagnosis; Other Diagnostic Tests for Pleural Fluid — pp. 1500–1505

6. Bacterial empyema

ASKED 1* · Intermediate answer

Asked in: Dec 2021 P-II Q1(b) [5]

Q: Bacterial empyema. [5]

Bacterial empyema

Definition

- **Empyema** is pus in the pleural space. It is the fibropurulent or organizing stage of pleural infection.
- **Parapneumonic empyema** follows pneumonia. **Primary empyema** arises from direct bacterial inoculation of the pleural space, either from the oropharynx or haematogenously.
- In primary empyema, bacteria invade the pleural space first and lead directly to the fibropurulent stage.
- **Uncomplicated parapneumonic effusion:** glucose >40 mg/dL, pH >7.2, negative Gram stain and culture, and no loculation on ultrasound.
- **Complicated parapneumonic effusion:** glucose <40 mg/dL, or pH <7.2, or loculated on ultrasound.

Why it matters

- Incidence and mortality are rising globally in adults and children.
- Standard culture is positive in only about **60%** of cases. Adding blood culture bottles raises the yield.
- Pleural organisms often differ from the lung pathogens.
- Community-acquired and hospital-acquired infections need different empirical antibiotics.

Pathophysiology

- Pneumonia is followed by an exudative stage, then a fibropurulent stage, then an organizing stage.
- The organizing stage thickens the pleura into a **pleural peel**, which can markedly reduce lung function. It should resolve with time if the infection is controlled.
- In the organizing stage the fluid is thick and consists of pus and cellular debris.

Clinical features

- Dyspnoea, cough, fever, malaise and pleuritic chest pain, often over a prolonged period.
- It is hard to separate from pneumonia. Many patients develop an effusion with no change in symptoms.
- No symptom discriminates complicated from uncomplicated effusion.
- Suspect it when there is no improvement within a few days of antibiotics, persistent fever, or sepsis.
- Chronic cases can mimic malignancy, with weight loss, sweats and anorexia.

Investigations

Table 1: Investigations in suspected empyema

Test	Finding	Meaning
Thoracic ultrasound	Septations, loculations, echogenic fluid	Guides a safe aspiration site, shows complexity, and is the initial imaging of choice
Contrast CT	Split-pleura sign (enhancing visceral and parietal pleura around a loculated collection)	Relatively specific for empyema; maps extent for drainage planning
Gross pleural fluid	Frank pus	Needs a chest tube; no further biochemistry needed, but send microbiology
Pleural fluid pH	<7.2	Drain. Measure in a blood gas analyser, taking the sample anaerobically in a heparinised syringe on ice
Pleural fluid glucose	<40 mg/dL (2.2 mmol/L)	Drain; an alternative when pH is unavailable
Pleural fluid LDH	>1000 IU/L	Supports complexity; a rising LDH on repeat taps means non-response
Gram stain and culture	Positive	Drain; bottle inoculation increases the yield

- The pH and glucose are also low in malignant effusion, rheumatoid effusion and oesophageal rupture. Use them to guide drainage only in parapneumonic effusion.
- Pitfalls for pH: residual heparin or local anaesthetic lowers it, and air in the syringe raises it.
- Parapneumonic effusions <2 cm thick on CT are unlikely to become complicated. They may be treated with antibiotics without sampling, with close monitoring.

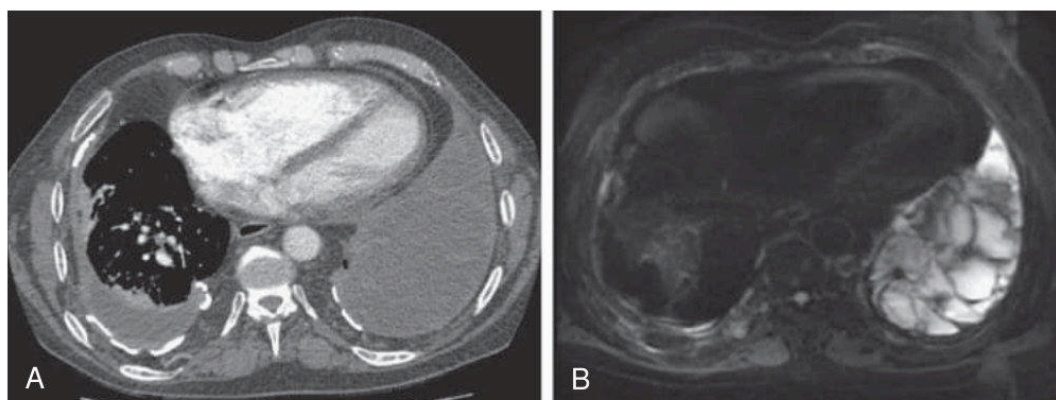


Figure 109.6 — Murray & Nadel 7e, pr.1531. Fig. 109.6 Imaging of pleural empyema. (A) Contrast-enhanced chest computed tomography revealing a complex, large left pleural fluid collection secondary to pleural infection. (B) T2-weighted magnetic resonance imaging in the same patient that shows the presence of multiple septations and loculations.

Differential diagnosis

- Malignant effusion with low pH or glucose.
- Rheumatoid effusion.