Internal Medicine — A Casebook for Medical Students

Cases, seminars and interpretation for the internal medicine clerkship.

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79 disease cases across ten system blocks · **16** approach-to-the-patient seminars · **11** interpretation chapters

128,653 words · husainalkhaldy.com/student-resources/internal-medicine-casebook

How to Use This Casebook

What each part is for, how a case is built, and how to read the book — whether you are preparing for a ward round, a viva, or an examination.

Front matter · 1,023 words

The book has two parts. **Part One** contains seventy-nine disease cases arranged by system, drawn from both internal medicine courses, and every one of them follows the same seven-part sequence set out below. The order is deliberate: it mirrors the order in which you will actually meet the patient on the ward, and it is the order in which an examiner will expect you to present.

Part Two contains sixteen **seminars** built around a presenting symptom rather than a diagnosis, and these follow a different sequence — the differential is generated **before** the history is taken, because the differential is what the history is for. That template is explained at the start of Part Two.

Part Three is different again: eleven chapters on reading an electrocardiogram, a blood count and film, renal and liver tests, a chest radiograph and lung function, and rheumatological serology. They are numbered as chapters rather than cases, and are meant to be returned to rather than read once.

Section	What it trains
1. Clinical vignette	Pattern recognition. Read the stem and commit to a working diagnosis before reading on.
2. Focused history	Not a checklist — every question is paired with the reason you are asking it.
3. Physical examination	What to look for, the sign you expect to find, and the mechanism that produces it.
4. Differential diagnosis	The competing diagnoses and the single discriminating feature for each.
5. Investigations	Bedside, laboratory, imaging — with the expected result and what it changes. Tests that do not change management are named as such.
6. Management	Immediate stabilisation, severity scoring and disposition, definitive treatment, complications, discharge.
7. Teaching points and viva questions	The pearls that separate a pass from a distinction, and the questions examiners actually ask.

A note on units. Glucose and urea are given in millimoles per litre (mmol/L) with the milligrams per decilitre (mg/dL) equivalent in brackets. Drug doses are for an adult with normal renal and hepatic function; always check against your local formulary and antibiogram, since resistance patterns are regional.

A note on protocols. Where national guidelines differ, the text follows the approach most widely taught and flags the alternative. Your hospital protocol overrides this book.

Navigating this volume. The three parts carry three separate sequences: Cases 1 to 79 in Part One, Seminars 1 to 16 in Part Two, and Chapters 1 to 11 in Part Three. Every cross-reference names the part

explicitly — "Case 37", "Seminar 14", "Chapter 9" — so no reference is ambiguous. All headings use built-in heading styles, so the document can also be navigated using the navigation pane in Word.

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Seminars

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2	Generalised anasarca
3	Acute chest pain
4	Acute dyspnoea
5	Headache
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Part Three · Interpretation

Eleven chapters on reading the investigations, numbered as **chapters** in their own sequence.

Chapters

Chapter	Title
1	Reading the electrocardiogram systematically
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3	The narrow-complex tachycardias
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PART ONE

Disease Cases by System

Seventy-nine cases in ten blocks

The Respiratory Block

Pneumonia, asthma, COPD, suppurative lung disease, hypercapnic failure, pleural effusion, lung cancer and pulmonary hypertension.

Cases 1–8 · 12,309 words

This block covers the respiratory teaching of both internal medicine courses. Bacterial pneumonia is taught in the infectious diseases block but presents as a respiratory case and is placed here for clinical coherence. The **second course** adds cases 7 and 8.

Case	Lecture it serves
System opener: the respiratory history and examination	History taking in respiratory; physical examination of respiratory
Case 1 — Community-acquired pneumonia	Bacterial pneumonia
Case 2 — Acute severe asthma	Bronchial asthma
Case 3 — Exacerbation of chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease
Case 4 — Bronchiectasis and lung abscess	Suppurative lung diseases
Case 5 — Acute-on-chronic hypercapnic respiratory failure	Respiratory failure
Case 6 — Pleural effusion	Pleural effusion
Case 7 — Lung cancer	Lung cancer
Case 8 — Pulmonary hypertension	Pulmonary arterial hypertension

Pulmonary thromboembolism is taught in the second course and is covered as Seminar 11 in Part Two, where the pre-test probability and imaging decisions can be set out properly. **The approach to obstructive airway disease**, a second-course seminar, is covered by Cases 2 and 3.

Case numbering is provisional and will be reconciled when the blocks are compiled into a single volume.

System Opener · The Respiratory History and Examination

This page is the framework the cases assume. Learn it once and the cases become variations on it rather than separate lists to memorise.

The history

The six cardinal symptoms

Symptom	What to establish
Cough	Duration (under 3 weeks is acute, 3–8 weeks subacute, over 8 weeks chronic), dry or productive, timing across the day, what provokes it, and whether it disturbs sleep.
Sputum	Daily volume — a teaspoon, an eggcup or a cupful. Colour, smell, and whether it settles into layers. Large volumes of purulent sputum every day is bronchiectasis until proved otherwise.
Haemoptysis	Quantify it: streaking, teaspoons or cupfuls. Establish it is truly from the chest and not the nose or stomach. Persistent haemoptysis in a smoker is cancer until proved otherwise.
Breathlessness	Onset over minutes, hours, days or months. Exercise tolerance in metres or flights of stairs against the patient's own baseline. Orthopnoea, paroxysmal nocturnal dyspnoea, and variation through the day and across the week.
Wheeze	Audible or not, when it occurs, what relieves it, and whether it is seasonal or occupational.
Chest pain	Pleuritic (sharp, worse on inspiration, localised) points to the pleura; central and heavy points elsewhere.

Then the four contexts that change the differential

- **Exposures.** Smoking in pack-years, including waterpipe and vaping. Occupation over the whole working life — dust, silica, asbestos with its decades of latency, farming, welding. Birds, mould, air conditioning. Travel and tuberculosis contact.
- **Drugs.** Beta blockers and aspirin provoke bronchospasm; amiodarone, methotrexate, nitrofurantoin and bleomycin cause parenchymal disease; angiotensin-converting enzyme inhibitors cause a dry cough.
- **Atopy and family history.** Eczema, allergic rhinitis, food allergy, and a family history of asthma, tuberculosis, cystic fibrosis or alpha-1 antitrypsin deficiency. Ask about consanguinity where relevant.
- **Disease burden.** Number of exacerbations, courses of oral steroids and admissions in the past year; any previous intensive care admission or intubation; home oxygen or non-invasive ventilation; current inhalers, adherence and technique; vaccination status.

The examination

From the end of the bed

- Respiratory rate counted over a full minute, respiratory distress, posture, ability to complete a sentence, cachexia, audible wheeze or stridor, pursed-lip breathing, the oxygen device and its flow rate, and the sputum pot — always look inside it.
- Chest shape: barrel chest of hyperinflation, kyphoscoliosis, pectus deformity, thoracoplasty or lobectomy scars.

Hands, face and neck

- **Clubbing.** In respiratory disease it means bronchial carcinoma, bronchiectasis, lung abscess or empyema, idiopathic pulmonary fibrosis, cystic fibrosis or mesothelioma. **It is not caused by asthma or**

by chronic obstructive pulmonary disease — if you find it in a patient labelled with either, you have found a second diagnosis.

- Tar staining, fine tremor of beta-agonist overuse, the coarse flapping tremor of carbon dioxide retention, wasting of the small hand muscles in an apical tumour, bounding pulse and warm hands in hypercapnia, pulsus paradoxus in severe asthma.
- Central cyanosis at the tongue, Horner syndrome, jugular venous pressure, supraclavicular and cervical lymph nodes, tracheal position, cricosternal distance (reduced in hyperinflation) and tracheal tug.

The chest, in the order that survives an examiner

- **Inspect** — symmetry of movement, scars, dilated veins, radiotherapy field markings.
- **Palpate** — expansion upper and lower, tactile vocal fremitus, apex beat position, chest wall tenderness.
- **Percuss** — including the clavicles and the axillae, and note the upper level of liver dullness, which is lost in hyperinflation.
- **Auscultate** — breath sound intensity and character, added sounds, vocal resonance. **Always examine the back**, where the lower lobes actually are.
- **Finish** — ankle and sacral oedema, calves, peak expiratory flow, and the observation chart.

Added sound	What it means
Polyphonic wheeze	Many airways of different calibre narrowed together — asthma, chronic obstructive pulmonary disease.
Monophonic, fixed wheeze	One airway narrowed — tumour or inhaled foreign body. Does not move with coughing.
Fine, late inspiratory crackles	Reopening of collapsed alveoli — pulmonary fibrosis, pulmonary oedema. Do not clear with coughing.
Coarse, early inspiratory crackles	Secretions in larger airways — bronchiectasis, chronic bronchitis. Shift or clear with coughing.
Pleural rub	Inflamed pleural surfaces moving on each other — pneumonia, infarction, pleurisy.
Stridor	Upper airway obstruction. Loudest over the neck, inspiratory. This is an emergency, not a sign to characterise at leisure.

Case 1 · Community-Acquired Pneumonia

CLINICAL VIGNETTE

A **68-year-old man** is brought to the emergency department by his son with three days of fever and cough. The cough is productive of thick rust-coloured sputum. He has a sharp right-sided chest pain that is worse on deep inspiration, and has become breathless walking to the bathroom. Since this morning he has been muddled and did not recognise his neighbour.

He has type 2 diabetes mellitus on metformin, and a 40 pack-year smoking history. He has had no vaccinations.

On arrival: temperature 38.9 °C, heart rate 112/min, blood pressure 96/58 mmHg, respiratory rate 28/min, oxygen saturation 88% on room air. He is orientated to person only.

1. Focused History

Characterise the presenting complaint

- **Onset and tempo.** Abrupt onset over hours with a rigor suggests bacterial, classically pneumococcal, disease. A gradual prodrome over one to two weeks with headache and myalgia points to an atypical organism.
- **Cough and sputum.** Ask about volume, colour and blood. Rust-coloured sputum is classically pneumococcal; foul-smelling sputum suggests anaerobic infection or abscess; copious purulent sputum daily for years suggests underlying bronchiectasis.
- **Pleuritic chest pain.** Localises the affected lobe and tells you the pleura is inflamed. Pain that persists or worsens after 48 hours of antibiotics raises the question of empyema.
- **Breathlessness.** Quantify against his own baseline — "how far could you walk last week, and how far today?" — not against an abstract scale.

Red flags to exclude at once

- Confusion or drowsiness, syncope, inability to speak in full sentences, cyanosis, haemoptysis, poor oral intake and reduced urine output. Any of these moves the patient to the resuscitation area before the history is finished.

Questions that discriminate between causes

Ask about	If positive, think
Rigors, single abrupt onset, rusty sputum, herpes labialis	Streptococcus pneumoniae
Young patient, dry cough, headache, arthralgia, rash, recent similar illness in the household	Mycoplasma pneumoniae
Recent hotel or air-conditioning exposure, travel, diarrhoea, confusion out of proportion, low sodium	Legionella pneumophila
Alcohol excess, seizure, stroke or dysphagia, poor dentition, vomiting, foul sputum	Aspiration and anaerobes
Cough over three weeks, night sweats, weight loss, haemoptysis, contact or endemic exposure	Pulmonary tuberculosis
Sudden pleuritic pain and breathlessness with little fever or sputum, calf pain, immobility	Pulmonary embolism
Bird or animal contact, farm or abattoir work, unpasteurised dairy	Psittacosis, Coxiella, Brucella
Known bronchiectasis or cystic fibrosis, recent hospital admission or antibiotics	Pseudomonas or resistant organisms

Risk factors and background

- **Host factors:** age, smoking, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney or liver disease, heart failure, malnutrition.
- **Immunosuppression:** corticosteroids, chemotherapy, biologic agents, human immunodeficiency virus (HIV) infection, asplenia, transplant. This changes the organism list and therefore the antibiotic.
- **Recent healthcare exposure and antibiotics** within 90 days — the strongest single predictor of resistance.
- **Vaccination status** for pneumococcus and influenza, and **drug allergies**, especially to penicillin.
- **Functional baseline and social circumstances.** Whether he lives alone, and who can observe him, decides admission as often as the physiology does.

2. Physical Examination

General inspection and vital signs

- Respiratory distress: accessory muscle use, nasal flaring, inability to complete a sentence, tripod posture.
- A **complete set of vital signs including the respiratory rate**. The respiratory rate is the earliest and most sensitive marker of deterioration and the one most often left unrecorded. Count it for a full minute.
- Level of consciousness — formally, using an abbreviated mental test or the Glasgow Coma Scale, because "confusion" scores a point on the severity index and must be documented objectively.
- Peripheral perfusion: capillary refill, warm vasodilated peripheries with a bounding pulse in early sepsis, cool and mottled in late shock.

Hands, face and neck

- Tar staining, peripheral and central cyanosis, a carbon dioxide retention flap if there is coexisting chronic obstructive pulmonary disease, herpes labialis around the mouth, dehydrated mucous membranes.
- Tracheal position — central in uncomplicated consolidation. Deviation means collapse (pulled towards) or a large effusion or tension pneumothorax (pushed away).

The chest, in sequence

- **Inspect:** reduced movement on the affected side, tachypnoea, scars, chest wall deformity.
- **Palpate:** chest expansion, comparing sides; tactile vocal fremitus is **increased** over consolidated lung because solid tissue transmits sound better than air.
- **Percuss:** dull over consolidation. **Stony** dullness means fluid, not consolidation — this single distinction changes your next step from antibiotics alone to a diagnostic pleural tap.
- **Auscultate:** bronchial breathing over the consolidated lobe, coarse late inspiratory crackles, increased vocal resonance and whispering pectoriloquy. A pleural rub may be heard where the pain is.
- **Then look for complications:** an area of stony dullness with absent breath sounds at the base (parapneumonic effusion or empyema), a new murmur (endocarditis as a source), neck stiffness (meningitis from the same pneumococcus).

The bedside distinction you must be able to make. Four processes reduce chest expansion and all four appear in examinations. The table below is the answer to the commonest viva question in respiratory medicine.

Sign	Consolidation	Pleural effusion	Pneumothorax	Lobar collapse
Trachea	Central	Central, pushed away if large	Central, pushed away if tension	Pulled towards
Expansion	Reduced	Reduced	Reduced	Reduced
Percussion	Dull	Stony dull	Hyper-resonant	Dull
Breath sounds	Bronchial	Absent or diminished	Diminished	Diminished
Vocal resonance	Increased	Decreased	Decreased	Decreased
Added sounds	Crackles, rub	Rub above the fluid	None	None

3. Differential Diagnosis

Diagnosis	The feature that discriminates it
Pulmonary embolism with infarction	Hypoxia out of proportion to the chest radiograph; risk factors for venous thromboembolism; little or no purulent sputum.
Acute pulmonary oedema	Orthopnoea and paroxysmal nocturnal dyspnoea, raised jugular venous pressure, bilateral basal crackles, third heart sound, no fever.
Exacerbation of chronic obstructive pulmonary disease	Wheeze and prolonged expiration dominate; the radiograph shows no consolidation.
Pulmonary tuberculosis	Weeks rather than days of symptoms, weight loss, night sweats, upper lobe or apical changes with cavitation.
Lung cancer with post-obstructive pneumonia	Smoker, weight loss, haemoptysis, and consolidation that fails to clear on the follow-up radiograph.
Empyema	Persisting fever and pain after 48–72 hours of appropriate antibiotics, with stony dullness at the base.

4. Investigations

At the bedside

- **Pulse oximetry on room air**, documented as such — a saturation on oxygen without the flow rate recorded is uninterpretable.
- **Arterial blood gas** if the saturation is below 94%, if there is shock, or if chronic obstructive pulmonary disease raises the possibility of carbon dioxide retention. Expect type 1 respiratory failure; a rising carbon dioxide in a tiring patient is an ominous sign.
- **Electrocardiogram** — to detect the atrial fibrillation that sepsis commonly precipitates, and because chest pain in a 68-year-old deserves one.
- **Capillary blood glucose** — infection destabilises diabetes and may precipitate a hyperglycaemic emergency.

Laboratory

Test	What you expect, and what it changes
Complete blood count	Neutrophil leucocytosis. A low white cell count (<4 × 10^9/L) is a marker of severe disease, not of mild disease.
Urea and electrolytes	Urea is one of the five severity criteria. Hyponatraemia raises the suspicion of Legionella.
C-reactive protein	Baseline for trend. Failure to fall by more than half by day four predicts treatment failure and should trigger reassessment.
Liver function, lactate	Lactate above 2 mmol/L in the presence of infection defines sepsis and mandates the one-hour bundle.
Blood cultures, two sets	Before the first antibiotic dose, but never delaying it. Yield is low in mild disease — reserve for moderate and severe cases.
Sputum Gram stain and culture	Useful only if a good deep specimen is obtained before antibiotics. Send acid-fast staining if tuberculosis is possible.
Urinary antigens	Pneumococcal and Legionella antigen in severe disease. They remain positive after antibiotics have been started.
Respiratory viral panel	Influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) — changes isolation and adds antiviral treatment.
Human immunodeficiency virus test	Offer in any severe or recurrent pneumonia, and whenever the organism is unusual.

Imaging

- **Chest radiograph, posteroanterior.** Expect lobar consolidation with an air bronchogram. Use the **silhouette sign** to localise: loss of the right heart border places the disease in the right middle lobe; loss of a hemidiaphragm places it in a lower lobe. Also inspect for effusion, cavitation and a mass.
- **Point-of-care chest ultrasound.** More sensitive than the radiograph for pleural fluid and it guides the needle. It has largely replaced the lateral decubitus film.
- **Computed tomography of the chest** if the pneumonia fails to resolve, if complications are suspected, or if the radiograph is equivocal in a very sick patient.
- **Repeat the chest radiograph at six weeks** in every smoker and in anyone over 50. Persistent consolidation is a bronchial carcinoma until proved otherwise. This is the single follow-up step most often forgotten.

Pleural fluid, if an effusion is present

Any effusion more than 1 cm deep on ultrasound in a febrile patient should be sampled. Send protein, lactate dehydrogenase, glucose, pH, Gram stain, culture and cytology. A **pH below 7.2**, glucose below 2.2 mmol/L, or frank pus means a complicated parapneumonic effusion or empyema, and the treatment is a chest drain, not more antibiotics.

5. Management

Immediate — the first hour

- **Oxygen** titrated to a saturation of 94–98%, or 88–92% if there is a risk of carbon dioxide retention.

- **Intravenous access, fluid resuscitation** with balanced crystalloid for hypotension, and hourly urine output measurement.
- **Antibiotics within one hour** if septic, and within four hours in all other cases. Take the cultures on the way, not instead.
- **Escalate early.** Persistent hypotension after fluid, a rising lactate, or exhaustion means a critical care referral now rather than at the next ward round.

Score the severity — CURB-65

Criterion	Threshold
C onfusion	New disorientation in person, place or time
U rea	Above 7 mmol/L (about 19 mg/dL)
R espiratory rate	30/min or more
B lood pressure	Systolic below 90 mmHg or diastolic 60 mmHg or less
65 — age	65 years or older

- **0–1:** low risk, suitable for treatment at home.
- **2:** moderate risk, admit to a general ward.
- **3–5:** high risk, consider critical care. Our patient scores 4 (confusion, respiratory rate, blood pressure, age) and requires a high-dependency bed.

The score guides but does not replace judgement. A hypoxic patient with a score of 1, or one who cannot manage at home, is still admitted.

Antibiotic therapy

Setting	Regimen	Duration
Low severity, outpatient	Amoxicillin 1 g three times daily orally. Doxycycline or a macrolide if penicillin-allergic.	5 days
Moderate, ward	Amoxicillin (or ceftriaxone) plus a macrolide such as azithromycin; or a respiratory fluoroquinolone as monotherapy.	5–7 days
Severe or critical care	Intravenous ceftriaxone or co-amoxiclav plus intravenous azithromycin.	7 days
Suspected aspiration	Co-amoxiclav, or add metronidazole to cover anaerobes.	7 days
Structural lung disease	Add antipseudomonal cover, for example piperacillin–tazobactam.	Guided by culture
Risk of resistant Staphylococcus aureus	Add vancomycin or linezolid; consider after influenza and in intravenous drug use.	Guided by culture

Switch from intravenous to oral once the patient has been afebrile for 48 hours, is haemodynamically stable and is absorbing enterally. **A macrolide is added, not substituted,** because atypical organisms are not covered by beta-lactams and cannot be excluded clinically at the front door.

Supportive care

- Venous thromboembolism prophylaxis, analgesia adequate to allow deep breathing and coughing, early mobilisation, chest physiotherapy if sputum retention is a problem, attention to nutrition and to glycaemic control.
- Corticosteroids are not given routinely, but there is now evidence of benefit in severe pneumonia requiring critical care. Follow your local protocol.

Complications to anticipate

- Parapneumonic effusion and empyema, lung abscess, acute respiratory distress syndrome, sepsis with acute kidney injury, new atrial fibrillation, and non-resolving pneumonia.

Discharge and follow-up

- Discharge when the patient is afebrile, saturating adequately on room air, eating and drinking, mentally back to baseline, and has no more than one instability criterion.
- At discharge: smoking cessation advice, pneumococcal and influenza vaccination, a clear safety-net for return, and **the six-week chest radiograph booked before he leaves the ward**.

6. Teaching Points and Viva Questions

- The respiratory rate is the most useful and most neglected vital sign. A rate of 30 in a quiet-looking patient is a medical emergency.
- Bronchial breathing requires a patent airway leading to solid lung; absent breath sounds with stony dullness means fluid between the lung and your stethoscope.
- The elderly may present with confusion, a fall or simply "off legs", and may be afebrile. Absence of fever does not exclude pneumonia.
- Urea appears in the severity score because it reflects both volume depletion and the catabolic burden of severe infection.
- Chest signs may be entirely normal in the first 24 hours. A normal examination does not exclude the diagnosis.

Questions you should be able to answer:

- Distinguish consolidation from a pleural effusion at the bedside using four signs.
- This patient is not improving on day three. What are your next four steps?
- When do you drain a parapneumonic effusion, and on what result?
- Why is a macrolide added to a beta-lactam rather than used alone?
- Why does a smoker need a repeat chest radiograph after recovery?

Case 2 · Acute Severe Asthma

CLINICAL VIGNETTE

A **19-year-old student** with asthma since childhood arrives with two days of worsening wheeze and breathlessness following a head cold. She has been using her salbutamol inhaler almost hourly with diminishing benefit and did not sleep last night. She stopped her preventer inhaler some months ago because she felt well.

She was admitted twice in the past year and spent two days in intensive care at the age of sixteen.

On arrival: she speaks in short phrases only. Temperature 37.2 °C, heart rate 128/min, respiratory rate 32/min, blood pressure 118/76 mmHg, oxygen saturation 91% on room air. Peak expiratory flow 38% of predicted. Widespread polyphonic wheeze with prolonged expiration.

1. Focused History

Take it in parallel with treatment. Nebulised salbutamol does not wait for the social history.

This attack

- Speed of onset — over hours suggests a viral or allergen trigger; over minutes raises anaphylaxis or an inhaled foreign body.
- The trigger: upper respiratory infection, allergen, exercise, cold air, cigarette or waterpipe smoke, emotion, occupational exposure, or a drug — **aspirin, other non-steroidal anti-inflammatory drugs, and beta blockers**, including eye drops.
- How much reliever has been used, and whether it is still working. Diminishing response to salbutamol is a severity marker.

Background asthma control

- Night waking, morning dipping, and days per week of symptoms — the practical measure of control.
- Current inhalers, **adherence, and technique**. Ask her to demonstrate rather than to describe. Poor technique is the commonest reason an apparently adequate regimen fails.
- Number of oral corticosteroid courses in the past twelve months and the number of reliever canisters used per month.

RISK FACTORS FOR NEAR-FATAL ASTHMA

Ask directly about every one of these. Their presence changes disposition even if the physiology improves:

Previous intubation or intensive care admission · two or more admissions in the past year · three or more classes of asthma drug · more than one reliever canister per month · repeated attendance at the emergency department · poor adherence or non-attendance · food allergy · psychiatric illness or major social difficulty.

2. Physical Examination

The four bedside measurements that grade the attack

- **Can she complete a sentence?** Ask her name and address and listen to the phrasing, not the answer.
- **Respiratory rate and heart rate**, counted, not estimated.

- **Oxygen saturation on room air.**
- **Peak expiratory flow** against predicted or her own best. It is the single most useful measurement in asthma and takes fifteen seconds.

Signs of danger

- Accessory muscle use, tracheal tug, tripod posture, inability to lie flat.
- **A silent chest.** Air must move to make a wheeze. A chest that has gone quiet in a distressed patient means airflow has fallen too low to generate sound, and is a pre-terminal sign.
- Cyanosis, exhaustion, drowsiness or confusion, bradycardia, hypotension, arrhythmia — the peri-arrest picture.
- Pulsus paradoxus, and subcutaneous emphysema or asymmetric signs suggesting pneumothorax or pneumomediastinum.

3. Grading the Attack

Grade	Features — any one is sufficient
Moderate	Peak flow above 50% predicted, speech normal, no features of a more severe grade.
Acute severe	Peak flow 33–50%, respiratory rate 25/min or more, heart rate 110/min or more, unable to complete a sentence in one breath.
Life-threatening	Peak flow below 33%, oxygen saturation below 92%, silent chest, cyanosis, poor respiratory effort, exhaustion, altered consciousness, arrhythmia or hypotension. A normal carbon dioxide level belongs in this group.
Near-fatal	Raised arterial carbon dioxide, or the need for mechanical ventilation.

4. Differential Diagnosis

Diagnosis	The feature that discriminates it
Anaphylaxis	Minutes from exposure, with urticaria, angio-oedema and hypotension. Treat with adrenaline first.
Chronic obstructive pulmonary disease	Older, heavy smoking history, fixed rather than variable airflow limitation, chronic daily sputum.
Inhaled foreign body	Sudden onset, unilateral monophonic wheeze, and no history of atopy.
Pneumothorax	Sudden pleuritic pain, unilateral hyper-resonance and absent breath sounds. Always suspect it when asthma deteriorates abruptly.
Acute pulmonary oedema	Orthopnoea, raised jugular venous pressure, bilateral basal crackles as well as wheeze, third heart sound.
Pulmonary embolism	Pleuritic pain with hypoxia but little wheeze, and risk factors for venous thromboembolism.
Inducible laryngeal obstruction	Noise loudest over the neck and inspiratory, normal saturations and peak flow, no response to bronchodilator.

5. Investigations

- **Peak expiratory flow** before and after treatment — the measure of response.
- **Pulse oximetry**, aiming to keep saturation at 94–98%.
- **Arterial blood gas** if saturation stays below 92% or there are life-threatening features. Expect a low carbon dioxide from hyperventilation. **A normal or rising carbon dioxide means the patient is tiring** and requires immediate senior and critical care involvement.
- **Chest radiograph** only if pneumothorax or consolidation is suspected, if there is no response to treatment, or if ventilation is being considered. It is not routine.
- **Potassium** — both beta agonists and corticosteroids lower it, and the treatment itself is the commonest cause of hypokalaemia here. Also glucose, complete blood count and C-reactive protein.

No investigation should delay the first nebuliser.

6. Management

Immediate, in this order

Intervention	Detail
Oxygen	Titrate to a saturation of 94–98%. Unlike in chronic obstructive pulmonary disease, there is no reason to restrict it.
Salbutamol	5 mg nebulised, oxygen-driven. Repeat every 15–20 minutes, or give continuously in severe attacks.
Ipratropium bromide	500 micrograms nebulised with the salbutamol, every 4–6 hours, in acute severe and life-threatening attacks.
Corticosteroid	Prednisolone 40–50 mg orally, or hydrocortisone 100 mg intravenously if she cannot swallow. Continue for at least 5 days. No taper is needed after a short course.
Magnesium sulfate	1.2–2 g intravenously over 20 minutes, as a single dose, in acute severe asthma not responding to initial nebulisers.
Escalation	Intravenous salbutamol or aminophylline only with senior input. Involve critical care early for exhaustion, a rising carbon dioxide, or a falling conscious level.

- **Antibiotics are not routine.** Most attacks are triggered by viruses. Give them only for genuine evidence of bacterial infection.
- **Never sedate a breathless asthmatic.** Agitation is hypoxia, not anxiety.

Monitoring

- Peak flow before and after every nebuliser; continuous oximetry; potassium after repeated doses; repeat blood gas if the first was abnormal or the patient is not improving.

Discharge and follow-up

- Discharge when peak flow exceeds 75% of best or predicted, when she has been off nebulisers for 24 hours, and when saturations are stable on air.

- Before she leaves: **inhaler technique observed and corrected**, the inhaled corticosteroid restarted or stepped up, the remainder of the prednisolone course dispensed, and a **written personalised asthma action plan** in her hand.
- Primary care review within 48 hours and a respiratory clinic appointment within four weeks. Every admission is a failure of chronic control and should trigger a review of it.

Complications

- Pneumothorax and pneumomediastinum, hypokalaemia, lactic acidosis from high-dose beta agonists, and respiratory arrest.

7. Teaching Points and Viva Questions

- The silent chest is the most dangerous sign in the room and the easiest to misread as improvement.
- A normal carbon dioxide in a patient who has been hyperventilating for hours is a warning, not a reassurance.
- Peak flow is objective, repeatable and free. Record it before and after every intervention.
- Overuse of reliever inhaler and underuse of preventer is the pattern behind almost every severe attack.
- Clubbing does not occur in asthma. If you see it, look for bronchiectasis or cancer.

Questions you should be able to answer:

- Grade this attack and justify each criterion you use.
- Why is a normal arterial carbon dioxide a life-threatening feature?
- When would you give magnesium, and what is the evidence for it?
- Her potassium is 2.9 mmol/L after four nebulisers. Explain why.
- What must be done before she is allowed home?

Case 3 · Exacerbation of Chronic Obstructive Pulmonary Disease

CLINICAL VIGNETTE

A **66-year-old retired driver** with a 50 pack-year smoking history is brought in with three days of increasing breathlessness. His sputum has increased in volume and turned green. His ankles have been swelling for a fortnight. He normally manages about 100 metres on the flat before stopping.

The ambulance crew found him hypoxic and gave oxygen at 15 litres per minute by reservoir mask. He has become progressively drowsier during the journey.

On arrival: temperature 37.4 °C, heart rate 104/min, respiratory rate 26/min, blood pressure 138/82 mmHg, oxygen saturation 99% on the reservoir mask. He is rousable but confused, with a coarse flapping tremor.

Arterial blood gas on 15 L/min: pH 7.24, carbon dioxide 9.1 kPa, oxygen 22 kPa, bicarbonate 30 mmol/L.

1. Focused History

Characterise the exacerbation

- The three cardinal symptoms: **increased breathlessness, increased sputum volume, and increased sputum purulence**. How many are present decides whether antibiotics are indicated.
- Baseline exercise tolerance, described in metres or stairs, and how far it has fallen.
- Fever, pleuritic pain, haemoptysis, unilateral leg swelling, chest pain — each pointing to a different complication or alternative diagnosis.

Establish the baseline disease

- Exacerbations, courses of steroids and admissions in the past year; **previous non-invasive ventilation or intubation, and whether it helped**; home nebulisers, home oxygen and its prescribed hours.
- Current inhalers, adherence and technique; vaccination status; smoking status now, not only historically.
- Comorbidity that mimics or coexists: ischaemic heart disease, heart failure, atrial fibrillation, anxiety, osteoporosis, malnutrition.
- Alpha-1 antitrypsin deficiency if the disease began young, if he is a light smoker, or if there is liver disease or a family history.
- **Function and wishes.** How he lives, who helps him, and whether escalation to ventilation has ever been discussed. This conversation is far easier now than at three in the morning.

2. Physical Examination

Signs of the underlying disease

- Pursed-lip breathing, accessory muscle use, tripod posture, barrel-shaped chest, reduced cricosternal distance, tracheal tug, indrawing of the lower ribs on inspiration.
- Hyperinflation: reduced expansion, hyper-resonant percussion with **loss of cardiac and liver dullness**, and quiet breath sounds throughout. Wheeze may be present or absent.

Signs of carbon dioxide retention

- Drowsiness and confusion, a coarse flapping tremor, bounding pulse, warm peripheries, headache, and in extreme cases papilloedema.

Signs of cor pulmonale

- Raised jugular venous pressure, right ventricular heave, loud pulmonary second sound, tender pulsatile hepatomegaly, ankle and sacral oedema.

Signs that mean something else is going on

- **Clubbing** — not a feature of chronic obstructive pulmonary disease; look for carcinoma or bronchiectasis. Focal consolidation, stony dullness, unilateral hyper-resonance, or an asymmetric swollen calf.

3. Differential Diagnosis

Diagnosis	The feature that discriminates it
Pneumonia	Focal consolidation on examination and radiograph, higher fever, greater inflammatory response.
Acute heart failure	Orthopnoea, raised jugular venous pressure, third heart sound, bilateral basal crackles, cardiomegaly and upper lobe diversion on the film.
Pulmonary embolism	Hypoxia disproportionate to the film, pleuritic pain, unilateral calf swelling. Consider it in every exacerbation that fails to respond.
Pneumothorax	Sudden deterioration with unilateral hyper-resonance. Emphysematous lungs are prone to it, and it can be subtle on the film.
Lung cancer	Weight loss, haemoptysis, clubbing, a mass or lobar collapse.
Sedative or opioid effect	Small pupils, a low respiratory rate rather than a high one, and the drug chart.

4. Investigations

READING THE BLOOD GAS

pH tells you how acute it is; bicarbonate tells you how chronic it is.

A raised carbon dioxide with a **normal** bicarbonate is acute — the kidney has not had time to compensate.

A raised carbon dioxide with a **raised** bicarbonate and a normal pH is chronic and compensated.

A raised carbon dioxide with a raised bicarbonate **and an acidaemia**, as here, is an acute deterioration on top of chronic retention. That combination is the indication to prepare for non-invasive ventilation.

- **Arterial blood gas** on a documented inspired oxygen concentration, repeated 30–60 minutes after any change in oxygen therapy or treatment.
- **Chest radiograph** — to exclude pneumonia, pneumothorax and a mass, and to look for hyperinflation with flattened hemidiaphragms.
- **Electrocardiogram** — right axis deviation, P pulmonale, right bundle branch block, atrial fibrillation or multifocal atrial tachycardia, and ischaemia.

- **Complete blood count** — secondary polycythaemia reflects chronic hypoxaemia; anaemia worsens breathlessness. **Urea and electrolytes**, **C-reactive protein**, glucose, and theophylline level if he takes it.
- **Sputum culture** if purulent or if he has failed previous antibiotics; **blood cultures** if febrile.
- **Natriuretic peptide, troponin, or computed tomographic pulmonary angiography** when heart failure, ischaemia or embolism cannot be excluded clinically.

Reading the film

- Hyperinflation is more than six anterior ribs above the diaphragm in the midclavicular line, flattened hemidiaphragms, a narrow vertical heart, and increased retrosternal air on the lateral view. Then look specifically at the apices and the lateral edges for a pneumothorax, which is easily missed against emphysematous lung.

5. Management

THE FIRST CORRECTION TO MAKE IN THIS PATIENT

His saturation of 99% is not reassuring — it is the problem. Uncontrolled oxygen has worsened his hypercapnia. **The answer is not to remove oxygen but to control it**: reduce to a 24–28% Venturi mask, target a saturation of 88–92%, and repeat the gas in 30 minutes. Hypoxia kills faster than hypercapnia; the aim is enough oxygen, not none.

Immediate treatment

Intervention	Detail
Controlled oxygen	Venturi mask 24–28%, target saturation 88–92%. Write the target on the observation chart. Reassess with a gas after 30–60 minutes.
Bronchodilators	Nebulised salbutamol 5 mg and ipratropium 500 micrograms. Drive the nebuliser with air, giving oxygen by nasal cannula alongside, in a patient who retains carbon dioxide.
Corticosteroid	Prednisolone 30 mg orally daily for 5 days.
Antibiotics	Indicated when sputum is purulent or when two of the three cardinal symptoms are present. Amoxicillin, doxycycline or a macrolide for 5 days, adjusted to local resistance patterns and previous cultures.
Non-invasive ventilation	For a pH below 7.35 with carbon dioxide above 6.5 kPa persisting after one hour of optimal medical therapy. This patient qualifies now.
Supportive	Venous thromboembolism prophylaxis, cautious diuresis for cor pulmonale, nutrition, early mobilisation. Avoid sedatives and opioids.

Non-invasive ventilation — what a student must know

- It is a **treatment**, not a sign of failure, and it reduces mortality and the need for intubation in this exact situation.
- Contraindications: inability to protect the airway, vomiting, facial trauma or burns, an undrained pneumothorax, haemodynamic instability, and a patient who cannot tolerate the mask.
- **Decide the ceiling of care before starting**, and document it: is non-invasive ventilation a bridge to intubation, or the ceiling itself? Involve the patient and family while he can still participate.

- Reassess with a blood gas one hour after starting. Failure to improve means escalation or a change of plan, not more of the same.

Before discharge, and for the long term

- **Smoking cessation** — the only intervention that alters the decline in lung function. Offer pharmacotherapy, not only advice.
- **Pulmonary rehabilitation** — the intervention with the largest effect on symptoms and quality of life, and the one most often not referred for.
- Inhaler technique reviewed and the regimen rationalised; influenza and pneumococcal vaccination; a rescue pack with a written plan for its use.
- **Long-term oxygen therapy assessment when stable**, at least 8 weeks after the exacerbation: arterial oxygen at or below 7.3 kPa, or at or below 8 kPa with polycythaemia, peripheral oedema or pulmonary hypertension. It must be used at least 15 hours a day to prolong life, and never with continued smoking.
- Nutritional assessment, anxiety and depression screening, and an honest conversation about the trajectory of the disease.

6. Teaching Points and Viva Questions

- Give oxygen, but give it in a measured concentration with a written target. Withholding it altogether is as much an error as flooding the patient with it.
- The bicarbonate is the historian of the blood gas — it tells you how long this has been going on.
- Smoking cessation and pulmonary rehabilitation change outcomes more than any inhaler.
- A patient with chronic obstructive pulmonary disease who deteriorates suddenly has a pneumothorax or a pulmonary embolism until proved otherwise.
- Ceiling-of-care decisions belong in the notes early, made with the patient, not improvised during a crisis.

Questions you should be able to answer:

- Explain the mechanism by which high-concentration oxygen raised this man's carbon dioxide.
- What are your criteria for starting non-invasive ventilation, and what would you do if it fails?
- When do you give antibiotics in an exacerbation, and why not always?
- List the criteria for long-term oxygen therapy and explain why it must be worn 15 hours a day.
- He has clubbing. Does that change your thinking?

Case 4 · Suppurative Lung Disease: Bronchiectasis and Lung Abscess

CLINICAL VIGNETTE

A **34-year-old woman** attends with two weeks of fever, worsening cough and foul-smelling sputum. For as long as she can remember she has coughed every morning and produced sputum daily; over the past two weeks the volume has risen to about half a cup a day and she has coughed up streaks of blood. She has lost 6 kg over three months.

She had severe pneumonia as a child and has had recurrent chest infections since. She has chronic nasal congestion. Her parents are first cousins.

On examination: she is thin. There is **clubbing**. Temperature 38.4 °C, respiratory rate 22/min, oxygen saturation 94% on air. Coarse early inspiratory crackles at both bases that alter after she coughs, with scattered wheeze. The sputum pot contains thick green sputum that has separated into layers.

1. Focused History

Characterise the sputum — this is the diagnostic history

- **Daily volume**, quantified against a household measure. Daily purulent sputum for years is bronchiectasis until proved otherwise, and no other common condition produces it.
- **Smell.** Foul or putrid sputum means anaerobic organisms, and therefore aspiration, abscess or empyema.
- **Haemoptysis**, quantified. Bronchiectasis is one of the commonest causes of massive haemoptysis.
- Whether the symptoms have been lifelong, or began after a specific illness.

Find the underlying cause

Ask about	Cause it points to
Severe childhood pneumonia, measles, whooping cough, previous tuberculosis	Post-infective bronchiectasis — the commonest cause
Chronic sinusitis, infertility, situs inversus	Primary ciliary dyskinesia
Steatorrhoea, poor growth, infertility, diabetes, family history, consanguinity	Cystic fibrosis — may present in adulthood with milder mutations
Recurrent sinopulmonary, skin or gut infections since childhood	Antibody deficiency, especially common variable immunodeficiency
Difficult asthma with brown sputum plugs and fleeting shadows	Allergic bronchopulmonary aspergillosis
Rheumatoid arthritis, inflammatory bowel disease	Associated bronchiectasis
Alcohol excess, seizures, stroke, poor dentition, oesophageal disease, reduced consciousness	Aspiration — the classic setting for lung abscess
Recurrent pneumonia always in the same lobe	Obstruction — inhaled foreign body or tumour

2. Physical Examination

- **Clubbing** — present in established suppurative lung disease and a key discriminator from chronic obstructive pulmonary disease.

- Cachexia and reduced muscle bulk, reflecting the metabolic cost of chronic sepsis.
- **Inspect the sputum pot.** Copious purulent sputum that separates into a frothy upper layer, a clear middle layer and a dense purulent lower layer is characteristic.
- **Coarse early inspiratory crackles that change or clear with coughing** — secretions moving in large airways. Wheeze is common. Signs may be focal or widespread.
- Look for complications: dullness with absent breath sounds (empyema), focal consolidation, and the raised jugular venous pressure, right ventricular heave and oedema of late cor pulmonale.
- Look for the cause: nasal polyps and sinus tenderness, dextrocardia, the teeth and gums, deforming arthropathy of the hands.

3. Differential Diagnosis

Diagnosis	The feature that discriminates it
Chronic obstructive pulmonary disease	Smoker, no clubbing, smaller sputum volumes, and a computed tomogram without dilated airways.
Pulmonary tuberculosis	Night sweats, upper zone disease with cavitation, positive acid-fast staining. It also causes bronchiectasis, so the two coexist.
Lung abscess	A single cavity with an air-fluid level, usually in a dependent segment, with an aspiration risk factor.
Empyema	Stony dullness with a pleural collection rather than a parenchymal cavity; pus on aspiration.
Lung cancer with post-obstructive infection	Older smoker, recurrent infection in the same lobe, a mass or collapse.
Cystic fibrosis	Upper lobe predominance, pancreatic insufficiency, raised sweat chloride.

4. Investigations

Establish the diagnosis

- **High-resolution computed tomography of the chest is the diagnostic test.** Look for a bronchoarterial ratio greater than one — the **signet ring sign** — failure of the airways to taper towards the periphery, and visible airways within one centimetre of the pleura.
- **Chest radiograph** — tramline and ring shadows, crowded markings, and in abscess a **cavity with an air-fluid level**. A normal film does not exclude bronchiectasis.
- **The distribution is a clue to the cause:** upper lobes in cystic fibrosis, tuberculosis and allergic bronchopulmonary aspergillosis; lower lobes in post-infective and aspiration disease; the right middle lobe and lingula in non-tuberculous mycobacterial infection.

Establish the organism

- Sputum for Gram stain and culture, **three specimens for acid-fast bacilli**, and fungal culture. Know the colonising organism: Haemophilus influenzae early, and **Pseudomonas aeruginosa** later, which marks more severe disease and changes every future antibiotic choice.

Establish the underlying cause

- Complete blood count with differential, immunoglobulins G, A and M, and specific antibody responses; human immunodeficiency virus test; total and aspergillus-specific immunoglobulin E and aspergillus precipitins; sweat chloride and cystic fibrosis genotyping where suggestive; rheumatoid factor and anti-cyclic citrullinated peptide antibodies; alpha-1 antitrypsin level.
- **Spirometry** — usually an obstructive pattern; used to follow progression.
- **Bronchoscopy** if disease is confined to one lobe, if a foreign body or tumour is possible, or for persistent haemoptysis.

5. Management

Treat the exacerbation

- Send sputum, then start antibiotics guided by previous isolates. **Treat for 14 days**, considerably longer than for pneumonia.
- If colonised with Pseudomonas: oral ciprofloxacin, or intravenous piperacillin–tazobactam or ceftazidime for severe episodes.
- For a lung abscess: **4–6 weeks of antibiotics with anaerobic cover** — co-amoxiclav or clindamycin — with postural drainage. Most resolve medically; percutaneous or surgical drainage is reserved for failure. **Arrange dental assessment**, since the mouth is usually the source.

The long-term programme — where the real benefit lies

- **Daily airway clearance physiotherapy** is the cornerstone of treatment. Active cycle of breathing, postural drainage, and oscillating positive expiratory pressure devices. Teach it, and check she is still doing it at every visit.
- Nebulised isotonic or hypertonic saline before physiotherapy to aid clearance.
- **Long-term azithromycin** three times weekly reduces exacerbation frequency. Exclude non-tuberculous mycobacterial infection and check the corrected QT interval and liver function before starting.
- Treat the underlying cause — immunoglobulin replacement in antibody deficiency, corticosteroids in allergic bronchopulmonary aspergillosis, modulator therapy in cystic fibrosis.
- Bronchodilators if there is demonstrable reversibility, vaccination, nutritional support, pulmonary rehabilitation, and surgical resection for localised disease that remains refractory.

EMERGENCY: MASSIVE HAEMOPTYSIS

Bronchiectasis is a common cause of massive haemoptysis, and it kills by asphyxiation rather than by exsanguination.

Protect the airway. Lie the patient with the bleeding side downwards to keep blood out of the good lung. Give oxygen, obtain large-bore access, correct clotting, and give tranexamic acid. Call for urgent bronchoscopy and **bronchial artery embolisation**, which is the definitive treatment; surgery if that fails.

6. Teaching Points and Viva Questions

- Clubbing with crackles is never simple chronic obstructive pulmonary disease. Think suppurative lung disease, fibrosis or cancer.
- The volume of daily sputum is the single most discriminating point in the history.
- High-resolution computed tomography makes the diagnosis; the plain film may be normal.
- Foul-smelling sputum means anaerobes, which means aspiration — so examine the teeth and ask why she aspirated.
- Physiotherapy is not an adjunct to treatment. In bronchiectasis it *is* the treatment, and antibiotics are the adjunct.

Questions you should be able to answer:

- How do you distinguish bronchiectasis from chronic obstructive pulmonary disease at the bedside?
- Name six causes of bronchiectasis and the single question that screens for each.
- Why does the distribution of disease on the computed tomogram matter?
- Why is Pseudomonas colonisation significant?
- She coughs up 400 mL of blood in an hour. What are your first five actions?

Case 5 · Acute-on-Chronic Hypercapnic Respiratory Failure

CLINICAL VIGNETTE

A **58-year-old man** is brought in by his wife because he has become increasingly drowsy over two days, following a week of cough and fever. For the past year she has noticed loud snoring with pauses in his breathing at night, and he has been falling asleep during the day and waking with headaches. His ankles have been swelling.

He takes no sedatives. He has never smoked.

On arrival: he is rousable to voice but falls asleep between questions. Temperature 37.8 °C, heart rate 96/min, respiratory rate 14/min and shallow, blood pressure 146/88 mmHg, oxygen saturation 86% on room air. Jugular venous pressure is raised and there is pitting oedema to mid-shin. A flapping tremor is present.

Arterial blood gas on air: pH 7.30, carbon dioxide 8.8 kPa, oxygen 7.4 kPa, bicarbonate 33 mmol/L.

1. The Framework

Respiratory failure is not a diagnosis. It is a physiological state with two patterns, and the whole of the assessment follows from deciding which one is in front of you.

	Type 1 — hypoxaemic	Type 2 — hypercapnic
Definition	Oxygen below 8 kPa with a normal or low carbon dioxide	Carbon dioxide above 6.0 kPa, usually with hypoxaemia
Mechanism	The lung fails as a gas exchanger — ventilation–perfusion mismatch or shunt	The pump fails — alveolar ventilation is inadequate
Alveolar–arterial gradient	Raised	Normal in pure hypoventilation; raised if there is lung disease as well
Typical causes	Pneumonia, pulmonary oedema, pulmonary embolism, acute respiratory distress syndrome, pneumothorax, interstitial lung disease	See the three questions below

For type 2 failure, ask three questions in order. They generate the entire differential.

- **Will he not breathe?** Central depression — opioids, benzodiazepines, alcohol, brainstem stroke, raised intracranial pressure, hypothyroidism.
- **Can he not breathe?** Pump failure — neuromuscular disease (Guillain–Barré syndrome, myasthenia gravis, motor neurone disease, muscular dystrophy), phrenic nerve palsy, or chest wall restriction from kyphoscoliosis, circumferential burns or obesity hypoventilation.
- **Is the load too great?** Airway and lung disease — chronic obstructive pulmonary disease, severe asthma late in an attack, bronchiectasis, advanced fibrosis.

2. Focused History

- Speed of onset. Minutes suggests drugs, a neurological event or a pneumothorax; days suggests infection on a chronic background; months suggests progressive neuromuscular or chest wall disease.
- **Symptoms of chronic hypoventilation:** morning headache, daytime somnolence, poor concentration, disturbed sleep, snoring with witnessed apnoeas, ankle swelling.

- **Neuromuscular screening questions:** difficulty rising from a chair or climbing stairs, double vision, slurred speech, choking on food, breathlessness on lying flat (a diaphragmatic sign), and recent gastrointestinal or respiratory infection preceding weakness.
- Every sedative, opioid, alcohol and recreational drug taken. Any oxygen given before arrival, and at what rate.
- Previous non-invasive ventilation or continuous positive airway pressure at home, and adherence to it.

3. Physical Examination

- **Conscious level**, scored and repeated — the most important single observation, and the one that decides whether non-invasive ventilation is safe.
- **Respiratory rate and pattern.** A high rate that falls as the patient tires is ominous. **Paradoxical inward abdominal movement on inspiration** indicates diaphragmatic fatigue or paralysis.
- **Bedside tests of respiratory muscle strength:** ask him to count aloud from one on a single breath, and test neck flexion strength. Both correlate with vital capacity and can be repeated hourly.
- Signs of retention — flapping tremor, bounding pulse, warm peripheries, papilloedema. Central cyanosis. Signs of cor pulmonale.
- Pupils and injection sites if opioids are possible; the chest wall for deformity; a full neurological examination when weakness is suspected.

4. Investigations

- **Arterial blood gas is the definitive investigation** and must be repeated. Record the inspired oxygen concentration every time or the result is uninterpretable.
- **Calculate the alveolar–arterial oxygen gradient.** A normal gradient with hypercapnia means pure hypoventilation — the lungs are healthy and the pump has failed. A raised gradient means there is lung disease as well. This single calculation separates the two mechanisms.
- Chest radiograph, electrocardiogram, complete blood count (polycythaemia in chronic hypoxaemia), urea and electrolytes, C-reactive protein, thyroid function, creatine kinase.
- **In suspected neuromuscular disease, measure the forced vital capacity serially and act on it.** A value below 15–20 mL/kg, or a fall of more than 30% from baseline, indicates the need for ventilatory support. **Do not wait for the carbon dioxide to rise — in neuromuscular failure hypercapnia is a late and pre-terminal finding.**
- Later, when the acute episode has settled: sleep studies, spirometry with lung volumes, and echocardiography for pulmonary hypertension.

5. Management

The oxygen ladder — and why the device matters

Device	When to use it
Nasal cannula, 1–4 L/min	Mild hypoxaemia. Delivered concentration varies with the patient's own breathing pattern.
Simple face mask, 5–10 L/min	Moderate hypoxaemia without a risk of retention. Never run below 5 L/min — the patient rebreathes carbon dioxide.
Venturi mask, 24–60%	The correct choice whenever the delivered concentration matters, because it provides a fixed concentration independent of the breathing pattern.
Reservoir mask, 15 L/min	Critical illness and trauma while the cause is being addressed. Not for a patient at risk of retention.
High-flow nasal oxygen	Type 1 failure needing high concentrations; provides humidification and some positive pressure.
Non-invasive ventilation	Type 2 failure with acidaemia. Bilevel support for hypercapnia; continuous positive airway pressure for cardiogenic pulmonary oedema and obstructive sleep apnoea.
Invasive ventilation	Failure of non-invasive support, inability to protect the airway, or a decision that full escalation is appropriate.

Sequence for this patient

- **Controlled oxygen** by Venturi mask, targeting a saturation of 88–92%, with a gas repeated in 30 minutes.
- **Reverse what is reversible:** treat the chest infection, give bronchodilators if there is any airflow obstruction, and give naloxone if opioids are conceivable.
- **Non-invasive ventilation** for the persisting acidaemia, since the pH is below 7.35 with a carbon dioxide above 6.5 kPa. His drowsiness makes this a decision for a senior clinician in a monitored area, because the same drowsiness raises the risk of aspiration.
- **Document the ceiling of care** and discuss it with the patient and family before he deteriorates further.
- Repeat the gas at one hour. Improvement in pH is the marker of success. No improvement means intubation or an explicit change of plan.

Complications and longer-term care

- Aspiration, barotrauma and pneumothorax, pressure injury from the mask, hypotension from positive pressure, and oxygen-induced hypercapnia.
- After recovery: sleep-disordered breathing assessment and home nocturnal ventilation, weight management referral, avoidance of sedatives, treatment of cor pulmonale, and long-term oxygen assessment when stable.

6. Teaching Points and Viva Questions

- Hypercapnia is a pump problem. Ask in order: will he not breathe, can he not breathe, or is the load too great?
- The alveolar–arterial gradient separates a failing lung from a failing pump, and costs nothing to calculate.
- In neuromuscular weakness, measure the vital capacity. By the time the carbon dioxide rises, the patient is close to arrest.
- A falling respiratory rate in a previously tachypnoeic patient means exhaustion, not recovery.
- Write the target saturation range on the chart. An unqualified instruction to "give oxygen" is how patients like this one become drowsy.

Questions you should be able to answer:

- Classify this man's respiratory failure and justify it from the gas.
- His bicarbonate is 33. What does that tell you about the timescale?
- Give four contraindications to non-invasive ventilation.
- Why is a Venturi mask preferred to nasal cannulae here?
- A patient with Guillain–Barré syndrome has a normal blood gas but a vital capacity of 1.1 litres. What do you do?

Case 6 · Pleural Effusion

CLINICAL VIGNETTE

A **62-year-old man** presents with six weeks of progressive breathlessness and a dull ache in the right side of his chest. He has lost 8 kg without trying and sweats at night. He worked for twenty years in construction and demolition. He is an ex-smoker of 30 pack-years.

On examination: respiratory rate 22/min, oxygen saturation 93% on air. The trachea is central. Expansion is reduced on the right. Percussion is **stony dull** to the mid-zone on the right, with absent breath sounds and reduced vocal resonance below, and bronchial breathing at the upper level of the dullness. There is no clubbing and no palpable lymphadenopathy.

1. Focused History

The two questions that shape everything

- **How quickly did it come on?** Days suggests infection, embolism or trauma. Weeks to months suggests malignancy, tuberculosis or heart failure.
- **Is it painful?** Pleuritic pain means the parietal pleura is inflamed and favours an exudate — infection, infarction, malignant invasion. Painless effusions are more often transudates.

Then screen for each cause directly

Ask about	Cause it points to
Orthopnoea, paroxysmal nocturnal dyspnoea, ankle swelling	Heart failure — the commonest cause overall, and usually bilateral
Jaundice, alcohol, known liver disease, abdominal swelling	Cirrhosis with hepatic hydrothorax
Frothy urine, facial and leg oedema	Nephrotic syndrome
Weight loss, night sweats, haemoptysis, smoking	Malignancy
Occupational asbestos exposure, with a latency of 20–40 years	Mesothelioma or benign asbestos-related effusion — ask about the whole working life, including construction, shipyards, insulation and brake linings
Tuberculosis contact, endemic exposure, prior treatment	Tuberculous pleurisy — typically a young patient with a lymphocytic exudate
Recent pneumonia with persisting or returning fever	Parapneumonic effusion or empyema
Immobility, surgery, malignancy, unilateral leg swelling	Pulmonary embolism with infarction
Joint pain, rash, photosensitivity, dry eyes	Rheumatoid arthritis or systemic lupus erythematosus
Severe epigastric pain, alcohol, gallstones	Pancreatitis

2. Physical Examination

Confirm the effusion

- Reduced expansion, **stony dullness**, absent or greatly reduced breath sounds, reduced vocal resonance and fremitus, with **bronchial breathing at the upper border** where compressed lung lies beneath.
- **Tracheal position:** central in a moderate effusion; pushed **away** by a massive one. If the trachea is pulled **towards** a white-out, the diagnosis is collapse, not effusion — and the management is entirely different.

Then find the cause

- Cervical and supraclavicular lymph nodes, breast examination, clubbing, chest wall masses or tenderness (mesothelioma), radiotherapy marks or surgical scars.
- Raised jugular venous pressure, third heart sound, bilateral oedema (heart failure); jaundice, spider naevi, ascites (cirrhosis); periorbital oedema (nephrotic syndrome); synovitis and deformity (rheumatoid disease); an abdominal or pelvic mass.

3. Investigations

Imaging — reading the film

- On the **posteroanterior radiograph**, about 200 mL is needed before the costophrenic angle blunts; on the **lateral** film as little as 50 mL is visible. Expect a homogeneous opacity with a concave upper border — the **meniscus sign**.
- A complete white-out: **look at the trachea**. Pushed away means effusion or a large mass; pulled towards means collapse or pneumonectomy; central suggests consolidation.
- **Thoracic ultrasound before every pleural procedure.** It confirms fluid, estimates depth, identifies septations, and marks the site. It has substantially reduced the complication rate of pleural aspiration and its use is now the standard of care.
- **Contrast-enhanced computed tomography** for any undiagnosed exudate, performed **before** complete drainage so the pleural surfaces can be assessed. Nodular or circumferential pleural thickening, thickening greater than one centimetre, or mediastinal pleural involvement all suggest malignancy.

Diagnostic aspiration

Note the appearance first: straw-coloured, turbid, frank pus, blood-stained, or milky. Then send the fluid for protein, lactate dehydrogenase, glucose, pH, Gram stain and culture, acid-fast staining and culture, adenosine deaminase, cytology, and triglycerides if it looks milky. Send **paired serum protein and lactate dehydrogenase at the same time** — without them the fluid results cannot be interpreted.

LIGHT'S CRITERIA

The fluid is an **exudate** if any one of the following is true:

pleural protein divided by serum protein is greater than 0.5 · pleural lactate dehydrogenase divided by serum lactate dehydrogenase is greater than 0.6 · pleural lactate dehydrogenase is greater than two-thirds of the upper limit of the normal serum range.

The known trap: in a patient on diuretics, a transudate concentrates and is misclassified as an exudate. When the clinical picture is heart failure but the criteria say exudate, calculate the **serum-to-fluid albumin gradient**; a value above 12 g/L confirms a transudate.

Transudate — the pressures are wrong	Exudate — the pleura is diseased
Heart failure (usually bilateral, right greater than left)	Parapneumonic effusion and empyema
Cirrhosis with hepatic hydrothorax	Malignancy — lung, breast, lymphoma, mesothelioma
Nephrotic syndrome and hypoalbuminaemia	Tuberculosis
Peritoneal dialysis	Pulmonary embolism with infarction
Hypothyroidism, constrictive pericarditis	Connective tissue disease, pancreatitis, drugs, chylothorax

Interpreting the fluid

Finding	What it means
pH below 7.2 in an infected effusion	Complicated parapneumonic effusion — insert a chest drain. This single number decides the management.
Low glucose (below 3.3 mmol/L)	Empyema, rheumatoid disease, tuberculosis, or malignancy.
Frank pus, or organisms on Gram stain	Empyema — drain regardless of the pH.
Lymphocyte predominance	Tuberculosis, malignancy, lymphoma, chronic disease.
Neutrophil predominance	Acute process — parapneumonic, pulmonary embolism, pancreatitis.
Adenosine deaminase above 40 U/L with a lymphocytic exudate	Strongly supports tuberculosis, particularly in a younger patient in an endemic setting.
Heavily blood-stained fluid	Malignancy, pulmonary infarction, or trauma.
Milky fluid with triglycerides above 1.24 mmol/L	Chylothorax — thoracic duct disruption from lymphoma, surgery or trauma.

- **Cytology is positive in only about six in ten malignant effusions.** A negative result does not exclude cancer. If two aspirates are non-diagnostic and suspicion persists, proceed to **local anaesthetic thoracoscopy with pleural biopsy**, which has the highest yield in both malignancy and tuberculosis.
- **Do not aspirate bilateral effusions in a patient with clear heart failure.** Treat the failure and reassess; tap only if the effusions are asymmetric, painful, febrile, or fail to resolve.

4. Management

- **Treat the cause.** Transudates resolve when the underlying disorder is treated — diuresis for heart failure, albumin and sodium restriction in cirrhosis. Drainage alone achieves nothing lasting.
- **Therapeutic drainage** for symptomatic relief. **Remove no more than 1–1.5 litres at one sitting**, and stop immediately for chest tightness, pain or persistent coughing, because of the risk of **re-expansion**

pulmonary oedema.

- **Empyema or complicated parapneumonic effusion:** prompt chest drain plus antibiotics covering anaerobes, continued for two to six weeks. Intrapleural fibrinolytic therapy for loculated collections, and surgical decortication when drainage fails.
- **Malignant effusion:** treat the underlying cancer. For recurrent symptomatic effusions, offer either an **indwelling pleural catheter** for drainage at home or **talc pleurodesis**; the choice depends on performance status, lung re-expansion and patient preference.
- **Tuberculous effusion:** standard antituberculous chemotherapy; most resolve without drainage.
- **Procedural complications:** pneumothorax, bleeding, infection, injury to liver or spleen, and re-expansion oedema. Ultrasound guidance, a properly positioned patient and a limited volume prevent most of them.

5. Teaching Points and Viva Questions

- Stony dullness with absent breath sounds is fluid. Dullness with bronchial breathing is consolidation. This distinction changes the next step from a prescription to a procedure.
- In a complete white-out, the trachea tells you the answer before any test does.
- Never perform a pleural procedure without ultrasound, and never on a patient who is sitting unsupported.
- Light's criteria misclassify diuretic-treated heart failure. Remember the albumin gradient.
- A lymphocytic exudate with a high adenosine deaminase in a young patient in this region is tuberculosis until proved otherwise.
- An occupational history taken properly can be the single most valuable part of this consultation, and it must cover the whole working life.

Questions you should be able to answer:

- State Light's criteria and explain the one situation in which they mislead.
- The pleural fluid pH is 7.05 after a pneumonia. What do you do, and why does the pH matter?
- List five causes of a lymphocytic exudative effusion.
- You drain 2.5 litres and the patient becomes acutely breathless. What has happened?
- Cytology is negative twice but you still suspect mesothelioma. What is your next investigation?

Case 7 · Lung Cancer

CLINICAL VIGNETTE

A **66-year-old man** with a 50 pack-year smoking history says his cough has **changed** over three months — it is now dry, harsher, and worse at night. He has coughed up streaks of blood on four occasions. He has lost 9 kg without trying, has a persistent dull ache between the right shoulder blade and the spine, and **his voice has been hoarse for six weeks**.

On examination: cachectic and hoarse. There is **finger clubbing**. A firm 2 cm node is palpable in the left supraclavicular fossa. Percussion is dull over the right upper zone with reduced breath sounds. No stridor.

Sodium 122 mmol/L · corrected calcium normal · haemoglobin 106 g/L. Chest radiograph: right hilar mass with right upper lobe collapse.

THE HISTORY THAT MATTERS

A smoker who has coughed for years does not present because he has a cough. He presents — if anyone asks — because **the cough has changed**.

The features that should trigger urgent investigation: a new cough or a change in a chronic cough lasting more than three weeks · **haemoptysis** · unexplained weight loss · chest or shoulder pain · breathlessness · **hoarseness** · a chest infection that fails to resolve · **new finger clubbing** · cervical or supraclavicular lymphadenopathy.

And a normal chest radiograph does not exclude lung cancer. In a patient with haemoptysis and weight loss, a normal film means you need a computed tomogram, not reassurance.

1. Focused History

Local invasion — each symptom localises the tumour

Symptom or sign	Structure involved
Hoarseness	Recurrent laryngeal nerve — not laryngitis. In a smoker with weight loss this is a red flag, and it also implies mediastinal involvement
Dysphagia	Oesophageal compression
Facial and arm swelling with distended chest wall veins, worse on bending forward	Superior vena caval obstruction
Shoulder and inner arm pain, wasting of the small hand muscles, Horner syndrome	Pancoast tumour at the apex, involving the brachial plexus and sympathetic chain
Breathlessness with stony dullness	Pleural effusion — or pericardial effusion with tamponade
Elevated hemidiaphragm	Phrenic nerve palsy

Metastatic and paraneoplastic disease

- **Metastases:** bone pain, headache, seizure or focal neurological deficit, jaundice or right upper quadrant pain, skin nodules.

Paraneoplastic syndrome	Usual histology
Syndrome of inappropriate antidiuresis — hyponatraemia, as here	Small cell
Ectopic adrenocorticotrophic hormone — rapid-onset Cushing syndrome with severe hypokalaemia	Small cell
Hypercalcaemia from parathyroid hormone-related peptide	Squamous cell
Lambert–Eaton myasthenic syndrome, cerebellar degeneration, limbic encephalitis	Small cell
Clubbing and hypertrophic pulmonary osteoarthropathy	Adenocarcinoma and squamous
Dermatomyositis; migratory thrombophlebitis and hypercoagulability; anaemia	Any

So the biochemistry hints at the histology before the biopsy does. Hyponatraemia points towards small cell disease; hypercalcaemia towards squamous.

Risk and context

- **Smoking quantified in pack-years, including waterpipe**, and second-hand exposure. **Asbestos** with its decades of latency, radon, silica, arsenic, chromium, diesel exhaust, and **biomass cooking smoke and heavy incense use**, which are relevant exposures here.
- Previous thoracic radiotherapy, chronic obstructive pulmonary disease, pulmonary fibrosis, human immunodeficiency virus, and family history.
- **Performance status, comorbidity and current lung function** — these determine what treatment is possible at least as much as the stage does. And ask, early and gently, what the patient understands and wants to know.

2. Physical Examination

- Cachexia; **clubbing and hypertrophic pulmonary osteoarthropathy**; tar staining; hoarseness; **Horner syndrome and wasting of the thenar and interosseous muscles**.
- **Cervical and supraclavicular nodes** — a palpable supraclavicular node is often the easiest route to tissue and should be sought before anything invasive is planned.
- Tracheal position; signs of collapse, consolidation or effusion; signs of superior vena caval obstruction.
- Liver edge, bone tenderness, skin nodules, and a full neurological examination.

3. Investigations

- **Chest radiograph:** mass, hilar enlargement, lobar collapse, effusion, bony lesion, elevated hemidiaphragm. Then **contrast-enhanced computed tomography of the chest, abdomen and pelvis**, which must include the adrenals and liver.
- **Positron emission tomography with computed tomography** for staging in anyone being considered for treatment with curative intent, and **magnetic resonance imaging of the brain** where indicated.
- **Tissue is essential, and the route depends on the location:** bronchoscopy with endobronchial ultrasound and mediastinal nodal sampling for central lesions; computed tomography-guided biopsy for

peripheral ones; pleural aspiration and biopsy; or biopsy of that supraclavicular node.

THE MOST IMPORTANT PRACTICAL CHANGE IN MODERN LUNG CANCER CARE

Take enough tissue for molecular testing, and say so on the request.

Treatment of advanced non-squamous non-small cell lung cancer now depends on **EGFR, ALK, ROS1, BRAF and KRAS status and on PD-L1 expression**, because a patient with a targetable mutation may respond to an oral tyrosine kinase inhibitor for years.

An inadequate sample means a second biopsy, or a patient given chemotherapy when a tablet would have served them better. This is a real change from the way lung cancer was managed a decade ago, and it is the commonest reason a diagnostic procedure has to be repeated.

- **Bloods:** complete blood count, **sodium**, corrected calcium, liver function with alkaline phosphatase, lactate dehydrogenase, renal function.
- **Before surgery:** spirometry with gas transfer, and cardiopulmonary exercise assessment where lung function is marginal.

4. The Division That Determines Everything

	Non-small cell (around 85%)	Small cell (around 15%)
Types	Adenocarcinoma, squamous cell, large cell	Small cell carcinoma
Behaviour	Grows and spreads more slowly; often localised at diagnosis	Aggressive, and effectively systemic at diagnosis even when imaging looks limited
Role of surgery	Yes — curative resection for early stage disease	Essentially no
Mainstay	Surgery, stereotactic radiotherapy, chemoradiotherapy, and molecularly guided systemic therapy or immunotherapy in advanced disease	Platinum-based chemotherapy with radiotherapy, plus immunotherapy in extensive stage; prophylactic cranial irradiation in selected patients
Course	Variable	Marked initial response, then early relapse

5. Management

- **Every case goes to a multidisciplinary team**, and the decision turns on histology, molecular profile, stage, lung function and performance status together.
- **Non-small cell:** lobectomy for early disease with adequate reserve; stereotactic ablative radiotherapy for the medically inoperable; concurrent chemoradiotherapy for locally advanced disease; and for advanced disease, **a targeted inhibitor where a driver mutation is present, or immunotherapy guided by PD-L1**, with or without chemotherapy.
- **Small cell:** chemotherapy with thoracic radiotherapy in limited stage, chemoimmunotherapy in extensive stage.

Emergency	Action
Malignant spinal cord compression	Back pain with leg weakness, a sensory level or sphincter disturbance. Urgent magnetic resonance imaging of the whole spine, high-dose dexamethasone, and same-day oncology and neurosurgical discussion. Hours, not days.
Superior vena caval obstruction	Rarely an immediate airway threat. Obtain tissue where possible before corticosteroids, then treat with radiotherapy, chemotherapy or stenting.
Hypercalcaemia	Fluids then a bisphosphonate — Case 23.
Massive haemoptysis	Airway protection, bleeding side down, bronchial artery embolisation — Case 4.
Pericardial tamponade; symptomatic brain metastases	Drainage; dexamethasone and urgent imaging.

THE REFERRAL MADE TOO LATE

Refer to palliative care at diagnosis in advanced disease, not when treatment options run out.

Early specialist palliative care alongside oncological treatment **improves quality of life, reduces depression, and in advanced lung cancer has been shown to improve survival**. It is not a signal that treatment has been abandoned, and it should not be presented to the patient as one.

Practical measures that make a real difference: opioids for breathlessness and pain, pleurodesis or an indwelling pleural catheter for recurrent effusion, endobronchial stenting or debulking for large airway obstruction, palliative radiotherapy for haemoptysis and bone pain, nutritional support, and **smoking cessation — which still improves outcomes and tolerance of treatment even after diagnosis**.

6. Teaching Points and Viva Questions

- It is the change in the cough, not the cough, that matters.
- A normal chest radiograph does not exclude lung cancer.
- Hoarseness in a smoker with weight loss is nerve involvement, not laryngitis.
- Hyponatraemia suggests small cell; hypercalcaemia suggests squamous.
- Small cell versus non-small cell decides whether surgery is even on the table.
- Take enough tissue for molecular testing, or the patient may be denied the best treatment.
- Palliative care belongs at diagnosis, and it improves survival.

Questions you should be able to answer:

- What does his hoarseness tell you anatomically, and what does it imply about stage?
- His sodium is 122. What is the mechanism and which histology does it suggest?
- Which single physical finding offers the easiest route to a diagnosis, and why does that matter?
- The biopsy confirms adenocarcinoma but there is insufficient tissue for molecular studies. What are the consequences?
- He develops mid-thoracic back pain and difficulty walking. What is your sequence of actions?

Case 8 · Pulmonary Hypertension

CLINICAL VIGNETTE

A **34-year-old woman** describes eighteen months of breathlessness on exertion which has progressed from hills to walking on the flat. She becomes dizzy on exertion and fainted once while climbing stairs. Over the past two months her ankles have swollen and her abdomen has become distended.

She has been treated for asthma with inhalers that made no difference, and was told last year that the problem was probably anxiety.

On examination: oxygen saturation 94% on air. **The jugular venous pressure is raised with a prominent a wave.** There is a **left parasternal heave and a loud pulmonary second sound**, with a pansystolic murmur at the left sternal edge that is **louder on inspiration**, giant systolic venous waves and a **pulsatile liver**. There is ascites and pitting oedema to the knees. **The chest is clear.**

Electrocardiogram: right axis deviation, right ventricular hypertrophy, P pulmonale. **Echocardiography:** dilated hypertrophied right ventricle, high estimated pulmonary artery pressure, severe tricuspid regurgitation, normal left ventricle. **Right heart catheterisation:** mean pulmonary artery pressure 48 mmHg, raised pulmonary vascular resistance, normal wedge pressure.

WHY THIS DIAGNOSIS IS MISSED FOR YEARS

The median delay from first symptom to diagnosis in pulmonary arterial hypertension remains **more than two years**, and this history shows exactly why: a young woman with breathlessness and a clear chest is labelled asthmatic, unfit, overweight or anxious.

Progressive unexplained exertional breathlessness with a clear chest and a loud pulmonary second sound needs an echocardiogram. That is the whole lesson of this case, and it costs one investigation.

Exertional dizziness and syncope are not vague symptoms here — they mean the right ventricle cannot increase output on demand, and they carry a poor prognosis.

1. Think First — Five Groups, and the Group Decides the Treatment

Group	Causes
1 — Pulmonary arterial hypertension	Idiopathic · heritable · drug-induced (appetite suppressants, some stimulants) · connective tissue disease, especially systemic sclerosis · human immunodeficiency virus · portal hypertension · congenital heart disease · schistosomiasis, which is one of the commonest causes worldwide
2 — Left heart disease	The commonest cause overall — heart failure with reduced or preserved ejection fraction, valve disease. The wedge pressure is raised
3 — Lung disease and hypoxia	Chronic obstructive pulmonary disease, pulmonary fibrosis, obstructive sleep apnoea, hypoventilation, and chronic residence at high altitude
4 — Chronic thromboembolic disease	The group that may be surgically curable — which is why every patient must be asked about previous venous thromboembolism and screened for it
5 — Multifactorial	Sarcoidosis · haematological disease including myeloproliferative neoplasms and chronic haemolysis in sickle cell disease and thalassaemia · metabolic and renal disease

2. Focused History

- **Breathlessness on exertion is the earliest and often the only symptom.** Then fatigue, exertional chest pain, **presyncope and syncope**, palpitations, and finally ankle swelling and abdominal distension as the right ventricle fails.

- Hoarseness from compression of the left recurrent laryngeal nerve by a dilated pulmonary artery.
- **Screen for each group by history:** cardiac symptoms and hypertension; known lung disease, smoking, snoring and daytime somnolence, **altitude of residence**; **previous deep vein thrombosis or pulmonary embolism**; Raynaud phenomenon, skin tightening and reflux for systemic sclerosis; liver disease; congenital heart disease and murmurs in childhood; appetite suppressant or stimulant use; **freshwater exposure in a schistosomiasis-endemic area**; sickle cell disease or thalassaemia.
- Family history — heritable disease is autosomal dominant with incomplete penetrance.
- **Pregnancy plans and contraception**, which must be discussed at the first consultation for the reason given below.

3. Physical Examination

THE SIGNS

Every physical sign in pulmonary hypertension is on the right side of the heart, and the lungs are clear. That combination is the diagnosis.

Raised jugular venous pressure with a prominent a wave (a hypertrophied right atrium contracting hard) · **left parasternal heave** · **loud pulmonary component of the second sound** · right ventricular third or fourth sound · pulmonary regurgitation · **tricuspid regurgitation with giant v waves and a pulsatile liver** · ascites and peripheral oedema.

- **Then examine for the cause:** sclerodactyly, telangiectasia, calcinosis and Raynaud changes; fine crackles of fibrosis; clubbing; stigmata of chronic liver disease; central cyanosis and shunt murmurs; body habitus and neck circumference.

4. Investigations

- **Echocardiography is the screening test** — right ventricular size and function, estimated pulmonary artery pressure, tricuspid regurgitation, and exclusion of left heart disease and intracardiac shunts.
- **Right heart catheterisation is required to confirm the diagnosis and is mandatory before any targeted therapy is started.** Pre-capillary disease is defined by a **mean pulmonary artery pressure above 20 mmHg with a raised pulmonary vascular resistance and a normal wedge pressure** — the wedge is what separates group 1 from group 2, and it cannot be inferred from an echocardiogram.
- Electrocardiogram — right axis deviation, right ventricular hypertrophy, P pulmonale, right bundle branch block. Chest radiograph — enlarged central pulmonary arteries with pruned peripheral vessels and right ventricular enlargement.

THE ONE TEST NOT TO GET WRONG

Use a ventilation–perfusion scan, not computed tomographic pulmonary angiography, to screen for chronic thromboembolic disease.

Chronic organised thrombus is flat, wall-adherent and easily missed on a computed tomogram, whereas the perfusion defects it causes are conspicuous on a ventilation–perfusion scan.

This matters more than any other investigation in the workup, because chronic thromboembolic pulmonary hypertension is potentially cured by pulmonary endarterectomy — and a missed diagnosis means a curable patient is treated palliatively with vasodilators for years.

- **The rest of the workup:** pulmonary function tests with gas transfer; high-resolution computed tomography; overnight oximetry or sleep study; autoimmune screen; human immunodeficiency virus test; liver function and abdominal ultrasound; **schistosomiasis serology where exposure is plausible**; and genetic testing where the history suggests heritable disease.

- **For risk stratification and follow-up:** functional class, **six-minute walk distance**, and N-terminal pro-B-type natriuretic peptide. Risk category, reassessed at every visit, drives escalation of therapy.

5. Management

- **Refer to a specialist pulmonary hypertension centre.** The diagnosis requires catheterisation and the targeted drugs require specialist prescribing and monitoring; this is not a condition to manage alone.

THE PRESCRIBING ERROR TO AVOID

Targeted pulmonary vasodilators are for group 1 and group 4. They are harmful in group 2 and generally not indicated in group 3.

In pulmonary hypertension due to left heart disease, vasodilating the pulmonary circulation increases flow into a left ventricle that cannot accept it, and precipitates pulmonary oedema. In lung disease, they worsen ventilation–perfusion matching and hypoxaemia.

So the group must be established before a drug is prescribed — which is another reason the wedge pressure matters. Treat groups 2 and 3 by treating the heart or the lung disease.

- **Group 4: refer for assessment for pulmonary endarterectomy, which may be curative**; lifelong anticoagulation; balloon pulmonary angioplasty and riociguat for inoperable disease.

- **Group 1 targeted therapy:** endothelin receptor antagonists, phosphodiesterase-5 inhibitors, riociguat and prostacyclin pathway agents. **Most patients now start on combination therapy**, escalated according to risk. **Calcium channel blockers are used only in the small minority shown to be vasoreactive at catheterisation** — given empirically they cause harm.

- **Supportive care:** diuretics for right heart failure, oxygen for hypoxaemia, iron replacement, supervised exercise rehabilitation, vaccination, and caution with anaesthesia — these patients tolerate hypotension and hypoxia very badly, and the anaesthetist must be told.

- **Lung transplantation** for disease refractory to maximal therapy, referred before the patient becomes too unwell to be a candidate.

THE CONVERSATION THAT MUST HAPPEN EARLY

Pregnancy in pulmonary arterial hypertension carries a very high maternal mortality, because the circulatory changes of pregnancy and delivery cannot be met by a failing right ventricle.

Discuss effective contraception at the first consultation — bearing in mind that combined oral contraceptives raise thrombotic risk and that some targeted drugs, notably endothelin receptor antagonists, are teratogenic and reduce hormonal contraceptive efficacy.

A woman who becomes pregnant needs immediate specialist multidisciplinary care, not a routine antenatal clinic.

6. Teaching Points and Viva Questions

- Progressive breathlessness with a clear chest and a loud pulmonary second sound: request an echocardiogram.

- All the signs are right-sided, which is why the chest sounds normal.
- Exertional syncope means the right ventricle cannot increase output — an ominous sign.
- Catheterisation confirms the diagnosis, and the wedge pressure assigns the group.
- Ventilation–perfusion scan, not computed tomography, to find the curable group.
- Do not give pulmonary vasodilators for left heart disease.
- Raise contraception at the first visit.

Questions you should be able to answer:

- Why is her chest clear, and why does that make the diagnosis rather than exclude it?
- What does the normal wedge pressure tell you, and what would a raised one have meant?
- Which imaging do you use to exclude chronic thromboembolic disease, and why not the other?
- A patient with heart failure and a preserved ejection fraction has pulmonary hypertension on echocardiography. Should you start sildenafil?
- She tells you she is hoping to start a family. What do you say?

The Cardiology Block

Rheumatic fever and mitral stenosis, STEMI, decompensated heart failure, endocarditis, hypertension, valve disease, pericardial disease and the cardiomyopathies.

Cases 9–18 · 13,852 words

This block covers the cardiology teaching of both internal medicine courses. The **first course** supplies cases 9 and 14; the **second course** supplies cases 15 and 18, which extend the block into valvular, pericardial and myocardial disease.

Case	Lecture it serves
System opener: the cardiovascular history and examination	History taking in cardiovascular; physical examination of the cardiovascular system
Case 9 — Acute rheumatic fever	Rheumatic fever
Case 10 — Rheumatic mitral stenosis	Rheumatic heart disease
Case 11 — ST-elevation myocardial infarction	Ischaemic heart disease
Case 12 — Acute decompensated heart failure	Heart failure
Case 13 — Infective endocarditis	Infective endocarditis
Case 14 — Newly diagnosed hypertension	Hypertension
Case 15 — Aortic stenosis	Valvular heart disease, part 1
Case 16 — Chronic regurgitant valve disease	Valvular heart disease, part 2
Case 17 — Pericardial disease	Pericardial disease
Case 18 — The cardiomyopathies	Cardiomyopathies (two lectures)

Hypertensive urgency and emergency is deliberately held back for the seminar case in Part II, so that Case 14 can concentrate on assessment of the newly diagnosed patient. **Pulmonary thromboembolism** is Seminar 11, and **the four pillars of heart failure therapy** are set out in Case 12 — both are cross-referenced from the second-course cases rather than duplicated.

System Opener · The Cardiovascular History and Examination

The history

The five cardinal symptoms

Symptom	What to establish
Chest pain	Site, character, radiation, duration, provoking and relieving factors, and associated autonomic symptoms. Ischaemic pain is heavy or gripping, retrosternal, radiates to arm, neck or jaw, comes on with exertion and settles with rest. Pain that is sharp, positional, or reproduced by pressing on the chest wall is usually not ischaemic — but "atypical" pain in a diabetic or elderly patient still needs an electrocardiogram.
Breathlessness	Exertional tolerance, orthopnoea counted in pillows, paroxysmal nocturnal dyspnoea, and the New York Heart Association class. Ask what changed and over what period.
Palpitations	Ask the patient to tap out the rhythm on the desk. Fast or slow, regular or irregular, abrupt or gradual in onset and offset, and whether accompanied by syncope or chest pain.
Syncope	The circumstances matter more than the event. Syncope during exertion is aortic stenosis or hypertrophic cardiomyopathy until proved otherwise. Cardiac syncope is sudden, without warning, with rapid full recovery. A long prodrome with sweating and nausea suggests a vasovagal cause.
Oedema and weight gain	Ankles by evening, sacral swelling in a bedbound patient, abdominal distension, and rapid weight gain — the most sensitive marker of fluid retention.

Risk and background

- Smoking, diabetes mellitus, hypertension, dyslipidaemia, obesity, physical inactivity, chronic kidney disease, and **premature cardiovascular disease in a first-degree relative** — before 55 in men and 65 in women.
- **Rheumatic history:** recurrent sore throats in childhood, a murmur heard at school or before marriage, previous rheumatic fever, and whether monthly penicillin injections were ever given and for how long.
- Family history of sudden death, cardiomyopathy or inherited arrhythmia, and consanguinity where relevant.
- Full drug history including over-the-counter and herbal preparations, and previous procedures — angiography, stents, bypass grafting, valve surgery, pacemakers.

The examination

General and peripheral

- Breathlessness at rest, cachexia, malar flush, marfanoid habitus, central cyanosis, and the observation chart.
- **Hands:** clubbing (cyanotic congenital heart disease, infective endocarditis), splinter haemorrhages, Osler nodes, Janeway lesions, tendon xanthomata, tar staining, peripheral cyanosis.
- **Pulse:** rate, rhythm and character. A slow-rising pulse indicates aortic stenosis; a collapsing pulse aortic regurgitation; pulsus alternans severe left ventricular dysfunction. Check for **radio-radial and radio-**

femoral delay — the latter is the sign of coarctation, and it is missed by not looking for it.

- **Blood pressure in both arms**, with a postural reading. A wide pulse pressure suggests aortic regurgitation, a narrow one severe aortic stenosis.

The jugular venous pressure

Students lose more marks here than anywhere else in the cardiovascular examination. Position the patient at 45 degrees, turn the head slightly away, and look across rather than at the neck.

How to know it is venous, not arterial	The waveform and what it means
It is not palpable	a wave — atrial contraction. Absent in atrial fibrillation. Large in pulmonary hypertension and tricuspid stenosis. Cannon waves in complete heart block, when the atrium contracts against a closed tricuspid valve.
It has two peaks per cardiac cycle	v wave — atrial filling. Giant systolic v waves are the sign of tricuspid regurgitation, and are accompanied by a pulsatile liver.
It varies with position and respiration	Kussmaul sign — the venous pressure rises rather than falls on inspiration: constrictive pericarditis, and also tamponade and right ventricular infarction.
It is obliterated by gentle pressure at the base of the neck, and rises with pressure over the liver	A raised pressure with a normal waveform means fluid overload or right heart failure.

The praecordium

- **Inspect** for a midline sternotomy scar, a left lateral thoracotomy scar (the old closed mitral valvotomy), a pacemaker or defibrillator box, and visible pulsation.
- **Palpate the apex beat** — its position, and then its character. A **tapping** apex is a palpable first heart sound and means mitral stenosis. A **heaving, sustained** apex is pressure loading: aortic stenosis or hypertension. A **thrusting, displaced** apex is volume loading: mitral or aortic regurgitation. Feel for thrills and for a left parasternal heave of right ventricular hypertrophy.
- **Auscultate** all four areas with diaphragm and bell. Identify the first and second sounds by timing against the carotid pulse before attempting to describe anything else. Listen for added sounds — a third sound, a fourth sound, an opening snap, an ejection click, a metallic prosthetic click, a pericardial rub.
- **Finish** at the lung bases, the liver (pulsatile in tricuspid regurgitation), for ascites, at the sacrum and ankles, at all peripheral pulses, and with the fundi and a urine dipstick where endocarditis is possible.

Murmurs — the table to know

Lesion	Timing and character	Best heard	Accentuating manoeuvre
Aortic stenosis	Ejection systolic, harsh, radiating to the carotids	Right second intercostal space	Sitting forward, expiration
Aortic regurgitation	Early diastolic, soft, high-pitched, decrescendo	Left sternal edge	Sitting forward, breath held in expiration
Mitral stenosis	Mid-diastolic, low-pitched rumble with presystolic accentuation	Apex, with the bell	Left lateral position, expiration
Mitral regurgitation	Pansystolic, blowing, radiating to the axilla	Apex	Left lateral position, expiration
Tricuspid regurgitation	Pansystolic with giant v waves and a pulsatile liver	Left sternal edge	Louder on inspiration
Ventricular septal defect	Harsh pansystolic with a thrill	Left sternal edge	Expiration
Hypertrophic cardiomyopathy	Ejection systolic, no carotid radiation	Left sternal edge	Louder on standing and Valsalva, softer on squatting

The rule that saves you in an examination: right-sided murmurs are louder on **in**spiration, left-sided murmurs on **ex**piration. And a murmur you cannot classify should still be described accurately — timing, site, radiation and what it does with respiration — because an accurate description scores more than a confident wrong label.

Case 9 · Acute Rheumatic Fever

CLINICAL VIGNETTE

A **12-year-old boy** from a rural district is brought in with fever and joint pain. Three weeks ago he had a severe sore throat that was not treated. Six days ago his right knee became hot, swollen and so painful he could not bear weight; that settled over two days and the pain moved to his left ankle, then to his left wrist.

His mother says he tires easily and has become breathless climbing stairs. He is the fourth of seven children in a crowded household.

On examination: temperature 38.4 °C, heart rate 128/min while asleep, respiratory rate 24/min. The left wrist is swollen and exquisitely tender. There is a **soft pansystolic murmur at the apex radiating to the axilla** that was not previously known. Over the trunk there are faint pink rings with clear centres that have changed position since admission.

1. Focused History

- **The preceding infection.** A sore throat two to four weeks earlier — this latent period is what makes the connection easy to miss, because the throat has long recovered. Ask whether antibiotics were given and completed.
- **Characterise the arthritis.** Rheumatic arthritis is **migratory**, affects large joints asymmetrically, is exquisitely painful relative to the swelling, and settles in each joint within days. It responds dramatically to anti-inflammatory drugs — so dramatically that failure to respond should make you question the diagnosis.
- **Symptoms of carditis:** breathlessness, orthopnoea, reduced exercise tolerance, chest pain, palpitations.
- **Symptoms of chorea:** clumsiness, dropping objects, deteriorating handwriting, emotional lability and behavioural change. Chorea may appear months after the infection, long after everything else has settled, and parents often report it as naughtiness.
- **Previous episodes and prophylaxis.** A previous attack is the strongest risk factor for another, and each recurrence damages the valves further. Ask specifically whether monthly injections were given and when they stopped.
- Household crowding, access to healthcare, and other affected family members.

2. Physical Examination

- **Fever and a tachycardia out of proportion to the fever**, persisting during sleep.
- **Arthritis** — hot, swollen, extremely tender large joints, asymmetric and migratory. Document which joints and when, because the migration itself is diagnostic.
- **Carditis** — the feature that determines the patient's future. Listen for a **new or changed murmur**: mitral regurgitation is the commonest, then aortic regurgitation. Listen for a pericardial rub and a third sound, and look for signs of heart failure. A resting tachycardia may be the only sign.
- **Erythema marginatum** — pink macules with a clear centre and a serpiginous margin, on the trunk and proximal limbs, **sparing the face**, evanescent and changing position over hours. Easily missed on darker skin, so look in good light.

- **Subcutaneous nodules** — firm, painless, mobile, over extensor surfaces and the occiput. Uncommon but strongly associated with severe carditis.
- **Sydenham chorea** — purposeless jerky movements, hypotonia, the **milkmaid grip** (irregular squeezing of the examiner's fingers) and the darting tongue that cannot be held protruded.

3. Diagnosis: The Revised Jones Criteria

BEFORE YOU APPLY THE CRITERIA

The criteria differ according to how common rheumatic fever is in the population. **This region is classified as moderate-to-high risk**, so the lower thresholds below apply — using the low-risk criteria here will cause you to miss cases.

Diagnosis requires **evidence of a preceding streptococcal infection**, plus either **two major** criteria or **one major and two minor**.

Major criteria	Minor criteria (moderate-to-high risk population)
Carditis — clinical or subclinical on echocardiography	Monoarthralgia
Arthritis — polyarthritis, or monoarthritis, or polyarthralgia in this risk group	Fever of 38 °C or above
Chorea	Erythrocyte sedimentation rate 30 mm/h or more, or raised C-reactive protein
Erythema marginatum	Prolonged PR interval for age
Subcutaneous nodules	

- **Two exceptions:** chorea alone, and indolent carditis, are sufficient without evidence of preceding streptococcal infection, because both appear so long after the throat infection that serology may already have fallen.
- A recurrence in a patient with established rheumatic heart disease may be diagnosed on **three minor criteria** with evidence of streptococcal infection.

4. Differential Diagnosis

Diagnosis	The feature that discriminates it
Septic arthritis	One joint, not migratory, systemically unwell, pus on aspiration. Aspirate any single hot joint before assuming rheumatic fever.
Brucellosis	Endemic in this region. Unpasteurised dairy or animal contact, sacroiliac or hip involvement, hepatosplenomegaly, undulant fever, positive serology.
Juvenile idiopathic arthritis	Persistent rather than migratory, symmetric small joints, morning stiffness, and a much longer course.
Infective endocarditis	Also produces fever and a murmur. Blood cultures and echocardiography separate them, and the two can be confused fatally.
Systemic lupus erythematosus	Rash on the face rather than sparing it, cytopenias, renal involvement, positive antinuclear antibody.
Sickle cell vaso-occlusive crisis	Known disease, bone rather than joint pain, anaemia with a raised reticulocyte count.
Reactive and post-streptococcal reactive arthritis	Shorter latent period, non-migratory, poor response to salicylates, and no carditis.

5. Investigations

- **Evidence of streptococcal infection:** throat swab culture and rapid antigen test — often negative by now — and **antistreptolysin O and anti-DNase B titres**, ideally paired two weeks apart to demonstrate a rise. A single raised titre is weaker evidence than a rising one.
- **Inflammatory markers:** erythrocyte sedimentation rate and C-reactive protein, used both for diagnosis and to follow the course.
- **Electrocardiogram** — a prolonged PR interval is a minor criterion. Higher grades of block can occur and are usually transient.
- **Echocardiography in every suspected case, even when no murmur is audible.** Subclinical carditis is a major criterion and changes both the diagnosis and the duration of prophylaxis. This is the single most important investigation.
- **Blood cultures** to exclude endocarditis, complete blood count, and joint aspiration if a single joint is involved.
- Chest radiograph if there is any suspicion of cardiac failure.

6. Management

Treat the streptococcus

- **Benzathine benzylpenicillin** as a single intramuscular dose, or oral penicillin V for ten days. Give it even when the throat swab is negative — you are eradicating carriage, not treating pharyngitis. Use a macrolide if penicillin-allergic.

Treat the inflammation

- Aspirin in anti-inflammatory doses, or naproxen, for the arthritis. The response is usually rapid and complete.
- Corticosteroids are used for severe carditis with heart failure, although the evidence that they alter long-term valve outcome is weak. Treat the heart failure itself on its merits.
- Chorea is usually self-limiting over weeks to months. Reassure the family that it is not behavioural. Carbamazepine or sodium valproate for severe or disabling movements.
- Rest during the acute illness, with gradual return to activity guided by the carditis.

SECONDARY PROPHYLAXIS — THE INTERVENTION THAT ACTUALLY CHANGES THE OUTCOME

The acute attack is rarely what harms the patient. **Recurrences are.** Each one adds valve damage, and the risk is highest in the first five years.

Benzathine benzylpenicillin intramuscularly every four weeks — every three weeks in high-risk patients or where breakthrough occurs. Oral penicillin V twice daily is an inferior alternative reserved for those who refuse injections.

Duration: no carditis — 5 years, or until age 21, whichever is longer · carditis without residual valve disease — 10 years, or until age 21, whichever is longer · **carditis with persistent valve disease — 10 years, or until age 40**, and often lifelong.

Register the patient in a recall system, warn the family that stopping early is the commonest reason young adults present with severe mitral stenosis, and arrange dental review.

7. Teaching Points and Viva Questions

- The arthritis moves; the carditis stays. The joints cause the symptoms, the heart causes the disease.
- Echocardiography in every suspected case — subclinical carditis is invisible at the bedside and alters the prophylaxis by decades.
- An unexplained resting tachycardia during sleep is carditis until proved otherwise.
- Aspirate any single hot joint. Septic arthritis destroys a joint in days and does not wait for serology.
- The most valuable thing you can do for this boy is not what you prescribe today, but ensuring he receives an injection every four weeks for the next ten years.

Questions you should be able to answer:

- State the Jones criteria and explain why they differ between populations.
- Why can chorea be diagnosed without evidence of streptococcal infection?
- What are the two most useful investigations here, and why?
- How long will this boy need prophylaxis, and on what does that depend?
- His antistreptolysin O titre is normal. Does that exclude the diagnosis?

Case 10 · Rheumatic Mitral Stenosis

CLINICAL VIGNETTE

A **28-year-old woman** attends with six months of breathlessness on exertion, now limiting her after one flight of stairs. Over the past two weeks she has felt her heart racing irregularly and has coughed up small amounts of blood twice. She is planning a pregnancy.

She had rheumatic fever at the age of nine and received penicillin injections for four years before they were stopped.

On examination: she has a **malar flush**. The pulse is 116/min and irregularly irregular, of small volume. Blood pressure 104/70 mmHg. The jugular venous pressure is raised. The apex beat is undisplaced and **tapping**. There is a left parasternal heave and a loud pulmonary second sound. On auscultation with the bell in the left lateral position: a **loud first heart sound, an opening snap, and a low-pitched rumbling mid-diastolic murmur** at the apex.

1. Focused History

- **Functional class** — quantify in stairs or metres, and establish over what period it changed. Deterioration over weeks usually means a new arrhythmia rather than progression of the valve lesion.
- **Orthopnoea, paroxysmal nocturnal dyspnoea and haemoptysis.** Haemoptysis in mitral stenosis arises from raised pulmonary venous pressure and rupture of dilated bronchial veins.
- **Palpitations** and their relation to the deterioration. **Atrial fibrillation is the event that unmasks mitral stenosis**, because losing atrial contraction and shortening diastole together collapse left ventricular filling.
- **Embolic events** — transient neurological symptoms, stroke, a cold painful limb, flank pain. The large fibrillating left atrium is an excellent source of thrombus.
- **Compression symptoms** from a dilated left atrium: hoarseness from recurrent laryngeal nerve compression, and dysphagia.
- **Pregnancy plans.** This is not a social question here — it is central to management, and the answer changes the timing of intervention.
- Rheumatic fever history and, specifically, when prophylaxis stopped.

2. Physical Examination

The classical signs, and what produces each

Sign	Mechanism
Malar flush	Low cardiac output with cutaneous vasodilatation
Small-volume, irregularly irregular pulse	Fixed low stroke volume, with atrial fibrillation
Tapping apex beat, undisplaced	A palpable loud first heart sound. The left ventricle is not dilated — it is underfilled.
Loud first heart sound	The stenosed, still-mobile valve closes from a wide-open position
Opening snap	The pliable valve opening abruptly. Its absence suggests a calcified, immobile valve.
Mid-diastolic rumble with presystolic accentuation	Turbulent flow across the narrowed valve; the presystolic component is atrial contraction and is lost once atrial fibrillation develops
Left parasternal heave, loud pulmonary second sound	Pulmonary hypertension and right ventricular hypertrophy
Raised venous pressure, pulsatile liver, ascites, oedema	Right heart failure — the end of the natural history

THREE BEDSIDE SIGNS OF SEVERITY

A shorter interval between the second sound and the opening snap — a high left atrial pressure forces the valve open sooner.

A longer murmur — the gradient persists throughout diastole.

Signs of pulmonary hypertension, and the presence of atrial fibrillation.

Note that the **loudness of the murmur says nothing about severity**. A very tight valve with low flow may be almost silent.

3. Differential Diagnosis

Diagnosis	The feature that discriminates it
Left atrial myxoma	A "tumour plop" rather than an opening snap, positional symptoms, systemic features and weight loss. Excluded by echocardiography.
Austin Flint murmur of aortic regurgitation	A diastolic rumble at the apex, but with a collapsing pulse, wide pulse pressure and an early diastolic murmur at the left sternal edge.
Tricuspid stenosis	Louder on inspiration, with giant a waves in the venous pulse.
Other causes of breathlessness in a young woman	Anaemia, thyrotoxicosis, pulmonary embolism, primary pulmonary hypertension.

4. Investigations

- **Electrocardiogram:** P mitrale — a broad bifid P wave — while sinus rhythm persists, then atrial fibrillation. Right axis deviation and right ventricular hypertrophy indicate pulmonary hypertension.
- **Chest radiograph — reading the film:** a straightened left heart border from the enlarged left atrial appendage, a **double density** behind the right heart border, **splaying of the carina**, upper lobe blood

diversion, Kerley B lines, and sometimes valve calcification. The heart is often not enlarged overall, which surprises students.

- **Echocardiography is the diagnostic and grading test.** It gives the valve area, the mean transmitral gradient, the pulmonary artery pressure, the left atrial size, and the presence of associated regurgitation.
- **Transoesophageal echocardiography** before any intervention, to exclude left atrial appendage thrombus, and to score valve morphology for suitability for balloon valvuloplasty.
- Complete blood count, thyroid function (atrial fibrillation), renal function, and natriuretic peptide where the cause of breathlessness is uncertain.

Valve area	Grade
Above 1.5 cm^2	Mild
1.0–1.5 cm^2	Moderate
Below 1.0 cm^2	Severe (the normal valve area is 4–6 cm^2)

5. Management

Medical

- **Rate control** with a beta blocker, or digoxin in atrial fibrillation. Slowing the heart lengthens diastole and improves filling — the opposite of the instinct to treat breathlessness by increasing output.
- **Anticoagulation with a vitamin K antagonist.** In atrial fibrillation with rheumatic mitral stenosis, **direct oral anticoagulants are contraindicated** and warfarin must be used. This is one of the few remaining absolute indications for warfarin and is a favourite examination question.
- Diuretics and salt restriction for pulmonary congestion.
- **Continue or restart secondary penicillin prophylaxis**, and maintain dental hygiene.

Intervention

- **Percutaneous balloon mitral valvuloplasty** is the treatment of choice for a pliable, non-calcified valve with little regurgitation and no left atrial thrombus. It is highly effective and avoids surgery — particularly valuable in a young woman planning pregnancy.
- **Surgical commissurotomy or valve replacement** when the valve is calcified, when there is significant mitral regurgitation, or when thrombus is present.
- **Indications:** symptomatic severe stenosis; and asymptomatic severe stenosis with pulmonary hypertension, new atrial fibrillation, or a planned pregnancy.

WHY THE PREGNANCY QUESTION MATTERED

Cardiac output rises by up to 50% and heart rate increases through pregnancy. Across a **fixed** stenotic valve, both changes raise left atrial pressure sharply, and women commonly decompensate in the second trimester or at delivery.

Severe mitral stenosis should be treated before conception. Counsel this patient now, not when she is 20 weeks pregnant.

6. Teaching Points and Viva Questions

- Mitral stenosis is a disease of diastole. Anything that shortens diastole — tachycardia, atrial fibrillation, fever, pregnancy, exercise — decompensates it.
- The interval from the second sound to the opening snap gauges severity; the loudness of the murmur does not.
- You will not hear the murmur with the diaphragm, or with the patient lying flat. Bell, left lateral, expiration.
- Warfarin, not a direct oral anticoagulant, when atrial fibrillation accompanies rheumatic mitral stenosis.
- An undisplaced apex in a breathless patient with a raised venous pressure should turn your attention to the mitral valve and the right heart.

Questions you should be able to answer:

- Explain each of the classical signs in terms of the underlying haemodynamics.
- Why does atrial fibrillation cause such abrupt deterioration in this condition?
- Why is warfarin required rather than a direct oral anticoagulant?
- Which patients are suitable for balloon valvuloplasty, and what must be excluded first?
- She becomes pregnant before any intervention. What are the risks and how would you manage her?

Case 11 · ST-Elevation Myocardial Infarction

CLINICAL VIGNETTE

A **58-year-old man** presents with 90 minutes of central chest pain, described as a weight on his chest, radiating to the left arm and jaw. He is sweating, nauseated and frightened. The pain began at rest and has not eased.

He smokes 20 cigarettes a day, has type 2 diabetes mellitus and hypertension, and his father died of a heart attack at 52.

On arrival: he is grey and clammy. Heart rate 92/min, blood pressure 148/88 mmHg in the right arm and 144/86 mmHg in the left, respiratory rate 22/min, oxygen saturation 96% on air. Heart sounds are normal with no murmur. Chest is clear.

Electrocardiogram, recorded 6 minutes after arrival: ST elevation of 3 mm in leads V1 to V4, with reciprocal ST depression in leads II, III and aVF.

1. Focused History — Taken While Treatment Proceeds

- **The time of symptom onset.** This is the single most important number in the history, because it determines the reperfusion strategy and the expected benefit. Establish it precisely, and record it.
- Characterise the pain, and ask specifically about features that suggest an alternative: **tearing pain radiating to the back** with maximal intensity at onset (aortic dissection), pleuritic or positional pain relieved by sitting forward (pericarditis), pain after vomiting (oesophageal rupture).
- Previous angina, infarction, angiography, stents or bypass grafting — and whether this pain is the same as before but worse.
- Whether aspirin has already been given, by the patient or by the ambulance crew.
- **Cocaine or amphetamine use**, particularly in a younger patient, which changes management.
- **Bleeding risk and contraindications to fibrinolysis**, in case primary angioplasty is not available within the time window: previous intracranial bleed, recent stroke, surgery, trauma or gastrointestinal bleeding, and anticoagulant use.

2. Physical Examination

Brief and targeted. It should not delay the electrocardiogram or reperfusion.

- **Blood pressure in both arms** and all peripheral pulses — a significant difference raises aortic dissection, which would make antiplatelet and anticoagulant therapy catastrophic.
- **Jugular venous pressure** — raised with clear lung fields in right ventricular infarction.
- **Auscultation** for a new murmur (mitral regurgitation from papillary muscle dysfunction, or a ventricular septal defect), a third or fourth heart sound, and a pericardial rub.
- **Lung bases**, to assign the Killip class, which predicts mortality directly.

Killip class	Findings
I	No crackles, no third heart sound
II	Crackles in less than half the lung fields, or a third heart sound, or a raised venous pressure
III	Frank pulmonary oedema
IV	Cardiogenic shock

3. Investigations

THE PRIORITY

The electrocardiogram must be recorded and interpreted within 10 minutes of arrival. Everything else follows from it.

ST elevation of 1 mm or more in two contiguous limb leads, or 2 mm in two contiguous chest leads (1.5 mm in women), or a new left bundle branch block in a patient with a compatible history.

Do not wait for the troponin. In ST-elevation infarction the troponin adds nothing to the decision and delays reperfusion.

Localise the infarct

Leads with ST elevation	Territory	Artery
V1–V4	Anterior / anteroseptal	Left anterior descending
I, aVL, V5–V6	Lateral	Circumflex
II, III, aVF	Inferior	Right coronary (or circumflex)
Tall R waves and ST depression in V1–V2	Posterior — record posterior leads V7–V9 to confirm	Circumflex or right coronary
ST elevation in V4R	Right ventricular — record right-sided leads in every inferior infarct	Proximal right coronary

- **Bloods:** troponin (for later confirmation and infarct size), complete blood count, urea and electrolytes, glucose and glycated haemoglobin, lipid profile, coagulation screen.
- **Portable chest radiograph** — but never allow it to delay reperfusion. It is looking for pulmonary oedema and for a widened mediastinum.
- **Echocardiography** — regional wall motion abnormalities, ejection fraction, and mechanical complications. Urgently if the diagnosis is uncertain or the patient is shocked.

4. Differential Diagnosis

Diagnosis	The feature that discriminates it
Aortic dissection	Tearing pain radiating to the back, maximal at onset, pulse or blood pressure differential, widened mediastinum. Must be excluded before anticoagulation.
Acute pericarditis	Sharp pleuritic pain relieved by sitting forward, saddle-shaped ST elevation in all territories with PR depression, no reciprocal change.
Pulmonary embolism	Pleuritic pain, hypoxia, sinus tachycardia, right heart strain pattern rather than territorial ST elevation.
Takotsubo cardiomyopathy	Preceded by intense emotional or physical stress, apical ballooning on echocardiography, unobstructed coronary arteries.
Oesophageal spasm or rupture	Related to swallowing or preceded by vomiting; surgical emphysema in rupture.
Early repolarisation	A young, well patient; concave elevation with notched J points, no reciprocal change, and no evolution on serial tracings.

5. Management

Immediate, at the bedside

- **Aspirin 300 mg chewed**, plus a second antiplatelet agent — ticagrelor, prasugrel or clopidogrel — according to the reperfusion pathway.
- **Anticoagulation** as specified by the local pathway.
- **Oxygen only if the saturation is below 90%.** Routine oxygen in the non-hypoxic patient confers no benefit and may cause harm.
- **Nitrate** sublingually or by infusion for pain — **withheld if the patient is hypotensive, has a right ventricular infarct, or has taken a phosphodiesterase inhibitor within 48 hours.**
- **Morphine** with an antiemetic for pain not relieved by nitrate.
- **Continuous cardiac monitoring beside a defibrillator.** Ventricular fibrillation is the commonest cause of death in the first hour and is entirely treatable if witnessed and monitored.

Reperfusion — the decision that determines outcome

Strategy	When, and the target
Primary percutaneous coronary intervention	Preferred whenever it can be delivered within 120 minutes of first medical contact. Target time from arrival at a capable centre to balloon inflation is under 60–90 minutes.
Fibrinolysis	When primary angioplasty cannot be delivered within that window. Give within 30 minutes of arrival, then transfer for angiography within 2–24 hours — or immediately if reperfusion fails.
Timing from onset	Benefit is greatest in the first 2–3 hours and persists to 12 hours. Beyond 12 hours, reperfusion is still indicated if symptoms or ST elevation continue, or the patient is unstable.

- **Absolute contraindications to fibrinolysis:** any previous intracranial haemorrhage; ischaemic stroke within 6 months; cerebral vascular malformation or tumour; major trauma, surgery or head injury within 3 weeks; gastrointestinal bleeding within a month; known bleeding disorder; **suspected aortic dissection**; non-compressible puncture within 24 hours.
- **Right ventricular infarction** — the patient is preload-dependent. **Give fluid, and avoid nitrates, diuretics and opioids**, all of which can precipitate profound hypotension.

Complications to anticipate

Timing	Complication
First hours	Ventricular fibrillation and ventricular tachycardia; bradycardia and atrioventricular block, particularly in inferior infarction; cardiogenic shock.
Days 2–5	Heart failure, atrial fibrillation, pericarditis, mural thrombus.
Days 3–7	Mechanical complications — papillary muscle rupture with acute mitral regurgitation, ventricular septal rupture, free wall rupture with tamponade. Each presents as sudden deterioration with a new murmur and each is a surgical emergency.
Weeks to months	Left ventricular aneurysm, Dressler syndrome, heart failure, ventricular arrhythmia.

Secondary prevention — started before discharge, not at follow-up

- **Dual antiplatelet therapy** for 12 months, then aspirin indefinitely.
- **High-intensity statin**, regardless of the baseline cholesterol.
- **Beta blocker** and **angiotensin-converting enzyme inhibitor**, both started early and titrated.
- **Mineralocorticoid receptor antagonist** if the ejection fraction is 40% or less with heart failure or diabetes.
- **Cardiac rehabilitation** — as effective as several of the drugs and referred to far less often. **Smoking cessation** with pharmacological support. Glycaemic and blood pressure control.
- Echocardiography before discharge; reassessment of the ejection fraction at 6–12 weeks for consideration of an implantable defibrillator if it remains at 35% or less.
- Practical advice the patient will actually ask about: driving restrictions, return to work, and resumption of sexual activity.

6. Teaching Points and Viva Questions

- Electrocardiogram within ten minutes. Time is myocardium, and the clock starts at symptom onset, not at arrival.
- Reciprocal ST depression supports a true infarction and helps distinguish it from pericarditis.
- Every inferior infarct gets right-sided leads before anyone gives a nitrate.

- A new murmur three days after infarction is a mechanical complication until proved otherwise, and needs a surgeon, not a diuretic.
- Check both arms once, at the start. Thrombolysing a dissection is among the worst errors in medicine.

Questions you should be able to answer:

- Localise this infarct and name the artery.
- Primary angioplasty is 3 hours away. What do you do and why?
- The blood pressure falls to 80/50 after a nitrate in an inferior infarct. Explain what happened.
- Distinguish the electrocardiogram of pericarditis from that of infarction.
- Name the four drugs he should leave hospital taking, and the indication for each.

Case 12 · Acute Decompensated Heart Failure

CLINICAL VIGNETTE

A **72-year-old woman** with known heart failure and a previous anterior myocardial infarction presents with four days of worsening breathlessness. She now sleeps upright in a chair and wakes at night gasping. Her ankles are swollen and she has gained 5 kg in ten days.

Two weeks ago she began taking a non-steroidal anti-inflammatory drug bought over the counter for knee pain, and she reduced her own diuretic dose because she disliked the trips to the bathroom.

On examination: she is sitting forward and speaking in short sentences. Heart rate 112/min and irregularly irregular, blood pressure 156/94 mmHg, respiratory rate 28/min, oxygen saturation 89% on air. The jugular venous pressure is 8 cm above the sternal angle. The apex is displaced to the anterior axillary line. There is a **third heart sound** and a pansystolic murmur at the apex. Crackles to the mid-zones bilaterally, and pitting oedema to the thighs.

1. Focused History

- **Quantify the change:** pillow count, distance walked, and the weight gain — which is the most sensitive marker of fluid retention and the easiest for the patient to measure at home.
- **Then find the precipitant.** Decompensation always has a cause, and treating the congestion without finding the cause simply returns the patient to hospital.

Precipitant	What to ask or check
Non-adherence, or self-adjusted diuretic	The commonest cause of all. Ask non-judgementally what she is actually taking, not what is on the list.
New arrhythmia, usually atrial fibrillation	Palpitations, an irregular pulse, and the electrocardiogram.
Ischaemia or infarction	Chest pain — which may be absent, particularly in diabetes and in the elderly.
Infection	Fever, cough, dysuria.
Drugs that cause fluid retention or depress the myocardium	Non-steroidal anti-inflammatory drugs, corticosteroids, verapamil and diltiazem, thiazolidinediones, some chemotherapy.
Excess salt or fluid intake	Diet, and the sudden weight rise.
High-output states	Anaemia, thyrotoxicosis, pregnancy, arteriovenous fistula.
Worsening renal function, uncontrolled hypertension, pulmonary embolism	Recent blood results and blood pressure readings.

2. Physical Examination

- **The jugular venous pressure is the single most reliable bedside sign of congestion** and the one most often not attempted. Measure it, record it in centimetres, and repeat it daily.
- Displaced, thrusting apex; a **third heart sound** — the most specific auscultatory sign of decompensation; a functional pansystolic murmur of mitral regurgitation from ventricular dilatation.
- Bibasal crackles that do not clear with coughing, and dullness at the bases from pleural effusions.
- Tender pulsatile hepatomegaly, ascites, and pitting oedema — ankles in the ambulant patient, **sacrum in the bedbound patient**, which is why you must roll them.

- **Assess perfusion as well as congestion:** cool peripheries, narrow pulse pressure, pulsus alternans, confusion and oliguria all indicate low output.

Classify the patient in one of four boxes. It takes seconds and directs treatment better than any score.

	Dry — no congestion	Wet — congested
Warm — adequately perfused	Compensated. Optimise oral therapy.	Warm and wet — the commonest presentation. Diuresis, with vasodilators if hypertensive.
Cold — poorly perfused	Underfilled. Reconsider the diagnosis; consider cautious fluid.	Cold and wet — the dangerous group. Requires inotropic support and critical care input.

3. Differential Diagnosis

Diagnosis	The feature that discriminates it
Pneumonia	Fever, focal consolidation, raised inflammatory markers, and a normal natriuretic peptide.
Exacerbation of chronic obstructive pulmonary disease	Wheeze dominates, sputum purulence, hyperinflated film, and a smoking history.
Pulmonary embolism	Sudden onset, pleuritic pain, hypoxia with a clear film, risk factors.
Renal failure with fluid overload	The same congestion, but with a very high creatinine — and it responds to dialysis, not to more diuretic.
Cirrhosis or nephrotic syndrome	Oedema and effusions with a normal or low jugular venous pressure, plus the stigmata of the underlying disease.

4. Investigations

- **Natriuretic peptide.** Its greatest value is a **negative** result: a normal level in an untreated breathless patient essentially excludes heart failure as the cause.
- **Electrocardiogram** — atrial fibrillation, ischaemia, prior infarction, left ventricular hypertrophy, and QRS duration for later resynchronisation decisions. A completely normal tracing makes heart failure unlikely.
- **Chest radiograph — reading the film:** cardiomegaly with a cardiothoracic ratio above 0.5, upper lobe blood diversion, **Kerley B lines**, perihilar alveolar shadowing in a bat's-wing distribution, pleural effusions, and fluid tracking into the horizontal fissure.
- **Bloods:** complete blood count (anaemia both causes and results from heart failure), urea, electrolytes and creatinine before and during diuresis, liver function (congestive hepatopathy), thyroid function, glucose, troponin, and **iron studies** — iron deficiency is common, symptomatic and treatable even without anaemia.
- **Echocardiography** — essential in every new case, and in decompensation of unclear cause. It gives the ejection fraction, which divides management into two entirely different pathways, and identifies valve disease and regional wall motion abnormality.

5. Management

The first hour

- Sit the patient upright. Oxygen only if hypoxic, targeting 94–98%.
- **Intravenous loop diuretic** — furosemide 40–80 mg, or one to two and a half times the usual home dose in a patient already taking it. Give it intravenously; gut absorption is unreliable in a congested patient.
- **Nitrate infusion** if the patient is hypertensive with pulmonary oedema — it reduces preload and afterload rapidly and is often more immediately effective than the diuretic.
- **Continuous positive airway pressure** for severe pulmonary oedema with persisting hypoxia or exhaustion. It reduces the need for intubation.
- **Inotropes and vasopressors only for hypoperfusion**, in a monitored setting with senior involvement. They are not a treatment for breathlessness.
- **Treat the precipitant:** rate control the atrial fibrillation, stop the non-steroidal anti-inflammatory drug, treat infection or ischaemia.

Monitoring

- **Daily weight before breakfast** is the best single measure of response — aim for 0.5–1 kg loss per day. Strict fluid balance, daily electrolytes and creatinine, and a repeated jugular venous pressure.
- Expect the creatinine to rise modestly during effective decongestion. A small rise is not a reason to stop diuresis in a patient who is still congested.

THE FOUR PILLARS OF CHRONIC THERAPY

These four drug classes each reduce mortality independently, and all four should be started and titrated in every patient with a reduced ejection fraction who tolerates them:

1. An angiotensin receptor–neprilysin inhibitor, or an angiotensin-converting enzyme inhibitor · **2.** A beta blocker · **3.** A mineralocorticoid receptor antagonist · **4.** A sodium–glucose co-transporter 2 inhibitor.

Diuretics relieve symptoms but **do not prolong life** — they are added on top for congestion, not instead. Do not start a beta blocker during acute decompensation, but do not stop an established one unless the patient is in shock.

For preserved ejection fraction: diuretics for congestion, a sodium–glucose co-transporter 2 inhibitor, and rigorous treatment of hypertension, atrial fibrillation, obesity and sleep apnoea.

Before discharge

- Euvolaemic, on oral diuretic for at least 24 hours, with a written **daily weight chart and an action plan** telling her what to do if she gains 2 kg in three days.
- A titration plan for the four pillars, a documented medication review, and an explicit instruction to avoid non-steroidal anti-inflammatory drugs — with an alternative offered for her knee.
- **Follow-up within seven days**, which measurably reduces readmission. Vaccination, cardiac rehabilitation, and consideration of devices at reassessment.

6. Teaching Points and Viva Questions

- The jugular venous pressure and the daily weight will tell you more about this patient than any blood test.
- A normal natriuretic peptide in an untreated breathless patient sends you looking for another diagnosis.
- Always name the precipitant. "Heart failure" is not a complete diagnosis.
- Diuretics treat symptoms; the four pillars treat the disease.
- Oedema with a normal venous pressure is not heart failure — look at the liver, the kidneys and the albumin.

Questions you should be able to answer:

- Name the two precipitants in this history and explain the mechanism of each.
- Why give the diuretic intravenously rather than orally?
- Her creatinine rises from 90 to 120 during diuresis. What do you do?
- Which of her drugs prolong life and which only relieve symptoms?
- How does management differ if the ejection fraction is 55% rather than 30%?

Case 13 · Infective Endocarditis

CLINICAL VIGNETTE

A **42-year-old man** with known rheumatic mitral valve disease presents with five weeks of fever, drenching night sweats, malaise and 7 kg of weight loss. He has been treated twice by his general practitioner with short courses of antibiotics, each of which improved things briefly. He had two teeth extracted seven weeks ago.

On examination: temperature 38.2 °C, pallor, heart rate 96/min. There are **splinter haemorrhages** in two fingernails and tender nodules on the pulps of two fingers. There is a pansystolic murmur at the apex which the notes record as previously soft and which is now loud. The spleen is palpable 3 cm below the costal margin. Urine dipstick shows blood ++ without protein.

1. Focused History

- **Duration and tempo.** A subacute course over weeks with sweats and weight loss suggests a viridans streptococcus on a damaged valve; a fulminant course over days suggests Staphylococcus aureus on a normal one.
- **The predisposing lesion:** rheumatic valve disease, prosthetic valve, previous endocarditis, congenital heart disease, degenerative valve disease, hypertrophic cardiomyopathy.
- **The portal of entry:** dental work and dental hygiene, skin infection, intravenous drug use, indwelling vascular catheters, haemodialysis, recent urological or gastrointestinal procedures, colorectal disease (which is associated with *Streptococcus gallolyticus* and warrants colonoscopy).
- **Regionally important exposures:** unpasteurised milk and dairy, and contact with sheep, goats or camels — **Brucella** and **Coxiella burnetii** are important causes of culture-negative endocarditis here and will be missed unless specifically requested.
- **Recent antibiotics** — the commonest reason blood cultures are sterile, and the reason this man has had five weeks of illness without a diagnosis.
- **Embolic symptoms:** transient neurological events, sudden limb pain, flank or left upper quadrant pain, sudden visual loss, and back pain suggesting spondylodiscitis.

2. Physical Examination

- **Fever and a murmur together is endocarditis until proved otherwise.** A **new or changed** murmur is the finding that matters; a longstanding unchanged murmur is much weaker evidence.
- **Peripheral stigmata** — uncommon now but classical: splinter haemorrhages; **Osler nodes**, which are painful and on the finger pulps; **Janeway lesions**, which are painless and on palms and soles; Roth spots on the retina; conjunctival and palatal petechiae; clubbing in longstanding disease.
- **Splenomegaly**, signs of heart failure, and a full neurological examination for embolic deficits.
- Examine the **teeth and gums**, injection sites, and any indwelling line.
- **Dipstick the urine** — microscopic haematuria from immune complex glomerulonephritis or renal infarction is a minor criterion and takes thirty seconds.

3. Investigations

THE INVESTIGATION THAT DECIDES EVERYTHING

Three sets of blood cultures from three separate venepuncture sites, before any antibiotic is given. In a subacute presentation, space them over at least an hour — there is time, and the diagnosis depends on it.

The bacteraemia of endocarditis is continuous, so cultures need not be timed to fever spikes. If the patient has already received antibiotics and is stable, **it is correct to stop them and re-culture after several days** rather than treat blindly for six weeks without an organism.

- **Serology for culture-negative causes:** Brucella, Coxiella burnetii, Bartonella, Legionella, and fungal cultures. Request these early in this region rather than as a last resort.
- **Echocardiography.** Transthoracic first; **transoesophageal** if that is negative and suspicion persists, if there is a prosthetic valve, or if a complication is suspected. Look for vegetations, abscess, new valve regurgitation and prosthetic dehiscence. **A negative study does not exclude the diagnosis** — repeat it in 5–7 days if suspicion remains.
- **Electrocardiogram, repeated daily. A new atrioventricular block means an aortic root abscess** and is an indication for urgent surgical assessment. This is the single most important electrocardiographic finding in the disease.
- Complete blood count (normocytic anaemia, neutrophilia), C-reactive protein and erythrocyte sedimentation rate for trend, urea and electrolytes, liver function, urinalysis and microscopy, rheumatoid factor and complement.
- Imaging for emboli where clinically indicated: brain, abdomen, and spine. Computed tomography and nuclear imaging have a defined role in prosthetic valve disease.

The modified Duke criteria

Major criteria	Minor criteria
Typical organism from two separate blood cultures, or persistently positive cultures	A predisposing cardiac lesion, or intravenous drug use
Positive Coxiella burnetii serology	Fever of 38 °C or above
Echocardiographic evidence: vegetation, abscess, or new prosthetic dehiscence	Vascular phenomena — emboli, mycotic aneurysm, intracranial or conjunctival haemorrhage, Janeway lesions
New valvular regurgitation	Immunological phenomena — glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
	Microbiological evidence not meeting a major criterion

Definite endocarditis: two major, or one major and three minor, or five minor criteria.

4. Management

- **Treatment is by a team** — cardiology, microbiology or infectious diseases, and cardiac surgery involved from the outset, not after complications appear.
- **Empirical therapy after cultures are taken**, guided by whether the valve is native or prosthetic and by local resistance patterns; then narrowed to the organism. **Intravenous therapy for four to six weeks** in

most cases.

- Monitor for response: daily examination for a new murmur or heart failure, daily electrocardiogram for conduction change, repeat cultures to confirm clearance, and monitoring of renal function and antibiotic levels.

Indication for surgery	Detail
Heart failure	Severe regurgitation or valve obstruction causing failure — the commonest and most urgent indication.
Uncontrolled infection	Abscess, false aneurysm, fistula, enlarging vegetation, persisting fever and positive cultures beyond 7–10 days of appropriate therapy, or a fungal or highly resistant organism.
Prevention of embolism	A vegetation greater than 10 mm with an embolic event despite antibiotics, or a very large vegetation greater than 15 mm.

Prevention

- **Dental hygiene and regular dental review** in every patient with a predisposing lesion — of far greater value than antibiotic prophylaxis.
- Antibiotic prophylaxis before dental procedures involving gingival manipulation is now restricted to the **highest-risk group**: prosthetic valves, previous endocarditis, and certain congenital heart disease.

5. Teaching Points and Viva Questions

- Fever plus a murmur means blood cultures before antibiotics. The single commonest reason this diagnosis is delayed is a well-meant prescription.
- A new atrioventricular block is an aortic root abscess until proved otherwise — do a daily electrocardiogram.
- A normal transthoracic echocardiogram does not exclude endocarditis.
- In this region, culture-negative endocarditis should prompt Brucella and Q fever serology early rather than late.
- Half of the peripheral stigmata are named after people; none of them is as useful as three sets of blood cultures.

Questions you should be able to answer:

- He has already had antibiotics. How does that change your approach to the cultures?
- Apply the Duke criteria to this patient and state your level of certainty.
- The PR interval lengthens on day four. What has happened and what do you do?
- List the three broad indications for surgery.
- Which patients still receive antibiotic prophylaxis before dental work, and why was the guidance narrowed?

Case 14 • Newly Diagnosed Hypertension

CLINICAL VIGNETTE

A **46-year-old man** is found to have a blood pressure of 168/104 mmHg at a workplace screening. He feels entirely well. In clinic a week later, after five minutes seated, it is 172/106 mmHg in the right arm and 168/104 mmHg in the left.

He works long hours at a desk, eats most meals outside the home, and does no regular exercise. He smokes 15 cigarettes a day. His father had a stroke at 58. His wife reports that he snores heavily and sometimes seems to stop breathing at night, and he falls asleep in the afternoon.

On examination: body mass index 33 kg/m^2, waist circumference increased. Pulse 78/min regular. No radio-femoral delay. Apex beat is forceful but undisplaced. No bruits. Fundoscopy shows arteriolar narrowing and arteriovenous nipping.

1. Focused History

Establish that it is real, and how long it has been present

- Previous readings — at dental visits, pre-employment checks, pharmacies, or during a previous illness. Patients often have years of unrecognised readings.
- Any home readings, and how the device was used.

Screen for end-organ damage

- Chest pain, exertional breathlessness, orthopnoea, palpitations, transient neurological symptoms, visual disturbance, claudication, and frothy urine or nocturia.

Screen for a secondary cause

Ask about	Cause it suggests
Snoring with witnessed apnoeas, daytime somnolence, morning headache	Obstructive sleep apnoea — the commonest secondary cause, and present in this patient
Muscle weakness, cramps, polyuria, unprovoked hypokalaemia	Primary aldosteronism — far commoner than traditionally taught
Episodic headache with palpitations and sweating, labile pressure	Phaeochromocytoma
Weight gain with thin skin, bruising, proximal weakness, striae	Cushing syndrome
Haematuria, oedema, known renal disease, family history of polycystic kidneys	Renal parenchymal disease
Young onset, abrupt onset, resistant hypertension, flash pulmonary oedema, renal bruit	Renovascular disease
Young patient with leg claudication or radio-femoral delay	Coarctation of the aorta
Drugs: non-steroidal anti-inflammatory drugs, combined oral contraceptive, corticosteroids, decongestants, ciclosporin, erythropoietin, liquorice, cocaine, amphetamines, some herbal preparations	Drug-induced hypertension — always ask, including over-the-counter and traditional remedies

Quantify total cardiovascular risk

- Smoking, diabetes, lipids, family history of premature vascular disease, alcohol, salt intake, physical activity, and body weight. **You are treating the total risk, not the number.**

2. Physical Examination

HOW TO MEASURE THE BLOOD PRESSURE

Everything downstream depends on this being done properly.

Seated and rested for **five minutes**, back supported, legs uncrossed, arm supported at heart level, no talking. A **cuff bladder encircling at least 80% of the arm** — a cuff that is too small is the commonest cause of a falsely high reading in a large arm. **Both arms at the first visit**, then use the higher-reading arm thereafter. Repeat and take the average. A **standing reading** after one and three minutes in the elderly and in diabetes.

- Body mass index and waist circumference; features of Cushing syndrome; **radio-femoral delay**; renal, carotid and femoral bruits; palpable kidneys.
- **Apex beat character** — a sustained, heaving apex suggests left ventricular hypertrophy. Listen for a fourth heart sound.
- **Fundoscopy.** Grade the retinopathy: arteriolar narrowing, arteriovenous nipping, then haemorrhages and exudates, and finally papilloedema — which changes the diagnosis to a hypertensive emergency and the timescale from months to hours.
- Peripheral pulses and a full neurological examination for evidence of previous events.

3. Investigations

- **Confirm the diagnosis out of the office** with ambulatory monitoring, or home readings twice daily for a week. This detects **white-coat hypertension**, which would otherwise commit a well man to lifelong drugs, and **masked hypertension**, which would otherwise be missed entirely. Out-of-office thresholds are lower than clinic thresholds.
- **End-organ assessment:** urinalysis and urine albumin-to-creatinine ratio, urea, electrolytes, creatinine and estimated glomerular filtration rate, and an **electrocardiogram** for left ventricular hypertrophy. Echocardiography if the tracing is abnormal or heart failure is suspected.
- **Cardiovascular risk profile:** fasting glucose or glycated haemoglobin, and a lipid profile.
- **Investigate for a secondary cause** if the patient is under 40, has resistant or abruptly worsening hypertension, has unprovoked hypokalaemia, or has suggestive features. Start with the **aldosterone-to-renin ratio**, plasma or urinary metanephrines, renal imaging, and — in this patient — a **sleep study**.

Grade	Clinic blood pressure
Grade 1	140–159 / 90–99 mmHg
Grade 2	160–179 / 100–109 mmHg
Grade 3	180 mmHg or more / 110 mmHg or more

Be aware that guidelines differ: some define hypertension from 130/80 mmHg while others retain 140/90 mmHg. Know which your institution follows and say so when asked — the examiner is testing whether you know that a threshold is a convention, not a fact of nature.

4. Management

Lifestyle — offered to everyone, and worth more than students assume

- Weight reduction; **salt below 5 g per day**; a diet rich in fruit, vegetables and low-fat dairy; regular aerobic activity of at least 150 minutes weekly; alcohol reduction; and smoking cessation — which does not lower blood pressure but reduces cardiovascular risk more than most drugs.
- Treating the obstructive sleep apnoea in this man may improve his blood pressure and will certainly improve his daytime function.

Drug treatment

- **When to start:** immediately in grade 2 and grade 3; in grade 1 when there is established cardiovascular disease, end-organ damage, diabetes, chronic kidney disease, or high estimated risk. This patient has grade 2 hypertension with retinopathy and starts today.
- **Start with two drugs, ideally in a single combination tablet.** Combination therapy from the outset achieves control faster than sequential single agents and improves adherence.
- **First-line combinations:** an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, plus either a calcium channel blocker or a thiazide-like diuretic.
- In patients of Black African or Caribbean origin, begin with a calcium channel blocker or thiazide-like diuretic rather than a renin–angiotensin blocker.
- **Beta blockers are not first line** for uncomplicated hypertension; reserve them for angina, previous infarction, heart failure, rate control, or pregnancy.
- In pregnancy: labetalol, nifedipine or methyldopa. **Renin–angiotensin system blockers are absolutely contraindicated.**

Targets and follow-up

- Aim below 140/90 mmHg for everyone, and below 130/80 mmHg if tolerated, particularly with diabetes, chronic kidney disease or established vascular disease. Be less aggressive in the frail elderly, and check for postural drop before intensifying.
- Recheck urea, electrolytes and creatinine **one to two weeks after starting** a renin–angiotensin blocker or diuretic. A creatinine rise beyond about 30% or a falling potassium prompts review.
- Review monthly until controlled, then at least annually with reassessment of risk and end-organ damage.

RESISTANT HYPERTENSION

Blood pressure above target on **three drugs including a diuretic at optimal doses**. Before adding a fourth, check in this order:

Adherence — by far the commonest explanation, and best explored without accusation · **measurement technique and cuff size** · **white-coat effect**, confirmed with ambulatory monitoring · **salt intake, alcohol, and interfering drugs** · **an undiagnosed secondary cause**, especially primary aldosteronism and sleep apnoea.

Once those are excluded, **spironolactone** is the fourth agent of choice.

5. Teaching Points and Viva Questions

- Do not diagnose lifelong hypertension on clinic readings alone. Confirm it outside the clinic.
- Measure it properly. Wrong cuff, unsupported arm and no rest period produce a wrong number, and everything that follows is built on it.
- Both arms once, at the first visit. Thereafter, the higher arm.
- Unprovoked hypokalaemia in a hypertensive patient means primary aldosteronism until proved otherwise.
- Snoring with daytime somnolence is not a lifestyle detail — it is a diagnosis with a treatment.
- You are treating total cardiovascular risk. Stopping the cigarettes will help this man more than any milligram adjustment.

Questions you should be able to answer:

- How would you confirm the diagnosis before committing him to treatment?
- Which secondary cause does this history point to, and how would you test for it?
- What would you start him on today, and why two drugs rather than one?
- His potassium is 3.1 mmol/L and he takes no diuretic. What now?
- At review his pressure is 158/96 on three drugs. Work through your approach.

Case 15 · Aortic Stenosis

CLINICAL VIGNETTE

A **74-year-old man** describes eight months of breathlessness on exertion, now limiting him to about 50 metres on the flat. On three occasions he has felt lightheaded while walking uphill, and last week he **lost consciousness briefly while climbing stairs**, recovering within seconds. He also describes a tightness across the chest on exertion that settles with rest.

On examination: the pulse is **slow-rising and of small volume**. Blood pressure 112/92 mmHg. The apex beat is **heaving but undisplaced**. There is a systolic thrill in the right second intercostal space. **The second heart sound is barely audible.** There is a fourth heart sound and a **harsh, late-peaking ejection systolic murmur radiating to both carotids**.

Electrocardiogram: left ventricular hypertrophy with repolarisation change. **Echocardiography:** peak aortic velocity 4.4 m/s, mean gradient 52 mmHg, valve area 0.7 cm^2, ejection fraction 55%.

WHY THE HISTORY MATTERS MORE THAN THE NUMBERS

Exertional syncope, exertional angina and exertional breathlessness — each of the three is a marker of severe disease, and each arises because a fixed valve cannot increase cardiac output on demand.

The onset of symptoms transforms the prognosis. Asymptomatic severe aortic stenosis is compatible with years of normal life; **untreated symptomatic severe aortic stenosis carries a mortality of roughly 50% at two years.** The symptom, not the gradient, is what triggers referral for intervention.

Which is why the single most important thing you will say to a patient under surveillance is: **tell us the day you become breathless, dizzy or develop chest pain on exertion.**

1. Focused History

- **Characterise the triad**, and quantify the exercise tolerance in metres or flights of stairs against the patient's own baseline.
- **Syncope**: establish that it was exertional, sudden, without warning, and with rapid complete recovery — the pattern of cardiac syncope.
- **Heart failure symptoms:** orthopnoea, paroxysmal nocturnal dyspnoea, oedema.
- **Gastrointestinal bleeding** — the association of aortic stenosis with colonic angiodysplasia and acquired von Willebrand abnormality (**Heyde syndrome**) is real and worth asking about in an anaemic patient with a murmur.
- **Establish the aetiology:** age and calcific degeneration in the elderly; **a bicuspid valve** in a younger patient, which may be familial and is associated with aortic root dilatation and coarctation; and **previous rheumatic fever**, which usually affects the mitral valve too.
- **Comorbidity, frailty and function** — because the whole management decision is which intervention, not whether to intervene, and that depends on the patient rather than the valve.

2. Physical Examination

Sign	Mechanism
Slow-rising, small-volume pulse	Prolonged, obstructed ejection. May be misleadingly normal in the elderly, whose stiff arteries transmit a sharper upstroke
Narrow pulse pressure	Reduced stroke volume
Heaving, undisplaced apex	Pressure-loaded, concentrically hypertrophied but not dilated ventricle
Soft or absent second heart sound	The calcified valve cannot close audibly. This is one of the most reliable bedside markers of severity
Fourth heart sound	Atrial contraction against a stiff hypertrophied ventricle
Late-peaking ejection systolic murmur radiating to the carotids	Turbulent flow across the stenosis; the later the peak, the tighter the valve
Reversed splitting of the second sound	Delayed aortic valve closure

BEDSIDE MARKERS OF SEVERITY

Soft or absent second heart sound · a late-peaking murmur · a slow-rising pulse · a narrow pulse pressure · a fourth heart sound · signs of heart failure.

The loudness of the murmur is not one of them. A very tight valve with a failing ventricle generates little flow and therefore little noise, so the quietest murmurs can accompany the most severe disease.

3. Differential Diagnosis

Diagnosis	The feature that discriminates it
Hypertrophic cardiomyopathy	The murmur does not radiate to the carotids, the pulse is jerky rather than slow-rising, and the murmur is louder on standing and Valsalva and softer on squatting — the reverse of aortic stenosis. See Case 18.
Aortic sclerosis	An ejection systolic murmur with a normal pulse character, normal second sound and no significant gradient. Common in the elderly and not obstructive.
Mitral regurgitation	Pansystolic rather than ejection systolic, radiating to the axilla, with a displaced thrusting apex.
Pulmonary stenosis	Loudest at the left sternal edge and louder on inspiration, with a right ventricular impulse.
Ventricular septal defect	Harsh pansystolic murmur at the left sternal edge with a thrill.

4. Investigations

- **Electrocardiogram:** left ventricular hypertrophy with strain, left bundle branch block, and atrial fibrillation in late disease.
- **Chest radiograph:** often unremarkable. Look for a **calcified valve**, post-stenotic dilatation of the ascending aorta, and cardiomegaly only when the ventricle has failed.
- **Echocardiography is the diagnostic and grading investigation.**

Severe aortic stenosis — any of	Value
Peak aortic velocity	4.0 m/s or above
Mean transvalvular gradient	40 mmHg or above
Valve area	1.0 cm^2 or below (or 0.6 cm^2/m^2 indexed)

- **The trap of low-flow, low-gradient stenosis:** a failing ventricle cannot generate a high gradient across even a very tight valve, so the gradient understates the severity. Where the valve area is small but the gradient low and the ejection fraction reduced, **dobutamine stress echocardiography** distinguishes true severe stenosis from pseudo-severe disease.

- **Before intervention:** coronary angiography or computed tomographic coronary imaging; **computed tomography for transcatheter planning** — annulus size, valve calcification, coronary heights and vascular access; natriuretic peptide; dental assessment; and a formal frailty assessment.

5. Management

WHAT MEDICINE CAN AND CANNOT DO

No drug alters the natural history of aortic stenosis. The treatment is to replace the valve.

Statins do not slow progression. Diuretics relieve congestion but do not help the obstruction.

And be careful with vasodilators. Nitrates, angiotensin-converting enzyme inhibitors and other vasodilators can cause profound hypotension and syncope in severe stenosis, because cardiac output is fixed and cannot rise to compensate for a fall in systemic resistance. Hypertension still needs treating — but cautiously, at low doses, with review.

Indications for intervention

- **Severe stenosis with any symptom** — this patient qualifies on all three counts.

- **Asymptomatic severe stenosis with:** an ejection fraction below 50%; an abnormal exercise test with symptoms or a fall in blood pressure; very severe stenosis with a velocity above 5 m/s; rapid progression; or a markedly raised natriuretic peptide.

- Severe stenosis in a patient undergoing cardiac surgery for another indication.

Which intervention

- **Surgical aortic valve replacement** or **transcatheter aortic valve implantation** — the decision belongs to a multidisciplinary heart team, weighing age, surgical risk, anatomy, frailty, comorbidity and life expectancy. Transcatheter implantation is now used across a wide spectrum of surgical risk, not only in inoperable patients.

- **Balloon valvuloplasty** has no lasting role in calcific adult disease; it is a bridge in extremis, or a treatment for non-calcific congenital stenosis in the young.

- **A mechanical prosthesis requires lifelong warfarin — not a direct oral anticoagulant**, which is contraindicated. A bioprosthesis does not require long-term anticoagulation but degenerates over time, which is the central trade-off to explain to a patient choosing between them.

Surveillance and prevention

- Echocardiographic follow-up at intervals determined by severity — annually in severe asymptomatic disease, less often in mild.
- **Dental hygiene and regular dental review**; antibiotic prophylaxis for the highest-risk group only, as in Case 13.
- **Educate the patient to report the first symptom immediately**, and record that you have done so.

6. Teaching Points and Viva Questions

- Exertional syncope in an older patient is aortic stenosis until proved otherwise.
- A soft second heart sound means severe disease; a loud murmur means nothing.
- Symptoms are the trigger for surgery, and untreated symptomatic severe stenosis kills half of patients within two years.
- Vasodilators in fixed obstruction cause syncope.
- A low gradient with a small valve area and a poor ventricle needs a stress study, not reassurance.
- Mechanical valves need warfarin, never a direct oral anticoagulant.

Questions you should be able to answer:

- Explain each of this man's physical signs in terms of the underlying haemodynamics.
- How would you distinguish this murmur from that of hypertrophic cardiomyopathy at the bedside?
- His valve area is 0.8 cm^2 but the mean gradient is only 25 mmHg and his ejection fraction is 35%. What is going on and what do you do?
- A colleague starts ramipril for his blood pressure of 150/95. What is your concern?
- He is asymptomatic with a velocity of 4.2 m/s and normal function. What do you do?

Case 16 · Chronic Regurgitant Valve Disease

CLINICAL VIGNETTE

A **42-year-old man**, known since childhood to have a **bicuspid aortic valve**, describes a year of gradually worsening breathlessness on exertion and an uncomfortable awareness of his own heartbeat, worst when lying on his left side. He has no chest pain and has never had rheumatic fever.

On examination: the pulse is **collapsing** in character. Blood pressure **160/48 mmHg**. Visible carotid pulsation is present, and the nail beds pulsate on gentle compression. The apex beat is **displaced to the anterior axillary line and thrusting**. There is a **soft early diastolic murmur at the left sternal edge, audible only with the patient sitting forward with the breath held in expiration**, and a separate low-pitched mid-diastolic murmur at the apex.

Echocardiography: severe aortic regurgitation; left ventricular end-diastolic diameter 68 mm; ejection fraction 48%; aortic root 48 mm.

THE GOVERNING PRINCIPLE OF THIS CASE

In stenosis, the patient tells you when to operate. **In regurgitation, the ventricle does.**

A regurgitant ventricle compensates by dilating, and it does so **silently for years**. By the time breathlessness appears, irreversible myocardial damage may already have occurred and the benefit of surgery is reduced.

So the timing of surgery in chronic regurgitation is decided by serial measurement of ventricular size and function on echocardiography, not by waiting for symptoms. This patient is already symptomatic with an ejection fraction of 48% and a markedly dilated ventricle — he has been under-surveilled.

1. Acute or Chronic? — Ask This First

	Chronic regurgitation	Acute severe regurgitation
Presentation	Years of compensation, then gradual breathlessness	Sudden pulmonary oedema and cardiogenic shock
Murmur	Loud and striking, with dramatic peripheral signs	Soft or absent — there is no time for a large gradient or for peripheral signs to develop
Heart size	Dilated	Normal — the ventricle has had no time to remodel
Causes	Bicuspid valve, rheumatic disease, aortic root dilatation, degenerative disease, mitral valve prolapse	Infective endocarditis · aortic dissection · papillary muscle or chordal rupture after infarction · trauma
Management	Surveillance, then elective surgery	Surgical emergency

The quiet murmur with a normal-sized heart in a shocked patient is the dangerous one. Students expect severe valve disease to be loud, and acute severe regurgitation is therefore missed.

2. Focused History

- Exertional breathlessness, orthopnoea, and **awareness of the heartbeat**, which reflects the large stroke volume of chronic aortic regurgitation.
- **Angina** can occur in aortic regurgitation without coronary disease, because a low diastolic pressure reduces coronary perfusion.
- **Aetiology:** bicuspid valve and its family history; rheumatic fever; **connective tissue disease — Marfan and Ehlers–Danlos syndromes**, with a family history of aortic dissection or sudden death; ankylosing spondylitis; hypertension; previous endocarditis; and recent dental or invasive procedures.

- For **mitral regurgitation:** previous rheumatic fever, mitral valve prolapse, previous myocardial infarction, and features of a dilated ventricle causing secondary regurgitation.

3. Physical Examination

Aortic regurgitation — and the eponyms, each with a mechanism

All of these arise from **one thing: a very large stroke volume ejected into a low-resistance circulation, giving a wide pulse pressure**. Learn the mechanism and the list becomes trivial.

Sign	What it is
Collapsing (water-hammer) pulse	Rapid upstroke and rapid collapse; best felt with the arm raised
Wide pulse pressure	High systolic, low diastolic — here 160/48
Corrigan sign	Visible vigorous carotid pulsation
de Musset sign	Head nodding with each beat
Quincke sign	Capillary pulsation visible in the nail bed
Müller sign	Pulsation of the uvula
Duroziez sign	To-and-fro murmur over the femoral artery under light compression
Traube sign	"Pistol-shot" femoral sounds
Displaced thrusting apex	Volume-loaded, dilated ventricle
Early diastolic decrescendo murmur	At the left sternal edge, sitting forward, breath held in expiration — you will not hear it otherwise
Austin Flint murmur	A mid-diastolic rumble at the apex from the regurgitant jet striking the mitral valve. Do not mistake it for mitral stenosis — there is no loud first sound and no opening snap

Mitral regurgitation

- **Pansystolic murmur at the apex radiating to the axilla**, loudest in expiration in the left lateral position; a soft first heart sound; a third heart sound; a displaced thrusting apex; atrial fibrillation; and, in advanced disease, the signs of pulmonary hypertension and right heart failure.
- **Mitral valve prolapse** gives a **mid-systolic click with a late systolic murmur**, and the timing of the click moves with manoeuvres that alter ventricular volume.

4. Investigations

- **Electrocardiogram:** left ventricular hypertrophy; atrial fibrillation in mitral disease.
- **Chest radiograph:** cardiomegaly, and **dilatation of the aortic root and ascending aorta** in aortic regurgitation.
- **Echocardiography, performed serially, with the numbers recorded and compared.** Severity of regurgitation, **left ventricular end-diastolic and end-systolic dimensions, and ejection fraction** — these are the values on which the surgical decision rests. Transoesophageal study to define the mechanism of mitral regurgitation and the feasibility of repair.

- **Cardiac magnetic resonance imaging** for accurate ventricular volumes and regurgitant fraction where echocardiography is equivocal.
- **Computed tomographic or magnetic resonance imaging of the aorta** whenever the root is dilated, with surveillance thereafter.
- Exercise testing to unmask symptoms in a patient who claims to be asymptomatic; natriuretic peptide.

5. Management

Medical

- **Vasodilators help here, in contrast to aortic stenosis.** Treat hypertension with an angiotensin-converting enzyme inhibitor or receptor blocker or a dihydropyridine calcium channel blocker; reducing afterload reduces the regurgitant fraction.
- **Use beta blockers cautiously in aortic regurgitation** — slowing the heart lengthens diastole and therefore increases the time available for regurgitation. They are, however, indicated for aortopathy in Marfan syndrome, alongside an angiotensin receptor blocker and root surveillance.
- Treat heart failure and atrial fibrillation conventionally. **Medical therapy does not substitute for surgery in severe disease** — it manages symptoms while the decision is made.

Indications for surgery — learn these numbers

Lesion	Operate if
Severe aortic regurgitation	Symptoms; or ejection fraction 50% or below; or left ventricular end-diastolic diameter above about 70 mm or end-systolic above about 50 mm (or the indexed equivalents); or aortic root 55 mm or more — with lower thresholds in Marfan syndrome and bicuspid valve disease
Severe primary mitral regurgitation	Symptoms; or ejection fraction 60% or below; or left ventricular end-systolic diameter 40 mm or more; or new atrial fibrillation or pulmonary hypertension

- **In degenerative mitral disease, repair is strongly preferred to replacement** — it preserves ventricular function, avoids a prosthesis and anticoagulation, and has better long-term outcomes. Refer to a centre with a high repair rate.
- **Transcatheter edge-to-edge repair** is an option in selected patients with secondary mitral regurgitation and heart failure, or where surgical risk is prohibitive.
- Endocarditis prevention and dental care; secondary penicillin prophylaxis where the disease is rheumatic (Case 9).

6. Teaching Points and Viva Questions

- In regurgitation the ventricle tells you when to operate, not the patient.
- Every eponymous sign of aortic regurgitation comes from a wide pulse pressure.
- You will not hear the murmur unless the patient sits forward and holds the breath out.
- The Austin Flint murmur is not mitral stenosis.

- Acute severe regurgitation is quiet, has a normal-sized heart, and is a surgical emergency.
- Vasodilators help in regurgitation and harm in stenosis.
- Repair the mitral valve rather than replace it wherever possible.

Questions you should be able to answer:

- Explain his blood pressure of 160/48 and list four signs that follow from it.
- Why does he have a mid-diastolic murmur at the apex, and how do you know it is not mitral stenosis?
- He says he feels well enough. Give three findings that would still make you refer him for surgery.
- A patient with endocarditis becomes acutely breathless with a barely audible murmur and a normal chest radiograph. What has happened?
- Why is a beta blocker a mixed blessing in aortic regurgitation?

Case 17 · Pericardial Disease

CLINICAL VIGNETTE

A **34-year-old man** presents with four days of sharp central chest pain. **It is worse when he lies flat and on deep inspiration, and eases when he sits forward.** It radiates to his left shoulder and up the side of his neck. He had a coryzal illness a week earlier.

On examination: temperature 37.9 °C, heart rate 96/min, blood pressure 124/78 mmHg. There is a **scratchy sound at the left sternal edge**, best heard with the patient leaning forward, which comes and goes.

Electrocardiogram: widespread **concave (saddle-shaped) ST elevation with PR segment depression**, present in both anterior and inferior leads, with ST depression and PR elevation in lead aVR. No Q waves.

C-reactive protein 68 · troponin mildly raised · echocardiography: small pericardial effusion, normal ventricular function.

1. Four Syndromes, One Pericardium

- **Acute pericarditis** — inflammation, with pain and a rub.
- **Pericardial effusion** — fluid, which may be silent.
- **Cardiac tamponade** — fluid under enough pressure to impair filling. A **haemodynamic** diagnosis, not a volume one.
- **Constrictive pericarditis** — a thickened, scarred pericardium restricting filling chronically.

2. Acute Pericarditis

DIAGNOSTIC CRITERIA

Two of the following four:

Characteristic chest pain — sharp, pleuritic, **worse lying flat and relieved by sitting forward**, often radiating to the trapezius ridge, which is close to specific because the phrenic nerve supplies both.

A pericardial rub — scratchy, often triphasic, best at the left sternal edge with the patient leaning forward. It is **evanescent**, so its absence at one examination means little.

Electrocardiographic change — widespread ST elevation with PR depression.

A new or worsening pericardial effusion.

The electrocardiogram — how it differs from infarction

	Pericarditis	ST-elevation myocardial infarction
Distribution	Widespread, crossing territories	Territorial, matching one artery
Shape of ST elevation	Concave, saddle-shaped	Convex, tombstoned
PR segment	Depressed — and elevated in aVR	Normal
Reciprocal ST depression	Absent, except in aVR and V1	Present
Q waves	Absent	Develop
Evolution	ST normalises, then diffuse T inversion	Territorial, with Q wave formation

Causes

- **Viral and idiopathic** — the great majority in young patients.

- **Tuberculous pericarditis** — a leading cause worldwide and an important one in this region. Subacute onset, fever, weight loss, a large effusion, and a high risk of progression to constriction. **Consider it in every patient who is not straightforwardly viral.**
- Bacterial and purulent; **uraemic**; after myocardial infarction — early, or late as **Dressler syndrome**; after cardiac surgery or a percutaneous procedure; malignant infiltration; autoimmune disease including lupus and rheumatoid arthritis; radiotherapy; drugs; hypothyroidism; trauma.

Investigation

- Electrocardiogram, C-reactive protein and erythrocyte sedimentation rate, **troponin**, complete blood count, renal function, thyroid function, chest radiograph.
- **Echocardiography in every patient** — for effusion, for tamponade physiology, and for ventricular function.
- **A raised troponin indicates myopericarditis.** If ventricular function is also impaired, the diagnosis is perimyocarditi, and the patient should be admitted and monitored.
- **Tuberculosis workup** where the picture is subacute or the effusion large: interferon-gamma release assay, chest imaging, and pericardial fluid for adenosine deaminase, acid-fast staining and culture if drained. Autoimmune screen; blood cultures if febrile; cross-sectional imaging in complicated cases.

Treatment

THE REGIMEN

A non-steroidal anti-inflammatory drug — aspirin or ibuprofen — at anti-inflammatory dose with a taper, PLUS colchicine for three months.

Colchicine roughly halves the rate of recurrence and is the single most important addition to the treatment of acute pericarditis in recent decades. It is regularly omitted.

Corticosteroids increase the rate of recurrence and are not first-line. Reserve them for specific indications — autoimmune disease, uraemic pericarditis, pregnancy, or a genuine contraindication to anti-inflammatory drugs.

Restrict exercise until symptoms have resolved and markers normalised — for longer in athletes and in myopericarditis.

- **Admit** if there is fever above 38 °C, a subacute onset, a large effusion or tamponade, myopericarditis, immunosuppression, trauma, anticoagulation, or failure to respond to a week of treatment.
- **Treat the specific cause:** antituberculous therapy for tuberculous disease (with corticosteroids in selected cases to reduce constriction); drainage and antibiotics for purulent pericarditis; intensified dialysis for uraemic disease.
- **Recurrent pericarditis:** colchicine for longer, then corticosteroids, then **interleukin-1 antagonists**, which are highly effective in colchicine-resistant disease.

3. Cardiac Tamponade

EMERGENCY

Tamponade is a clinical diagnosis. The echocardiogram supports it; it does not make it, and waiting for one can kill the patient.

Beck triad: hypotension · raised jugular venous pressure · muffled heart sounds. Add **tachycardia** and **pulsus paradoxus greater than 10 mmHg**, and the diagnosis is made at the bedside.

Electrocardiogram: sinus tachycardia, low voltage, and sometimes **electrical alternans**. **Echocardiogram:** effusion with right atrial and right ventricular diastolic collapse, a dilated inferior vena cava, and respirophasic septal shift.

Management: urgent pericardiocentesis, echo-guided where possible, or surgical drainage.

Give fluid. Avoid diuretics, avoid vasodilators, and avoid positive pressure ventilation if you can — this is a preload-dependent state and every one of those reduces preload. The instinct to treat a raised venous pressure with a diuretic is the error to avoid.

4. Constrictive Pericarditis

- Presents as **right heart failure with preserved ventricular systolic function** — progressive oedema, ascites often out of proportion to peripheral oedema, hepatomegaly, fatigue and breathlessness.
- **Tuberculosis is a leading cause worldwide**, along with previous cardiac surgery, radiotherapy, and any cause of chronic pericarditis.
- Signs: raised venous pressure with a **prominent y descent**, **Kussmaul sign** (venous pressure rises on inspiration), a **pericardial knock**, atrial fibrillation, ascites and hepatomegaly.

	Tamponade	Constriction
Jugular venous waveform	Absent y descent	Prominent y descent
Kussmaul sign	Absent	Present
Pulsus paradoxus	Prominent	Usually absent or mild
Onset	Acute or subacute	Chronic, over months
Treatment	Drainage	Pericardiectomy

- **Distinguishing constriction from restrictive cardiomyopathy** is the hard part, and it matters because one is surgically curable: look for pericardial thickening or calcification on computed tomography, septal bounce and respirophasic variation in filling on echocardiography, and characteristic changes on cardiac magnetic resonance imaging. Natriuretic peptide is typically **lower** in constriction than in restrictive cardiomyopathy.
- **Treatment is pericardiectomy**, with diuretics for symptomatic relief in the interim and antituberculous therapy where relevant.

5. Teaching Points and Viva Questions

- Pain relieved by sitting forward and radiating to the trapezius ridge is pericardial.
- Widespread saddle ST elevation with PR depression and no reciprocal change is not an infarct.
- Colchicine for three months, for everybody. Steroids make recurrence more likely.

- A raised troponin means the myocardium is involved and changes the disposition.
- Tamponade is diagnosed at the bedside; give fluid, not furosemide.
- Absent y descent means tamponade; prominent y descent and Kussmaul sign mean constriction.
- Think of tuberculosis in any pericardial disease here that is not clearly viral.

Questions you should be able to answer:

- Give four ways this electrocardiogram differs from that of an anterior infarction.
- What will you prescribe, for how long, and what will you deliberately not prescribe?
- His troponin is raised. Does that change your management?
- Two days later his blood pressure is 84/60 with a raised venous pressure and quiet heart sounds. What is happening and what do you do?
- How would you distinguish constrictive pericarditis from restrictive cardiomyopathy?

Case 18 · The Cardiomyopathies

CLINICAL VIGNETTE

A **28-year-old man** is referred after **losing consciousness while playing football**. He has noticed breathlessness and chest tightness on hard exertion for a year and had assumed he was unfit. **His brother died suddenly at the age of 32, also while playing football.** His parents are first cousins.

On examination: the pulse is **jerky** — a brisk upstroke with a mid-systolic dip. Blood pressure 118/76 mmHg. The apex beat has a **double impulse**. There is a fourth heart sound and an **ejection systolic murmur at the left sternal edge that does not radiate to the carotids**. **The murmur becomes louder when he stands and on Valsalva, and quieter when he squats.**

Electrocardiogram: left ventricular hypertrophy with deep T wave inversion in the lateral leads. **Echocardiography:** asymmetric septal hypertrophy of 19 mm, systolic anterior motion of the mitral valve, and a resting left ventricular outflow tract gradient of 60 mmHg.

1. Three Phenotypes

	Dilated	Hypertrophic	Restrictive
Problem	Systolic failure of a dilated ventricle	Hypertrophy with dynamic outflow obstruction and arrhythmia	Impaired filling with a non-dilated ventricle and preserved systolic function
Causes	Idiopathic and genetic · alcohol · peripartum · myocarditis · anthracyclines and trastuzumab · iron overload, including transfused thalassaemia · thyroid disease · sustained tachycardia · sarcoidosis · cocaine · thiamine deficiency	Autosomal dominant sarcomeric protein mutations. The commonest cause of sudden cardiac death in young athletes	Amyloidosis · sarcoidosis · haemochromatosis · endomyocardial fibrosis · radiation · storage disorders
Treatment	The four pillars of heart failure therapy (Case 12), devices, and treating the cause	Beta blocker, avoidance of vasodilators, risk stratification for implantable defibrillator, septal reduction	Treat the cause — and amyloidosis is now treatable, so it must be actively sought

2. Hypertrophic Cardiomyopathy

THE MANOEUVRE THAT MAKES THE DIAGNOSIS

The murmur of hypertrophic cardiomyopathy gets louder when you reduce ventricular filling and quieter when you increase it.

Louder: standing, Valsalva manoeuvre, nitrates, dehydration, exercise — a smaller cavity brings the hypertrophied septum and the mitral valve closer together and worsens obstruction.

Quieter: squatting, passive leg raise, handgrip — all of which increase preload or afterload.

In aortic stenosis the reverse is true, because the obstruction is fixed and depends on flow. This one manoeuvre, performed at the bedside in fifteen seconds, separates the two diagnoses.

Focused history

- **Exertional syncope or presyncope** — the red flag, and the reason this patient was referred.
- Exertional breathlessness, chest pain, palpitations.
- **A detailed family history across three generations: sudden death, unexplained drowning or road death in a young relative, cardiomyopathy, defibrillators, and consanguinity.** This is a family disease,

and the consultation concerns everybody in it.

- Competitive and recreational sport, and the intensity of it.

Examination

- **Jerky pulse** with a rapid upstroke and mid-systolic decline; **double apical impulse**; fourth heart sound; **ejection systolic murmur at the left sternal edge that does not radiate to the carotids**, with the dynamic behaviour above; and often a pansystolic murmur of mitral regurgitation from systolic anterior motion of the valve.

Investigations

- **Electrocardiogram — abnormal in over 90%**: left ventricular hypertrophy, deep lateral T wave inversion, pathological Q waves, and **giant negative T waves in the apical variant**. A completely normal tracing makes the diagnosis unlikely.

- **Echocardiography:** asymmetric hypertrophy of 15 mm or more, or 13 mm with a family history; systolic anterior motion of the mitral valve; and the **outflow tract gradient measured at rest and with provocation**, since obstruction is dynamic and may be absent at rest.

- **Cardiac magnetic resonance imaging** for apical and unusual variants and to quantify **myocardial fibrosis**, which contributes to arrhythmic risk.

- **Ambulatory electrocardiographic monitoring** for non-sustained ventricular tachycardia, and **exercise testing with blood pressure response**.

- **Genetic testing, and cascade screening of first-degree relatives.**

Management

- **Avoid dehydration, vasodilators, nitrates and excessive diuresis** — all reduce preload and worsen obstruction. **Avoid digoxin and inotropes**, which increase contractility and therefore obstruction.

- **Beta blocker first line**; verapamil or disopyramide as alternatives or additions. **Cardiac myosin inhibitors such as mavacamten** are a targeted treatment for obstructive disease.

- **Septal reduction therapy** — surgical myectomy or alcohol septal ablation — for symptoms refractory to drugs.

- **Risk stratification for sudden death and consideration of an implantable defibrillator**, using a validated risk score. The features that raise risk: **family history of sudden death, unexplained syncope, massive hypertrophy, non-sustained ventricular tachycardia, apical aneurysm, extensive fibrosis on imaging, and an abnormal blood pressure response to exercise.** This patient has two of them.

- **Exercise advice, individualised** rather than blanket prohibition, though high-intensity competitive sport is generally discouraged in higher-risk patients.

THE MOST IMPORTANT THING YOU WILL DO IN THIS CONSULTATION

Every first-degree relative needs an electrocardiogram and an echocardiogram, repeated periodically through adolescence and early adulthood, because the phenotype develops with growth. Where a causative mutation is identified, **genetic cascade testing lets you discharge the relatives who did not inherit it** — which is as valuable as identifying those who did.

Given the consanguinity in this family, the pedigree should be drawn out properly and the extended family offered assessment. **His brother's death was probably preventable, and his cousins' may be.**

3. Dilated Cardiomyopathy

- Management is the management of heart failure with reduced ejection fraction — **the four pillars set out in Case 12**, with device therapy and, ultimately, transplantation.
- **But look for the reversible causes, because several are entirely correctable:** alcohol (abstinence can restore function), **iron overload from transfusion — relevant in thalassaemia, where chelation and T2* monitoring are the treatment**, thyroid disease, sustained tachyarrhythmia, thiamine deficiency, and cardiotoxic chemotherapy.
- **Peripartum cardiomyopathy** presents in late pregnancy or the early puerperium; function often recovers, and a subsequent pregnancy carries significant risk if it does not. Specialist joint care is required.

4. Restrictive Cardiomyopathy — and the Diagnosis Not to Miss

CARDIAC AMYLOIDOSIS

Cardiac amyloidosis is now treatable, which makes it a diagnosis worth chasing rather than a post-mortem finding.

Suspect it in heart failure with preserved ejection fraction plus any of: a **low-voltage electrocardiogram despite thickened walls** — a striking discordance · bilateral **carpal tunnel syndrome**, often years earlier · lumbar spinal stenosis · macroglossia · periorbital purpura · proteinuria · autonomic neuropathy · intolerance of standard heart failure drugs.

Investigate with serum free light chains and immunofixation (for the AL type), **bone scintigraphy** (for transthyretin amyloidosis, which it can diagnose non-invasively), cardiac magnetic resonance imaging, and biopsy where needed.

Treat: tafamidis and other stabilisers for transthyretin disease; chemotherapy for AL amyloidosis. **Use diuretics carefully, and expect beta blockers and angiotensin-converting enzyme inhibitors to be poorly tolerated.** Anticoagulate for atrial fibrillation at a low threshold.

5. Teaching Points and Viva Questions

- Stand the patient up. The murmur that gets louder is hypertrophic cardiomyopathy; the one that gets quieter is aortic stenosis.
- Exertional syncope in a young person with a family history of sudden death is an emergency referral, not a routine one.
- The electrocardiogram is abnormal in almost every case of hypertrophic cardiomyopathy.
- Avoid vasodilators, nitrates, digoxin and dehydration.
- Screen the family — that is where the lives are saved.
- Alcohol and iron are reversible causes of a dilated cardiomyopathy.

- A low-voltage electrocardiogram with thick walls and a history of carpal tunnel syndrome is amyloidosis.

Questions you should be able to answer:

- Which single bedside manoeuvre separates this from aortic stenosis, and what happens to the murmur?
- Name four features that increase his risk of sudden death, and say which he has.
- What do you do about his parents, his sister and his cousins?
- A colleague prescribes glyceryl trinitrate for his chest pain. What is your concern?
- A 68-year-old has heart failure with a normal ejection fraction, thick ventricular walls and a low-voltage electrocardiogram. What is your diagnosis and how do you confirm it?

The Endocrinology Block

DKA, type 2 diabetes and its chronic complications, HHS, thyrotoxicosis, hypercalcaemia, pituitary and adrenal disorders, and lipids.

Cases 19–27 · 12,505 words

This block covers the endocrine teaching of both internal medicine courses. The **first course** supplies cases 19, 20 and 23; the **second course** supplies cases 24 and 27, adding pituitary and adrenal disease, the chronic complications of diabetes, and the lipid disorders.

Case	Lecture it serves
System opener: the endocrine history and examination	History taking in endocrinology; physical examination of the endocrine system
Case 19 — Diabetic ketoacidosis	Acute complications of diabetes
Case 20 — Newly diagnosed type 2 diabetes mellitus	Diabetes mellitus; diabetes mellitus part 2 (management)
Case 21 — Hyperosmolar hyperglycaemic state, with hypoglycaemia	Acute complications of diabetes; diabetic emergencies
Case 22 — Thyrotoxicosis, with hypothyroidism	Disorders of the thyroid gland
Case 23 — Hypercalcaemia and primary hyperparathyroidism	Disorders of the parathyroid and calcium metabolism
Case 24 — Pituitary disorders	Pituitary disorders: acromegaly and hypopituitarism
Case 25 — The chronic complications of diabetes	Chronic complications of diabetes mellitus
Case 26 — Cushing syndrome and adrenal insufficiency	Cushing and Addison diseases
Case 27 — Lipid and lipoprotein disorders	Lipid and lipoprotein disorders

System Opener · The Endocrine History and Examination

Endocrine disease is harder to recognise than cardiac or respiratory disease because its symptoms are systemic, non-specific and slow. Fatigue, weight change and mood disturbance describe half of general practice. The discipline that makes the history work is to stop thinking in symptoms and start thinking in **axes**, asking of each: is there too much hormone, or too little?

The history

The combinations that discriminate

Symptom pattern	What it points to
Weight loss with a good or increased appetite	Thyrotoxicosis, or uncontrolled diabetes mellitus — calories are being lost or burned, not refused
Weight loss with a poor appetite	Adrenal insufficiency, malignancy, chronic infection
Weight gain with fatigue, cold intolerance and constipation	Hypothyroidism
Weight gain with thin skin, bruising, proximal weakness and striae	Cushing syndrome — the distinguishing features are catabolic, not the weight itself
Thirst and polyuria	Diabetes mellitus, hypercalcaemia, diabetes insipidus, chronic kidney disease
Proximal muscle weakness	Thyroid disease in either direction, Cushing syndrome, osteomalacia, hypokalaemia of aldosteronism

Then screen the other axes briefly

- **Reproductive:** menstrual pattern, galactorrhoea, hirsutism, libido, erectile function, infertility, gynaecomastia. Menstrual history is one of the most sensitive indicators of endocrine disturbance and is regularly omitted.
- **Pituitary mass effect:** headache and visual field loss.
- **Change in appearance over time:** ring, shoe or hat size, coarsening features, skin darkening. **Ask to see old photographs** — the patient and family adapt to a change that occurs over years and cannot see it.
- **Autoimmune clustering:** personal and family history of thyroid disease, type 1 diabetes, coeliac disease, vitiligo, pernicious anaemia, adrenal insufficiency. Also multiple endocrine neoplasia syndromes and consanguinity.
- **Drugs:** corticosteroids in any form including inhaled, injected and topical; amiodarone; lithium; immune checkpoint inhibitors; and **weight-loss, energy or thyroid-containing preparations bought without prescription** — ask directly, because patients rarely consider them medicines.
- Previous neck surgery, radioiodine or radiotherapy.

The examination

- **General:** body habitus and fat distribution, hydration, voice, and the skin — pigmentation, vitiligo, thinning and bruising, striae, acanthosis nigricans, hair distribution and loss.
- **Hands:** tremor, warm sweaty or cold dry palms, onycholysis, palmar erythema, acromegalic soft-tissue changes, carpal tunnel signs.
- **Pulse and blood pressure, including a standing reading** — a postural drop is one of the few bedside clues to adrenal insufficiency.

- **Eyes:** lid retraction and lid lag, proptosis assessed from above and behind the patient, ophthalmoplegia, chemosis, and **visual fields by confrontation** for the bitemporal defect of a pituitary lesion.
- **Neck — the sequence:** inspect from the front, then ask the patient to **swallow** (a thyroid swelling rises) and then to **protrude the tongue** (a thyroglossal cyst rises). Palpate from behind: size, symmetry, consistency, nodules, tenderness, mobility. Then percuss for retrosternal extension, listen for a bruit, examine the cervical nodes, and check the tracheal position.
- **Neuromuscular:** ask the patient to stand from a chair with arms folded to demonstrate proximal myopathy; test reflexes for the **slow-relaxing ankle jerk** of hypothyroidism; examine for peripheral neuropathy.
- **Legs:** pretibial myxoedema, oedema, and in every diabetic patient a full foot examination — inspection between the toes, pulses, monofilament and vibration sensation.
- **Bedside tests:** capillary glucose, urinalysis, weight, body mass index, waist circumference.

Case 19 · Diabetic Ketoacidosis

CLINICAL VIGNETTE

A **22-year-old woman** with type 1 diabetes mellitus of eight years is brought in by her sister. For two days she has vomited repeatedly and been unable to keep food down. She has diffuse abdominal pain, has been passing large volumes of urine and drinking constantly. She has had a sore throat and fever since the weekend and, because she was not eating, **stopped taking her insulin**.

Her sister reports she has become drowsy since this morning and is breathing strangely.

On arrival: temperature 37.6 °C, heart rate 124/min, blood pressure 98/60 mmHg, respiratory rate 30/min and deep, oxygen saturation 99% on air, Glasgow Coma Scale 14. Mucous membranes are dry. Capillary glucose 28 mmol/L (504 mg/dL); capillary ketones 5.8 mmol/L.

1. Focused History

The diagnosis here is already almost certain from the bedside tests. **The history has a different job: to find the precipitant.** Diabetic ketoacidosis is always provoked by something, and the provocation kills more often than the acidosis does.

Hunt the precipitant systematically

Category	What to ask
Infection	Fever, dysuria, cough, sore throat, diarrhoea, foot ulcer or cellulitis, dental pain. Infection accounts for a third of episodes.
Insulin omission or failure	Exactly which insulins, what doses, when was the last dose. Pump users: site problems, occlusion alarms, cannula age. Cost or supply problems. Deliberate omission to lose weight.
Infarction and other vascular events	Chest pain, breathlessness, focal neurological symptoms. Silent myocardial infarction occurs in long-standing diabetes.
Intercurrent illness	Pancreatitis, cholecystitis, trauma, surgery, pregnancy.
Iatrogenic and drugs	Corticosteroids, thiazides, atypical antipsychotics, and sodium–glucose co-transporter 2 (SGLT2) inhibitors, which cause ketoacidosis at near-normal glucose.
Intoxication	Alcohol binge, cocaine or other stimulant use.

Also establish

- Whether this is **new-onset diabetes** — weeks of thirst, polyuria and weight loss in a previously well person.
- Number of previous admissions with ketoacidosis. Recurrent episodes in a young woman should raise the question of insulin omission for weight control, and of psychological distress; ask about it gently but ask.
- Whether she knows the **sick-day rules** — that insulin is never stopped during illness, and that requirements usually rise.
- Last menstrual period, and a pregnancy test in any woman of childbearing age.

Red flags

- Falling conscious level, headache with bradycardia and rising blood pressure (cerebral oedema), chest pain, and abdominal pain that persists or localises after the acidosis has been corrected, which points to a surgical cause rather than to ketoacidosis itself.

2. Physical Examination

General and neurological

- **Level of consciousness**, formally scored and repeated. Deterioration during treatment is the warning sign of cerebral oedema.
- **Kussmaul respiration** — deep, sighing, unlaboured hyperventilation. It is the respiratory compensation for metabolic acidosis, and its disappearance in a still-acidotic patient means exhaustion, not improvement.
- **Ketotic breath** — the sweet acetone smell. Roughly a third of people cannot detect it genetically, so its absence proves nothing.

Volume status — the assessment that guides the first two hours

- Dry mucous membranes, reduced skin turgor, sunken eyes, delayed capillary refill, tachycardia, postural or frank hypotension, low jugular venous pressure, reduced urine output. The typical adult deficit is around 100 mL/kg — six litres in a 60 kg woman.

Search for the source of infection

- Examine the chest, throat, ears, abdomen, skin, perineum and **especially the feet, between the toes**; inspect cannula and insulin injection sites. **Ketoacidosis itself does not cause fever** — a temperature means infection until proved otherwise, and a normal or low temperature does not exclude it.

Abdomen

- Diffuse tenderness with guarding is common in ketoacidosis itself and typically resolves within hours of treatment. Tenderness that persists, localises, or is accompanied by rebound after correction requires a surgical opinion and imaging.

3. Diagnosis and Differential

The diagnostic triad — all three must be present:

- **Hyperglycaemia:** glucose above 11 mmol/L (200 mg/dL), *or* known diabetes mellitus.
- **Ketonaemia:** capillary beta-hydroxybutyrate 3.0 mmol/L or more, or ketonuria of 2+ or greater.
- **Acidosis:** venous pH below 7.30 *or* bicarbonate below 15 mmol/L.

Condition	Glucose	Ketones	Acidosis	The discriminator
Diabetic ketoacidosis	High	High	Yes, high anion gap	All three present together
Hyperosmolar hyperglycaemic state	Very high, often >33 mmol/L	Minimal	No	Osmolality >320 mosmol/kg; older patient; days to weeks of onset
Euglycaemic ketoacidosis	Normal or mildly raised	High	Yes	On an SGLT2 inhibitor, or pregnant, or starved
Alcoholic ketoacidosis	Normal or low	High	Yes	Binge then vomiting and starvation; glucose not raised
Starvation ketosis	Normal	Mild, <3	Minimal	Bicarbonate largely preserved
Lactic acidosis	Variable	Normal	Yes	Raised lactate; shock, sepsis or metformin accumulation
Salicylate or toxic alcohol	Variable	Normal	Yes	Raised osmolar gap or the drug history

Anion gap = sodium − (chloride + bicarbonate); normal is 8–16 mmol/L. **Corrected sodium** = measured sodium + 2.4 mmol/L for every 5.5 mmol/L (100 mg/dL) that glucose exceeds 5.5. **Effective osmolality** = 2 × sodium + glucose.

4. Investigations

At the bedside — within minutes

- **Capillary glucose** and **capillary beta-hydroxybutyrate**. Blood ketones are preferred over urine dipstick: the dipstick measures acetoacetate, which paradoxically *rises* early in successful treatment and lags behind recovery.
- **Venous blood gas** for pH, bicarbonate and potassium. A venous sample is sufficient — arterial puncture adds pain and little information unless there is respiratory failure.
- **Electrocardiogram** for the peaked T waves of hyperkalaemia and for silent ischaemia.
- **Urinalysis** for ketones and infection, and a **pregnancy test**.

Laboratory

Test	Interpretation
Potassium	The most important number in the chart. Total body potassium is always depleted, yet the serum level is often normal or high on arrival because acidosis and insulin deficiency drive potassium out of cells. It falls fast once insulin is started.
Sodium	Often low on arrival because glucose draws water into the vascular space. Use the corrected value. A rising sodium during treatment is expected and reassuring, not a complication.
Urea and creatinine	Raised from volume depletion. Some assays are interfered with by ketones.
Complete blood count	A leucocytosis up to 25 × 10^9/L occurs in ketoacidosis without infection. A left shift, or a count above that, is more suggestive of sepsis.
C-reactive protein, blood and urine cultures	Directed at the precipitant.
Amylase and lipase	Amylase is non-specifically raised in ketoacidosis. Only lipase with a compatible picture supports pancreatitis.
Troponin, glycated haemoglobin, lactate, osmolality	Troponin if there is any cardiac risk; glycated haemoglobin to document control before the episode.

Imaging and monitoring

- Chest radiograph for occult infection; further imaging directed by findings. Computed tomography of the head only for unexplained deterioration in conscious level.
- **Monitoring schedule:** hourly capillary glucose and hourly capillary ketones; venous gas with potassium at one, two, four, eight, twelve and twenty-four hours; strict fluid balance with hourly urine output.

5. Management

THE SINGLE MOST IMPORTANT PRINCIPLE

Resolution is defined by the ketones and the pH, not by the glucose: ketones below 0.6 mmol/L, venous pH above 7.30 and bicarbonate above 18 mmol/L. A normal glucose with ketones of 4 is not a treated patient.

Step 1 — Fluid, before insulin

Time from start	Fluid
If systolic blood pressure <90 mmHg	500 mL of 0.9% sodium chloride over 10–15 minutes, repeated as needed, then reassess.
Hour 1	1 litre of 0.9% sodium chloride
Hours 2–3	1 litre over each 2 hours, with potassium
Hours 4–7	1 litre over each 4 hours, with potassium
Hours 8–13	1 litre over 6 hours, with potassium

Give fluid more cautiously — and with senior input — in the young, the elderly, the pregnant, and in heart or kidney failure. Young people are the group at risk of cerebral oedema.

Step 2 — Potassium

Serum potassium (mmol/L)	Action
Above 5.5	No potassium in this litre. Recheck within the hour.
3.5 – 5.5	Add 40 mmol of potassium chloride to each litre.
Below 3.5	Senior review now. Higher-rate replacement through an appropriate line, in a monitored bed. Do not start or continue insulin until potassium is being replaced.

Step 3 — Insulin

- **Fixed-rate intravenous insulin infusion at 0.1 units/kg/hour** of soluble insulin. A bolus is not required.
- **Continue the patient's usual long-acting basal insulin** at the usual dose throughout. Stopping it is a common error and causes rebound ketosis when the infusion ends.
- **Targets per hour:** ketones falling by at least 0.5 mmol/L, bicarbonate rising by at least 3 mmol/L, glucose falling by at least 3 mmol/L. If these are not met, increase the infusion by 1 unit/hour and check the giving set and cannula.
- **When glucose falls below 14 mmol/L (250 mg/dL), add 10% glucose at 125 mL/hour** alongside the saline and **continue the insulin**. Insulin is being given to clear ketones, not to lower glucose.

Step 4 — What not to do

- **Bicarbonate** is not given routinely. It may worsen intracellular acidosis and hypokalaemia. Consider it only at a pH below 6.9 and only with senior involvement.
- **Phosphate** replacement is not routine and has no demonstrated outcome benefit.
- Do not use a sliding scale in place of a fixed rate, and do not stop the infusion because the glucose has normalised.

Step 5 — Supportive care and the precipitant

- Treat the infection or other cause. Give venous thromboembolism prophylaxis. Consider a nasogastric tube if there is vomiting with a reduced conscious level, because of aspiration risk, and a urinary catheter if there is no urine output after four hours.

Step 6 — Transition and discharge

- Move to subcutaneous insulin only when ketones are below 0.6, pH is above 7.3, and the patient is eating and drinking. **Give the short-acting subcutaneous dose 30–60 minutes before stopping the infusion** so that the two overlap.
- Every patient is reviewed by the diabetes specialist team before discharge. Revisit sick-day rules, provide a blood ketone meter, review the insulin regimen and injection technique, and address any psychological or eating-related contributor.

Complications — mostly of treatment

Complication	Prevention
Hypokalaemia	The commonest preventable cause of death in ketoacidosis. Potassium in every litre once it is below 5.5, and hourly measurement early.
Hypoglycaemia	Add 10% glucose once the level falls below 14 mmol/L rather than reducing insulin.
Cerebral oedema	Mainly in children and young adults. Avoid over-rapid fluid and osmolality shifts; monitor conscious level hourly.
Aspiration pneumonia	Nasogastric tube if vomiting with impaired consciousness.
Hyperchloraemic acidosis	A recognised consequence of large-volume saline; self-limiting and not a treatment failure.
Venous thromboembolism	Prophylactic anticoagulation.

6. Teaching Points and Viva Questions

- Patients die of hypokalaemia and cerebral oedema during treatment, not of hyperglycaemia on arrival.
- Fluid comes before insulin. Insulin given to an unresuscitated, potassium-depleted patient is dangerous.
- The basal insulin continues. The intravenous infusion supplements it; it does not replace it.
- A normal glucose does not exclude ketoacidosis — check the ketones in any acidotic patient on an SGLT2 inhibitor.
- A white cell count of 20×10^9/L may be the acidosis alone; a fever is never the acidosis alone.

Questions you should be able to answer:

- Why is the serum potassium normal on arrival when total body potassium is severely depleted?
- Why does the sodium rise during successful treatment, and why is that reassuring?
- Why is capillary beta-hydroxybutyrate better than urine ketone testing for monitoring?
- The abdomen is tender. How do you decide whether to call the surgeons?
- Glucose is now 9 mmol/L but ketones are 3.5. What do you do with the insulin infusion?

Case 20 · Newly Diagnosed Type 2 Diabetes Mellitus

CLINICAL VIGNETTE

A **52-year-old man** attends because of three months of tiredness, passing urine frequently at night, and constant thirst. He has lost about 6 kg without trying, although his appetite is good. His vision has become blurred over the past few weeks and he has already booked an appointment for new glasses. He has had two episodes of itching and soreness of the foreskin.

His father and two brothers have diabetes. He works long hours as a driver, eats most meals outside the home and takes no exercise.

On examination: body mass index 32 kg/m^2 with central adiposity, blood pressure 148/90 mmHg. There is **acanthosis nigricans** at the neck and axillae. Foot pulses are present; monofilament sensation is reduced at both great toes.

Random plasma glucose 16.8 mmol/L (302 mg/dL). Glycated haemoglobin 10.2% (88 mmol/mol). Urine ketones negative.

1. Focused History

Confirm the syndrome

- Osmotic symptoms — thirst, polyuria, nocturia — and their duration. Weight change and its direction relative to appetite.
- Recurrent infections: candidal balanitis or vulvovaginitis, skin sepsis, urinary infection, poor wound healing.
- **Blurred vision.** Explain that this is osmotic swelling of the lens, that it will resolve within weeks of glycaemic control, and that he should **postpone the new glasses for six to eight weeks** — otherwise he will pay for lenses he cannot use.

Decide which type of diabetes this is

Feature	Type 1	Type 2
Onset	Weeks, often abrupt	Months to years, often found on screening
Body habitus	Usually lean, marked weight loss	Usually overweight with central adiposity
Ketosis	Prominent; may present in ketoacidosis	Absent or mild
Associated features	Personal or family autoimmune disease	Hypertension, dyslipidaemia, fatty liver, acanthosis nigricans
Tests when uncertain	Low C-peptide; positive glutamic acid decarboxylase or islet antigen-2 antibodies	Preserved C-peptide; antibodies negative

- Do not assume from age alone. **Latent autoimmune diabetes in adults** presents in a lean middle-aged patient who fails oral therapy quickly, and **monogenic diabetes** should be considered where there is diabetes in three consecutive generations with young onset and no obesity.
- **Screen for secondary causes:** pancreatic disease and pancreatic surgery, corticosteroids and antipsychotics, Cushing syndrome, acromegaly, and haemochromatosis — ask about arthralgia, skin bronzing and family history.

Assume complications are already present, and ask about them

- Numbness, burning or tingling in the feet; foot ulcers; claudication; chest pain or breathlessness; erectile dysfunction — often the earliest reported complication and rarely volunteered; visual symptoms; frothy urine.
- Occupation, driving licence category and shift pattern, which affect the choice of drugs; and a full cardiovascular risk history.

2. Physical Examination

- Weight, body mass index, waist circumference, and blood pressure with a standing reading.
- Acanthosis nigricans, skin and genital candidal infection, injection sites where relevant, lipohypertrophy.
- **The foot examination, performed at diagnosis, not at the first ulcer:** inspect the dorsum, sole and **between the toes**; look for deformity, callus, dry skin and nail disease; palpate dorsalis pedis and posterior tibial pulses; test protective sensation with a 10 g monofilament and vibration with a tuning fork; and inspect the footwear.
- Fundoscopy through dilated pupils, or arrange retinal photography.

3. Diagnosis

Test	Diagnostic threshold
Fasting plasma glucose	7.0 mmol/L (126 mg/dL) or above
Two-hour glucose in an oral glucose tolerance test	11.1 mmol/L (200 mg/dL) or above
Glycated haemoglobin	6.5% (48 mmol/mol) or above
Random plasma glucose with classical symptoms	11.1 mmol/L (200 mg/dL) or above

In an **asymptomatic** patient a single abnormal result must be confirmed on a second occasion. This man has classical symptoms with a random glucose above threshold, so the diagnosis is made today.

> **A CAUTION THAT MATTERS HERE**
>
> Glycated haemoglobin measures the average lifespan of the red cell as much as the average glucose. **It is unreliable, and may be frankly misleading, in:**
>
> **Haemoglobinopathies and thalassaemia trait** · haemolysis of any cause · recent blood transfusion or blood loss · iron and vitamin B12 deficiency and their treatment · advanced chronic kidney disease · pregnancy.
>
> Given how common sickle cell disease, sickle trait and thalassaemia are in this region, this is not an examination footnote. **Where the glycated haemoglobin is unreliable, diagnose and monitor with glucose measurements or fructosamine instead**, and be alert to a result that does not match the clinical picture.

4. Investigations at Diagnosis

Type 2 diabetes has usually been present for several years before it is diagnosed. Complication screening therefore begins today, not after five years — that is the single most important structural difference from type 1.

- **Renal:** urine albumin-to-creatinine ratio on an early morning sample, urea, electrolytes, creatinine and estimated glomerular filtration rate.
- **Eyes:** retinal screening at diagnosis.
- **Feet:** risk stratification from the examination above.
- **Cardiovascular and metabolic:** lipid profile, blood pressure, electrocardiogram, liver function tests for fatty liver disease.
- Thyroid function; C-peptide and autoantibodies only if the type is genuinely uncertain.

5. Management

Education and lifestyle — the foundation, not the preamble

- Structured education and dietetic referral. Explain the diagnosis, the natural history and the purpose of each intervention; adherence follows understanding.
- **Weight reduction of 5–10% improves glycaemia substantially, and substantial sustained weight loss can produce remission** of type 2 diabetes, particularly within the first few years of diagnosis. Say this to the patient — it changes the conversation from managing decline to reversing a condition.
- At least 150 minutes of moderate activity weekly, dietary change appropriate to how he actually eats, and smoking cessation.

Drug therapy

- **Metformin** first line unless contraindicated. Titrate slowly with food to limit gastrointestinal effects; review the dose against renal function; monitor vitamin B12 with long-term use.
- **Choose the second agent by comorbidity, not by glucose alone:** a sodium–glucose co-transporter 2 inhibitor where there is established cardiovascular disease, heart failure or chronic kidney disease; a glucagon-like peptide-1 receptor agonist where obesity or atherosclerotic disease dominates.
- Sulfonylureas are effective and inexpensive but cause hypoglycaemia and weight gain — relevant to a professional driver and during fasting. Dipeptidyl peptidase-4 inhibitors are weight-neutral and well tolerated. Insulin is used where glycaemia is severe, catabolic symptoms are marked, or other agents fail.
- **Glycated haemoglobin target, individualised:** around 7% (53 mmol/mol) for most; tighter in a young, newly diagnosed patient without vascular disease; more relaxed in the frail elderly, in advanced complications, and where hypoglycaemia awareness is impaired.
- **Treat the vascular risk, not only the glucose:** blood pressure control, a statin according to risk assessment, and an angiotensin-converting enzyme inhibitor or receptor blocker where albuminuria is present.

FASTING DURING RAMADAN

Most patients with diabetes intend to fast, and most do not raise it with their doctor. **Ask, and plan before Ramadan, not during it.**

Risk-stratify: recent ketoacidosis or hyperosmolar state, severe or unaware hypoglycaemia, advanced complications, pregnancy or dialysis place a patient at very high risk and fasting is inadvisable.

Adjust the regimen: sulfonylureas and insulin need dose reduction and timing changes — in general the larger dose moves to the sunset meal. Metformin is redistributed. **Sodium–glucose co-transporter 2 inhibitors carry a dehydration and euglycaemic ketoacidosis risk** during a long fast in a hot climate.

Educate: capillary glucose testing does **not** invalidate the fast. The fast must be broken for hypoglycaemia below 3.9 mmol/L, for glucose above 16.7 mmol/L, or for symptoms of dehydration. Encourage generous fluid between sunset and dawn.

Ongoing review

- Annually: retinal screening, foot assessment, urine albumin-to-creatinine ratio, renal function, lipids, blood pressure and weight. Vaccination, sick-day rules, and driving advice where relevant.

6. Teaching Points and Viva Questions

- Type 2 diabetes is diagnosed years after it begins. Screen for complications on the day you diagnose it.
- Blurred vision at presentation is osmotic and reversible — tell the patient to delay new spectacles.
- Glycated haemoglobin lies in haemoglobinopathy, haemolysis and recent transfusion. Know when not to trust it.
- Examine the feet and ask about erectile dysfunction. Neither will be volunteered.
- Choose the second drug for the heart and the kidney, not only for the glucose.

Questions you should be able to answer:

- What features would make you doubt this is type 2 diabetes, and what would you test?
- His glycated haemoglobin is 6.1% but his fasting glucose is 9.4 mmol/L. Explain the discrepancy.
- Which complications must be screened for today, and by what test?
- He drives a lorry for a living. How does that affect your prescribing?
- He intends to fast for Ramadan in two months. What do you do now?

Case 21 · Hyperosmolar Hyperglycaemic State

CLINICAL VIGNETTE

A **74-year-old woman** with type 2 diabetes treated with gliclazide is brought in by her son. Over the past ten days she has become steadily more confused and drowsy. She has been drinking constantly and passing large volumes of urine. She had burning on passing urine a fortnight ago. She lives alone and has mild dementia.

On examination: she is very dry, with reduced skin turgor and sunken eyes. Temperature 37.9 °C, heart rate 118/min, blood pressure 96/58 mmHg, respiratory rate 18/min and **not deep**. Glasgow Coma Scale 11. There is no ketotic breath. There is a mild left-sided facial droop that her son says is new.

Glucose 42 mmol/L (756 mg/dL) · sodium 152 mmol/L · urea 19 mmol/L · calculated osmolality 355 mosmol/kg · pH 7.34 · bicarbonate 20 mmol/L · capillary ketones 0.9 mmol/L.

1. Recognising the Syndrome

	Diabetic ketoacidosis	Hyperosmolar hyperglycaemic state
Typical patient	Younger, type 1	Older, type 2, often with impaired access to fluid
Onset	Hours to a day	Days to weeks
Glucose	Usually 20–40 mmol/L	Usually above 30 mmol/L, often far higher
Ketones	3.0 mmol/L or more	Below 3.0 mmol/L
Acidosis	pH below 7.3, bicarbonate below 15	pH above 7.3, bicarbonate above 15
Osmolality	Variable	320 mosmol/kg or above — the defining feature
Fluid deficit	Around 100 mL/kg	Greater — 100 to 220 mL/kg
Mortality	Low with correct treatment	Substantially higher, reflecting age and comorbidity

Calculated osmolality = (2 × sodium) + glucose + urea, all in mmol/L. Learn it; it is the number that defines the diagnosis and the number that governs the speed of treatment.

2. Focused History

- The slow tempo — days to weeks of thirst, polyuria and declining function — distinguishes this from ketoacidosis and explains the size of the deficit.
- **Hunt the precipitant.** Infection, particularly urinary and respiratory; myocardial infarction and stroke, both of which may be silent; drugs including corticosteroids, thiazides and sodium–glucose co-transporter 2 inhibitors; and, very commonly, **simple inability to obtain enough fluid** because of frailty, dementia, immobility or living alone.
- This may be the **first presentation of diabetes**. Ask about the preceding months.

3. Physical Examination

- **Profound dehydration** — the dominant physical finding, and the one that guides the first 24 hours.
- Conscious level, formally scored and repeated. Depression of consciousness correlates with osmolality rather than with glucose.

- **Focal neurological signs and seizures occur in the hyperosmolar state itself and usually reverse with treatment.** Do not assume a stroke — but do not dismiss one either. Reassess after correction.
- A full search for the precipitant: chest, urine, skin, **feet**, and pressure areas.
- Assess pressure areas and thrombotic risk, both of which are high in an immobile, hyperviscous, dehydrated patient.

4. Investigations

- Capillary and laboratory glucose; **capillary ketones**, to confirm this is not ketoacidosis; venous blood gas for pH, bicarbonate and potassium.
- **Sodium and calculated osmolality**, repeated hourly at first — these, not the glucose, are what you titrate treatment against.
- Urea, creatinine, complete blood count, C-reactive protein, blood and urine cultures, chest radiograph, electrocardiogram and troponin, creatine kinase for rhabdomyolysis, lactate.
- Computed tomography of the head only if focal signs persist after biochemical correction, or if the conscious level deteriorates.

5. Management

THE GOVERNING PRINCIPLE

The instinct carried over from ketoacidosis — fluid fast, insulin early — is wrong here and is dangerous.

Correct slowly. Aim to fall in glucose by no more than **4–6 mmol/L per hour** and in osmolality by no more than **3–8 mosmol/kg per hour**. Replace the fluid deficit over **48 hours**, not over 12. Rapid shifts risk cerebral oedema and osmotic demyelination.

Fluid is the treatment; insulin is secondary. Glucose falls with rehydration alone.

Sequence

- **1. Fluid.** Sodium chloride 0.9% is the fluid of choice. Give 500 mL to 1 litre in the first hour, faster if shocked, then continue at a rate that replaces the deficit over 48 hours while monitoring for overload in an elderly heart.
- **2. Expect the sodium to rise as the glucose falls.** This is predictable and is not by itself a reason to change fluid. Judge progress by the **osmolality**: if it is falling appropriately, continue; if it plateaus or rises despite adequate volume, then consider 0.45% saline.
- **3. Potassium** as in ketoacidosis — none if above 5.5 mmol/L, 40 mmol per litre if 3.5–5.5, and senior review below 3.5.
- **4. Insulin — later and lower.** Do not start it while the glucose is still falling with fluid alone. When it is needed, use a fixed rate of **0.05 units/kg/hour**, half the ketoacidosis rate. If significant ketonaemia is present, treat as a mixed picture at the full ketoacidosis rate.
- **5. Thromboprophylaxis in every patient.** Hyperviscosity, dehydration and immobility together make this one of the most thrombogenic states in medicine.

- **6. Treat the precipitant**, protect the pressure areas and the feet, and involve the diabetes team early.

Expectations and recovery

- **Recovery of consciousness lags behind the biochemistry, often by 24 hours or more.** Do not escalate treatment because the patient is still drowsy when the numbers have normalised.
- Many patients do not need long-term insulin and can return to oral therapy once the acute illness resolves.
- Address the reason it happened: fluid access, care arrangements, medication review, and recognition of sick days.

THE OTHER ACUTE COMPLICATION: HYPOGLYCAEMIA

Definition: glucose below 3.9 mmol/L (70 mg/dL). **Severe** means requiring the help of another person, whatever the number.

Conscious and able to swallow: 15–20 g of rapid-acting carbohydrate; recheck at 15 minutes and repeat if still low; then **give long-acting carbohydrate** to prevent relapse.

Impaired consciousness: intravenous glucose, or intramuscular glucagon if there is no access. **Glucagon fails** where hepatic glycogen is depleted — in alcohol excess, liver disease, starvation and prolonged sulfonylurea hypoglycaemia.

The trap: sulfonylurea hypoglycaemia is prolonged and relapsing. These patients must be admitted and observed, not corrected once and discharged from the emergency department. Refractory cases may require an octreotide infusion. Renal impairment prolongs it further.

Afterwards: identify the cause, review the regimen and targets, and ask about **hypoglycaemia unawareness** — which is an indication to deliberately relax control until awareness returns.

6. Teaching Points and Viva Questions

- Older, slower, drier and without ketones — and the osmolality, not the glucose, makes the diagnosis.
- Fluid first and generous, insulin later and half-rate.
- A rising sodium during treatment is expected. Judge by the osmolality.
- Focal neurological signs may be the hyperosmolar state and may reverse. Reassess rather than committing to a stroke diagnosis at the door.
- Every one of these patients receives thromboprophylaxis.
- Never discharge a sulfonylurea hypoglycaemia after a single correction.

Questions you should be able to answer:

- Calculate her osmolality and explain why it matters more than the glucose.
- Why is the insulin rate half that used in ketoacidosis, and why is it started later?
- Her sodium rises from 152 to 158 in four hours. What do you do?
- Why does this condition carry such a high thrombotic risk?
- A patient on gliclazide has a corrected hypoglycaemia and feels well after an hour. Can she go home?

Case 22 · Thyrotoxicosis

CLINICAL VIGNETTE

A **31-year-old woman** presents with four months of weight loss — 9 kg — despite eating more than usual. She feels her heart racing, cannot tolerate heat, sweats constantly, and describes herself as anxious and short-tempered in a way that is unlike her. Her periods have become light and infrequent. Her bowels open three or four times daily. Her eyes feel gritty and her husband says they look prominent.

She smokes 10 cigarettes a day. Her mother has hypothyroidism.

On examination: pulse 118/min and **irregularly irregular**. Blood pressure 142/62 mmHg. Warm sweaty palms with a fine tremor. There is **lid retraction, lid lag and bilateral proptosis** with conjunctival injection. The thyroid is **diffusely enlarged, smooth and non-tender, with an audible bruit**. She cannot rise from a chair without using her arms.

1. Focused History

- The symptoms of hormone excess: weight loss with preserved appetite, heat intolerance, sweating, palpitations, tremor, anxiety and irritability, insomnia, frequent loose stools, oligomenorrhoea, proximal weakness, and fatigue.
- **Neck symptoms.** A **painful, tender** thyroid points to subacute thyroiditis rather than Graves disease and changes the treatment entirely.
- **Eye symptoms:** grittiness, watering, prominence, **double vision**, retro-orbital pain, and any change in vision or colour perception — the last is sight-threatening and demands same-day referral.
- **Recent pregnancy or delivery**, which raises postpartum thyroiditis.
- **Drugs and preparations:** amiodarone, lithium, iodinated contrast, immune checkpoint inhibitors, and **thyroid hormone taken for weight loss or energy, often in unlabelled preparations**. Ask directly and without judgement.
- **Smoking** — it markedly worsens Graves orbitopathy and reduces the response to its treatment. This is the strongest modifiable factor in the eye disease and must be raised at the first consultation.
- Personal and family autoimmune history; previous radioiodine or thyroid surgery.

2. Physical Examination

- **Hands and pulse:** fine tremor, warm moist palms, onycholysis, thyroid acropachy, palmar erythema; tachycardia and **atrial fibrillation**, which occurs in around one in ten and more often in older patients.
- **Eyes — and the distinction that matters: lid retraction and lid lag occur in thyrotoxicosis of any cause**, being due to sympathetic overactivity. **Proptosis, chemosis, conjunctival injection, periorbital oedema and ophthalmoplegia are specific to Graves orbitopathy**, an autoimmune orbital process. Assess proptosis by looking down over the patient's forehead from behind, and always check **visual acuity, colour vision and eye movements**.
- **Neck:** a diffuse, smooth, non-tender goitre with a bruit is Graves disease; a lumpy multinodular gland suggests toxic multinodular goitre; a single nodule suggests a toxic adenoma; a tender gland suggests thyroiditis.

- **Legs and skin:** pretibial myxoedema — raised, non-pitting, orange-peel plaques over the shins, uncommon but essentially diagnostic of Graves disease.
- Proximal myopathy, brisk reflexes, and signs of high-output cardiac failure.

3. Differential Diagnosis — Which Cause?

Cause	Distinguishing features
Graves disease	Diffuse smooth goitre with bruit, orbitopathy, pretibial myxoedema, positive thyrotropin receptor antibodies, diffusely increased isotope uptake.
Toxic multinodular goitre	Older patient, lumpy gland, no eye signs, patchy uptake. Often presents with atrial fibrillation alone.
Toxic adenoma	Solitary nodule, single area of uptake with suppression of the remaining gland.
Subacute (de Quervain) thyroiditis	Painful tender gland, preceding viral illness, raised inflammatory markers, absent isotope uptake, followed by a hypothyroid phase then recovery.
Postpartum or silent thyroiditis	Painless, within a year of delivery, absent uptake, self-limiting biphasic course.
Iodine-induced, including amiodarone	Recent contrast or amiodarone; two distinct types requiring different treatment.
Factitious thyrotoxicosis	No goitre, absent uptake, and a low thyroglobulin — the test that exposes it.

4. Investigations

- **Thyroid function:** suppressed thyroid-stimulating hormone with raised free thyroxine, or raised triiodothyronine alone in T3 toxicosis. A suppressed hormone with normal free levels is subclinical thyrotoxicosis.
- **Thyrotropin receptor antibodies** — positive in Graves disease, and their presence removes the need for isotope scanning in a typical case.
- **Radionuclide uptake scan** when the cause is not clear from the clinical picture and antibodies: diffusely increased in Graves, patchy in multinodular disease, focal in an adenoma, and **absent in thyroiditis, factitious ingestion and iodine excess**. This single distinction — high uptake versus no uptake — separates conditions treated with antithyroid drugs from those that must not be.
- **Before starting treatment:** complete blood count and liver function tests as a baseline, since the important drug reactions affect both.
- Electrocardiogram, and a pregnancy test before any radioiodine — this is mandatory, not a formality.
- Erythrocyte sedimentation rate if thyroiditis is suspected; thyroglobulin if factitious ingestion is suspected.

5. Management

Symptom control

- **A beta blocker such as propranolol** relieves tremor, palpitations, anxiety and sweating within hours, long before any antithyroid drug works. Start it at the first visit.

Antithyroid drugs

- **Carbimazole** (or methimazole) is first line. **Propylthiouracil** is reserved for the first trimester of pregnancy and for thyroid storm.
- Either a titration regimen or block-and-replace. For Graves disease, continue for 12–18 months and then withdraw; about half remain in remission, and relapse is commonest in the first year.

THE WARNING YOU MUST GIVE

Every patient starting carbimazole or propylthiouracil must be told, and it must be documented:

"If you develop a sore throat, mouth ulcers or a fever, stop the tablet immediately and get an urgent white cell count." Agranulocytosis is rare but abrupt, and it is fatal when missed.

Also warn about **hepatotoxicity** — particularly with propylthiouracil — and about rash. Give the warning in writing.

Definitive treatment

- **Radioiodine** — effective and simple. Contraindicated in pregnancy and breastfeeding, and avoided in **active moderate-to-severe orbitopathy**, which it can worsen. Hypothyroidism is the expected outcome, not a complication, and lifelong thyroxine follows.
- **Surgery** — for a large or compressive goitre, suspected malignancy, patient preference, or failure of medical therapy in pregnancy. Risks are **recurrent laryngeal nerve palsy and hypoparathyroidism**; the patient must be rendered euthyroid before operation.

Graves orbitopathy

- **Stop smoking** — the most effective single intervention. Artificial tears, head elevation at night, and prisms for diplopia in mild disease. Selenium may help mild disease.
- Moderate-to-severe active disease requires intravenous glucocorticoids, and in selected cases orbital radiotherapy, immunomodulatory therapy or surgical decompression.
- **Same-day ophthalmology referral** for reduced acuity, impaired colour vision, corneal exposure or optic nerve compression.

EMERGENCY: THYROID STORM

Recognise it: fever above 38.5 °C, marked tachyarrhythmia or heart failure, agitation, delirium or coma, and vomiting, diarrhoea or jaundice, in a thyrotoxic patient. Usually precipitated by infection, surgery, trauma, labour, an iodine load or ketoacidosis.

Treat in this order, and the order is examinable:

1. Propylthiouracil, to block synthesis and peripheral conversion. **2. Iodine (Lugol solution) at least one hour later** — given first, iodine provides substrate and makes matters worse. **3.** A beta blocker. **4.** Hydrocortisone, which also reduces peripheral conversion. **5.** Active cooling, fluid resuscitation, treatment of the precipitant, and high-dependency care.

6. The Other Direction: Hypothyroidism

	Detail
Symptoms	Fatigue, weight gain, cold intolerance, constipation, dry skin, hair loss, hoarseness, menorrhagia, low mood, cognitive slowing, carpal tunnel syndrome.
Signs	Bradycardia, dry coarse skin, periorbital puffiness, loss of the outer eyebrow, goitre or an absent gland, and the slow-relaxing ankle reflex.
Causes	Autoimmune (Hashimoto) thyroiditis; after radioiodine or surgery; iodine deficiency; drugs including amiodarone and lithium; and central causes with a low or normal stimulating hormone.
Diagnosis	Raised thyroid-stimulating hormone with low free thyroxine. Raised hormone with normal thyroxine is subclinical disease. Thyroid peroxidase antibodies confirm autoimmune cause.
Treatment	Levothyroxine, taken on an empty stomach and separated from iron, calcium and proton pump inhibitors. Start at a low dose in the elderly and in ischaemic heart disease, where rapid replacement can precipitate angina. Recheck at 6–8 weeks and titrate against the stimulating hormone.
Myxoedema coma	Hypothermia, bradycardia, hypoventilation with carbon dioxide retention, hyponatraemia and reduced consciousness. Requires intravenous thyroid hormone and hydrocortisone until adrenal insufficiency is excluded, plus supportive care.

7. Teaching Points and Viva Questions

- Lid lag and lid retraction come with any thyrotoxicosis; proptosis and ophthalmoplegia mean Graves disease.
- A painful thyroid is thyroiditis. Antithyroid drugs will not help, because the gland is leaking hormone rather than making it.
- The isotope scan question is simply: is uptake high, or absent?
- Warn every patient about agranulocytosis, in writing, and document it.
- In thyroid storm, propylthiouracil before iodine — never the reverse.
- Smoking cessation does more for the eyes than anything else you can offer.

Questions you should be able to answer:

- Which of her eye signs indicate Graves disease specifically, and why?
- How would you distinguish Graves disease from subacute thyroiditis without a scan?
- She is planning pregnancy. How does that change your treatment options?
- Explain why iodine must follow rather than precede propylthiouracil in thyroid storm.
- Her atrial fibrillation persists. What do you do about it?

Case 23 · Hypercalcaemia and Primary Hyperparathyroidism

CLINICAL VIGNETTE

A **58-year-old woman** is referred after a routine blood test showed a **calcium of 2.94 mmol/L (11.8 mg/dL)** with an albumin of 41 g/L. She was told she felt well, but on direct questioning she describes months of fatigue, constipation, low mood and difficulty concentrating, and she passes urine several times each night. She passed a renal stone two years ago and thought no more of it.

She takes no regular medication and no supplements. There is no weight loss, cough or bone pain.

Initial results: parathyroid hormone 8.9 pmol/L (upper limit of normal 6.8) · phosphate 0.72 mmol/L · alkaline phosphatase mildly raised · creatinine normal · vitamin D low-normal.

1. Focused History

The old mnemonic is crude but it works: **bones, stones, abdominal groans and psychic moans** — with **thirst and polyuria** added, since hypercalcaemia causes a nephrogenic diabetes insipidus.

- **Bones:** bone pain, fragility fracture, previous osteoporosis diagnosis.
- **Stones:** renal colic, haematuria, recurrent urinary infection.
- **Abdominal:** constipation, nausea, dyspepsia and peptic ulceration, and pancreatitis.
- **Psychic:** fatigue, low mood, poor concentration, and in severe cases confusion and drowsiness. Patients frequently describe themselves as well until questioned, then recognise months of change.
- **Screen for malignancy**, which is the other major cause: weight loss, smoking history, breast symptoms, cough or haemoptysis, bone pain, haematuria, and change in bowel habit.
- **Drugs and supplements:** thiazide diuretics, lithium, calcium and vitamin D preparations, vitamin A, and antacids taken in quantity.
- **Granulomatous disease:** sarcoidosis and tuberculosis raise calcium by unregulated vitamin D activation.
- **Family history and age.** Hypercalcaemia in a young patient, or with a family history, raises **multiple endocrine neoplasia** and **familial hypocalciuric hypercalcaemia**. Ask about pituitary and pancreatic tumours, phaeochromocytoma and medullary thyroid cancer.
- Prolonged immobilisation.

2. Physical Examination

- Hydration and conscious level — hypercalcaemia causes polyuria and therefore volume depletion, which in turn worsens the hypercalcaemia. This cycle is the reason fluid is the mainstay of acute treatment.
- A **deliberate search for malignancy**: breast, lymph nodes, chest, abdomen, prostate and rectum where appropriate, and bone tenderness over the spine, ribs and long bones.
- Neck scars from previous surgery; proximal myopathy; band keratopathy at the corneal margin in longstanding disease, which is rare but memorable.

3. Investigations

THE STEP STUDENTS SKIP

First, correct for albumin. Only about half of plasma calcium is free and active; the rest is protein-bound.

Corrected calcium = measured calcium + 0.02 × (40 − albumin in g/L)

A patient with a low albumin can be genuinely hypercalcaemic with a normal total calcium, and a dehydrated patient with a high albumin can appear hypercalcaemic when they are not. Where available, an ionised calcium settles the question directly.

Then measure parathyroid hormone. It divides the entire differential in two, and no other test does as much work.

Parathyroid hormone raised or inappropriately normal	Parathyroid hormone suppressed
Primary hyperparathyroidism — the commonest cause in an outpatient	Malignancy — the commonest cause in an inpatient: parathyroid hormone-related peptide, bone metastases, myeloma
Tertiary hyperparathyroidism in chronic kidney disease	Granulomatous disease — sarcoidosis, tuberculosis
Familial hypocalciuric hypercalcaemia	Vitamin D or vitamin A toxicity, milk-alkali syndrome
Lithium therapy	Thyrotoxicosis, immobilisation, adrenal insufficiency

A "normal" parathyroid hormone in the face of hypercalcaemia is abnormal. A healthy parathyroid gland should be fully suppressed. This trips up students who compare the number to the reference range instead of to the calcium.

- **Supporting tests:** phosphate (low in primary hyperparathyroidism), alkaline phosphatase, magnesium, renal function, and 25-hydroxyvitamin D.
- **Twenty-four hour urinary calcium, with the calcium-to-creatinine clearance ratio.** A ratio below 0.01 indicates **familial hypocalciuric hypercalcaemia** — a benign lifelong condition that requires **no treatment and must not be operated on**. Failing to check this before referring a patient for parathyroidectomy is a classic and consequential error.
- **If parathyroid hormone is suppressed:** parathyroid hormone-related peptide, myeloma screen with protein electrophoresis and serum free light chains, imaging directed at the likely primary, and angiotensin-converting enzyme with chest imaging for sarcoidosis.
- **Electrocardiogram** — a short QT interval, and arrhythmia in severe hypercalcaemia.
- **Once primary hyperparathyroidism is confirmed biochemically:** bone densitometry, including the **distal radius**, which is affected preferentially; and renal imaging for stones or nephrocalcinosis. **Localisation imaging — ultrasound and sestamibi scanning — is performed to guide the surgeon, not to make the diagnosis.** A negative scan does not exclude the disease.

4. Management

Acute severe hypercalcaemia

Symptomatic, or a corrected calcium above about 3.5 mmol/L, is an emergency.

- **Intravenous sodium chloride 0.9%** — typically 3 to 6 litres over 24 hours, adjusted for age and cardiac function. Rehydration alone lowers calcium substantially and is the first and most important step.
- **Loop diuretics are not given routinely.** They were once standard and are now reserved for managing fluid overload during rehydration, in a patient who is already volume-replete.
- **Intravenous bisphosphonate**, such as zoledronic acid, after rehydration. The effect takes two to four days, so it is not the treatment for the first hour.
- **Calcitonin** produces a rapid but modest and short-lived fall, useful as a bridge in the first 48 hours.
- **Corticosteroids** for granulomatous disease, vitamin D toxicity and some haematological malignancies. **Denosumab** where bisphosphonates are contraindicated by renal impairment or have failed. Dialysis in extremis.
- Stop the contributing drugs — thiazides, lithium, calcium and vitamin D supplements.

Definitive treatment of primary hyperparathyroidism

Parathyroidectomy is the only cure. Operate if the patient is symptomatic. In an asymptomatic patient, operate if **any one** of the following is present:

- Corrected calcium more than 0.25 mmol/L above the upper limit of normal.
- Estimated glomerular filtration rate below 60 mL/min, nephrolithiasis or nephrocalcinosis on imaging, or urinary calcium excretion above 10 mmol per day.
- Osteoporosis on densitometry, or any vertebral or fragility fracture.
- Age below 50 years.
- **If surgery is not undertaken:** maintain hydration, avoid thiazides, **keep vitamin D replete** — which is counterintuitive but correct, since deficiency drives the parathyroid glands harder — and monitor calcium, renal function and bone density. **Cinacalcet** lowers calcium where surgery is not possible, but does not improve bone density.
- **After surgery**, watch for hypocalcaemia and **hungry bone syndrome**, and for recurrent laryngeal nerve injury.

5. Teaching Points and Viva Questions

- Correct for albumin before you do anything else.
- Parathyroid hormone splits the differential in two, and an unsuppressed level in the presence of hypercalcaemia is abnormal however normal the number looks.
- Check the urinary calcium before anyone books a neck operation.
- Fluid, not furosemide, is the treatment for acute hypercalcaemia.
- Hypercalcaemia of malignancy has a suppressed parathyroid hormone, rises quickly and usually declares its cause within weeks. Primary hyperparathyroidism is mild, chronic and often incidental.

- Localisation imaging tells the surgeon where to cut. It does not tell you whether to operate.

Questions you should be able to answer:

- Her albumin is 28 g/L and calcium 2.62 mmol/L. Is she hypercalcaemic?
- Parathyroid hormone is 4.1 pmol/L with a calcium of 2.95. Interpret that.
- What must you exclude before referring her for parathyroidectomy, and how?
- She is asymptomatic. Give three findings that would still make you operate.
- A patient with lung cancer has a calcium of 3.8 mmol/L. Outline your first six hours.

Case 24 · Pituitary Disorders

CLINICAL VIGNETTE

A **44-year-old man** attends because his wedding ring no longer fits and he has gone up two shoe sizes over about three years. He sweats excessively, has headaches most days, and wakes with numb tingling hands. His wife says he snores heavily and stops breathing at night. His dentures no longer fit. He was told last year that he had hypertension and borderline diabetes.

On examination: large hands with **doughy soft palms**, prognathism with separation of the lower teeth, macroglossia, frontal bossing and deep nasolabial folds. Multiple skin tags. Blood pressure 158/94 mmHg. **Confrontation testing shows a bitemporal field defect.** Photographs from ten years ago show a strikingly different face.

Insulin-like growth factor 1 markedly raised · growth hormone fails to suppress during an oral glucose tolerance test · magnetic resonance imaging: 18 mm pituitary adenoma with suprasellar extension.

THE MOST USEFUL QUESTION IN THIS CONSULTATION

Acromegaly develops over years, and **the patient and their family cannot see it** because they adapt to the change day by day. It is frequently first suspected by a dentist, an optician or a doctor meeting the patient for the first time.

So ask about ring, shoe, hat and glove size, about dentures no longer fitting, and ask to see photographs from ten years ago. That single request often makes the diagnosis in the consultation, and it costs nothing.

1. Think in Three Layers

A pituitary lesion causes trouble in three separate ways, and you must assess all three in every patient — not just the one that brought them in.

Layer	What to look for
Mass effect	Headache; bitemporal hemianopia from chiasmal compression; diplopia from third, fourth or sixth nerve involvement in the cavernous sinus; cerebrospinal fluid rhinorrhoea
Hormone excess	Growth hormone — acromegaly · prolactin — galactorrhoea, amenorrhoea, loss of libido, erectile dysfunction, infertility · adrenocorticotrophic hormone — Cushing disease (Case 26) · thyroid-stimulating hormone — rare
Hormone deficiency	Hypopituitarism. The axes typically fail in a characteristic order: growth hormone, then gonadotrophins, then thyroid-stimulating hormone, then adrenocorticotrophic hormone — and the posterior pituitary, causing diabetes insipidus, in infiltrative or surgical disease

2. Focused History

- **Acromegaly:** the somatic changes above, plus sweating, headache, **carpal tunnel symptoms**, arthralgia, deepening voice, snoring and daytime somnolence.
- **Complications of acromegaly, all of which need looking for:** hypertension, diabetes mellitus, **obstructive sleep apnoea**, cardiomyopathy and heart failure, arthropathy, **colonic polyps with an increased risk of colorectal cancer**, and thyroid nodules.
- **Hypopituitarism:** loss of libido, erectile dysfunction or amenorrhoea, fatigue, cold intolerance, weight change, postural dizziness, loss of axillary and pubic hair, and — in a woman — failure of lactation.
- **Causes of hypopituitarism to ask about:** an adenoma and its treatment; **pituitary apoplexy**; **Sheehan syndrome after postpartum haemorrhage — ask every parous woman with unexplained fatigue and**

amenorrhoea; craniopharyngioma; infiltrative disease including sarcoidosis, tuberculosis, haemochromatosis and histiocytosis; **hypophysitis, including that caused by immune checkpoint inhibitors**; head injury; and cranial irradiation.

- Family history and features of multiple endocrine neoplasia type 1 — parathyroid, pancreatic and pituitary disease.

3. Physical Examination

- **Hands:** size, doughy soft texture, and Tinel and Phalen tests for carpal tunnel syndrome.
- **Face:** prognathism, interdental separation, macroglossia, frontal bossing, coarse features, and the bite.
- **Skin:** excessive sweating, oiliness, skin tags and acanthosis nigricans.
- **Visual fields by confrontation, and visual acuity** — then formal perimetry. Cranial nerves three, four and six.
- Blood pressure, capillary glucose, signs of heart failure, thyroid, joints, and **testicular volume and body hair distribution** for hypogonadism.

4. Investigations

- **Insulin-like growth factor 1 is the screening test for acromegaly. A random growth hormone level is useless**, because secretion is pulsatile and a normal value means nothing.
- **Confirm with failure of growth hormone suppression during an oral glucose tolerance test** — in health, glucose suppresses growth hormone.
- **Magnetic resonance imaging of the pituitary with contrast**, and formal visual field perimetry.

ASSESS ALL THE AXES, EVERY TIME

Whatever the presenting hormone, **test every axis** — the mass may be secreting one hormone while destroying the production of others.

Prolactin · 9 a.m. cortisol, with a short synacthen or insulin tolerance test if borderline · free thyroxine · luteinising and follicle-stimulating hormone with testosterone or oestradiol · insulin-like growth factor 1.

Use free thyroxine, not thyroid-stimulating hormone, to assess the thyroid axis in pituitary disease. In central hypothyroidism the stimulating hormone is low or inappropriately normal, so relying on it will miss the diagnosis entirely.

THE ONE MEASUREMENT NOT TO OMIT

Measure prolactin in every pituitary mass, because the answer may change the treatment from an operation to a tablet.

A **macroprolactinoma is treated medically with a dopamine agonist**, which shrinks the tumour and restores fields and function — surgery is not first line. Operating on one that was never measured is an avoidable harm.

Two pitfalls: the **hook effect**, in which extremely high prolactin levels give a falsely low reading unless the sample is diluted — ask the laboratory; and **stalk compression**, in which any mass causes a modest prolactin rise by interrupting dopamine inhibition. A very high level suggests a prolactinoma; a modest one suggests compression.

- **Screen for complications of acromegaly:** glycated haemoglobin, lipids, blood pressure, electrocardiogram and echocardiography, sleep study, and colonoscopy.

5. Management

- **Acromegaly: transsphenoidal surgery is first-line treatment.** Residual or persistent disease is treated with somatostatin analogues, the growth hormone receptor antagonist pegvisomant, or cabergoline; radiotherapy is reserved for refractory disease. **Monitor insulin-like growth factor 1.** Mortality is increased in active disease and returns towards normal with biochemical control — which is the argument for treating a slowly progressive cosmetic-seeming condition aggressively.
- Treat the comorbidities in their own right — the hypertension, the diabetes and the sleep apnoea will not resolve simply because the adenoma has been removed.

THE ORDER OF REPLACEMENT MATTERS

Replace hydrocortisone before levothyroxine — always.

Thyroxine increases metabolic demand and the clearance of cortisol. Giving it to a patient with unrecognised adrenocorticotrophic hormone deficiency can **precipitate an adrenal crisis**. If both axes are deficient, the glucocorticoid goes first.

Then: **levothyroxine titrated against free thyroxine, not the stimulating hormone**; sex steroid replacement; growth hormone in selected adults; and desmopressin for diabetes insipidus.

Every patient on glucocorticoid replacement needs **sick-day rules, a steroid emergency card, and an emergency injection kit** — see Case 26.

EMERGENCY: PITUITARY APOPLEXY

Sudden severe headache with vomiting, visual loss or ophthalmoplegia, meningism, and often hypotension, caused by haemorrhage or infarction into a pituitary adenoma. Precipitants include anticoagulation, surgery, pregnancy and dynamic pituitary testing.

It is missed because it looks exactly like subarachnoid haemorrhage or meningitis — and the computed tomogram may be reported as normal.

Give intravenous hydrocortisone immediately, arrange urgent magnetic resonance imaging, and refer to neurosurgery and endocrinology the same hour. The steroid is given before any confirmation, because the patient may be in adrenal crisis.

6. Teaching Points and Viva Questions

- Ask for the old photographs and the ring and shoe sizes.
- Insulin-like growth factor 1, never a random growth hormone.
- Test every axis in every pituitary mass, and use free thyroxine rather than the stimulating hormone.
- Measure prolactin — a macroprolactinoma is treated with a tablet.
- Hydrocortisone before thyroxine.
- Sudden headache with visual loss in a patient with a known adenoma is apoplexy — give steroid first.

Questions you should be able to answer:

- Why is a random growth hormone level of no use, and what do you send instead?
- Explain the anatomical basis of his visual field defect.

- His prolactin is 190 mU/L. Does that change anything? What if it were 19,000?
- His free thyroxine is low with a thyroid-stimulating hormone of 1.2. Interpret that.
- A colleague starts levothyroxine while awaiting the cortisol result. What is your concern?

Case 25 · The Chronic Complications of Diabetes

CLINICAL VIGNETTE

A **61-year-old woman** with type 2 diabetes of fourteen years attends for annual review. Her glycated haemoglobin is **9.4%**. On questioning she describes **burning numbness in both feet, worse at night**, blurred vision, frothy urine, dizziness on standing, and a feeling of fullness after a few mouthfuls with occasional vomiting. She has twice had a hypoglycaemic episode **without any warning symptoms**.

On examination: blood pressure 156/88 mmHg lying, falling to 128/74 mmHg on standing. **Monofilament sensation is absent to the mid-foot bilaterally, ankle jerks are absent, and both posterior tibial pulses are impalpable.** Under the right first metatarsal head there is a **1 cm ulcer surrounded by thick callus, which she had not noticed**. It does not probe to bone.

Retinal photography: moderate non-proliferative retinopathy with macular oedema · urine albumin-to-creatinine ratio 38 mg/mmol · estimated glomerular filtration rate 52.

WHY THIS CASE EXISTS

This patient has **six** complications and reported none of them until asked. She did not notice a foot ulcer. She has lost her warning of hypoglycaemia. Her vision is threatened and her kidneys are failing.

Complication screening is a protocol, not a clinical judgement. It is performed on a schedule, in full, whether or not the patient volunteers symptoms — because the complications that matter most are the ones that are silent until they are irreversible.

1. Retinopathy

- **The stages:** background or non-proliferative change (microaneurysms, dot-and-blot haemorrhages, hard exudates, cotton wool spots) → severe non-proliferative disease → **proliferative retinopathy** with new vessels, vitreous haemorrhage and tractional detachment.
- **Maculopathy is the commonest cause of visual loss in type 2 diabetes** and can occur at any stage, including with otherwise mild retinopathy.
- **Screening: annual retinal photography through dilated pupils**, from diagnosis in type 2 diabetes.
- **Treatment:** glycaemic and blood pressure control; **intravitreal anti-vascular endothelial growth factor therapy for macular oedema**; **panretinal photocoagulation for proliferative disease**. **Refer urgently** for new vessels, vitreous haemorrhage, or any sudden change in vision.
- **A caution:** rapid improvement in glycaemic control can **transiently worsen** retinopathy. Screen the retina before intensifying treatment substantially, and particularly before and during pregnancy.

2. Nephropathy

- **Annual urine albumin-to-creatinine ratio and estimated glomerular filtration rate.** Albuminuria usually precedes the fall in filtration.
- **Treatment:** an angiotensin-converting enzyme inhibitor or receptor blocker, a **sodium–glucose co-transporter 2 inhibitor**, and consideration of a non-steroidal mineralocorticoid receptor antagonist; blood pressure control; avoidance of anti-inflammatory drugs; sick-day rules. The management is that of Case 29.

- **Question the diagnosis** if there is haematuria, rapidly declining function, a very high protein load, or **no retinopathy** — diabetic nephropathy rarely occurs without retinal disease, and another renal diagnosis should be considered.

3. Neuropathy

Pattern	Features and management
Distal symmetrical sensorimotor	Glove-and-stocking numbness with loss of protective sensation — the reason the ulcer went unnoticed. Screen annually with a 10 g monofilament and a tuning fork.
Painful neuropathy	Burning, shooting or allodynic pain, worse at night. Treat with duloxetine, amitriptyline, gabapentin or pregabalin. Explain that relief will be partial — promising abolition guarantees disappointment.
Autonomic neuropathy	Postural hypotension · gastroparesis with early satiety, vomiting and erratic glycaemia · diabetic diarrhoea or constipation · erectile and bladder dysfunction · loss of hypoglycaemia awareness · silent myocardial ischaemia and an increased risk of sudden death.
Mononeuropathy and amyotrophy	Cranial or peripheral nerve palsies; and painful asymmetrical proximal wasting in diabetic amyotrophy.

- **Loss of hypoglycaemia awareness is itself an indication to relax the glycaemic target deliberately** until awareness returns. Chasing a low glycated haemoglobin in a patient who cannot feel a hypoglycaemic episode is dangerous.

THE FOOT — WHERE LIMBS ARE LOST

Examine both feet at every review — shoes and socks off, including between the toes — and look inside the footwear.

Risk factors for ulceration: neuropathy, peripheral arterial disease, foot deformity, callus, previous ulcer or amputation, poor vision, and renal disease.

Any ulcer is referred to a multidisciplinary foot service — within one week, and the same day if it is infected or the foot is ischaemic. Treatment is offloading, debridement, vascular assessment, imaging for osteomyelitis where the ulcer probes to bone, and antibiotics for infection rather than for colonisation.

Charcot neuroarthropathy: a **hot, swollen, red foot with palpable pulses** in a neuropathic patient, often with little pain. It is repeatedly mistaken for infection, gout or a sprain. **Immediate immobilisation and offloading; every week of delay produces permanent deformity.**

Prevention, taught explicitly: inspect the feet daily including with a mirror, never walk barefoot, check bath water with the hand or a thermometer, professional nail care, and properly fitted footwear.

4. Macrovascular Disease

- Ischaemic heart disease — **frequently silent**, which is why a diabetic patient with unexplained breathlessness, fatigue or vomiting needs an electrocardiogram; stroke; and peripheral arterial disease.

- **Treat total cardiovascular risk rather than glucose alone:** statin therapy, blood pressure control, antiplatelet therapy where indicated, smoking cessation, and an agent with proven cardiovascular benefit — a sodium–glucose co-transporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist.

5. The Annual Review — What Must Actually Be Done

Domain	Action
Glycaemia	Glycated haemoglobin with an individualised target; review of hypoglycaemia frequency and awareness
Vascular risk	Blood pressure with a standing reading, lipid profile, smoking status, weight and waist
Eyes	Retinal photography through dilated pupils
Feet	Inspection, pulses, monofilament and vibration, footwear — and risk stratification
Kidneys	Urine albumin-to-creatinine ratio, creatinine and estimated filtration rate
Treatment review	Injection sites and lipohypertrophy, inhaler-style technique check for injectables, adherence, drug rationalisation
The conversation nobody has	Mood, sexual function, driving, hypoglycaemia awareness, contraception and pregnancy plans, fasting during Ramadan (Case 20), and structured education
Other	Vaccination, dental review, and screening for fatty liver disease

6. Teaching Points and Viva Questions

- Screen on a schedule. The complications that matter announce themselves too late.
- Take the shoes and socks off. That is where you find the limb-threatening problem.
- A hot swollen red foot with good pulses is Charcot, not cellulitis.
- Check the retina before you intensify glycaemic control sharply.
- Loss of hypoglycaemia awareness is a reason to loosen the target, not tighten it.
- Proteinuria without retinopathy should make you doubt that this is diabetic nephropathy.

Questions you should be able to answer:

- List this patient's complications and say which she reported spontaneously.
- Why does her ulcer matter more than her glycated haemoglobin this week?
- She has no warning of hypoglycaemia. What do you do about her targets?
- A month later the same foot is hot, red and swollen with strong pulses and no fever. What is your diagnosis?
- Her albumin-to-creatinine ratio is 300 with visible haematuria and no retinopathy. What now?

Case 26 · Cushing Syndrome and Adrenal Insufficiency

CLINICAL VIGNETTE — PART ONE

A **38-year-old woman** describes eighteen months of weight gain across the abdomen with **thinning of the arms and legs**, bruising after the slightest knock, and wide purple marks on her abdomen. She cannot rise from a chair without using her arms. Her periods have stopped, she has developed facial hair and acne, and she feels persistently low. She was recently diagnosed with diabetes and hypertension, and **fractured a vertebra lifting a bag**.

On examination: round plethoric face, an interscapular fat pad, thin skin with multiple bruises, **broad purple striae**, proximal weakness, and blood pressure 168/104 mmHg.

Overnight dexamethasone fails to suppress cortisol · late-night salivary cortisol raised · 24-hour urinary free cortisol raised · adrenocorticotrophic hormone not suppressed.

BEFORE ANYTHING ELSE

By far the commonest cause of Cushing syndrome is prescribed or purchased glucocorticoid, and the diagnosis is made by asking rather than by testing.

Ask about **oral steroids, inhalers, nasal sprays, skin creams, eye drops, joint injections, and traditional, herbal or imported remedies** — some of which contain potent steroids undeclared. Patients do not think of a cream as a drug.

Establish this before requesting a single test.

1. Cushing Syndrome — Recognising It

Distinguish **Cushing syndrome**, the clinical state of glucocorticoid excess, from **Cushing disease**, which is specifically a pituitary corticotroph adenoma.

WHICH FEATURES ACTUALLY DISCRIMINATE

Obesity, hypertension, diabetes and low mood are common and do not discriminate. **The features that do are the catabolic ones:**

Proximal myopathy · thin skin with easy bruising · wide purple striae · unexplained osteoporosis or fragility fracture in a young person · facial plethora · **unprovoked hypokalaemia** · and the combination of central weight gain with **wasted limbs**.

A patient who has gained weight all over is unlikely to have Cushing syndrome. One who has gained it centrally while their thighs have wasted, and who cannot get out of a chair, very possibly does.

Screening and pitfalls

- **Any two of: an overnight 1 mg dexamethasone suppression test, a late-night salivary cortisol, and a 24-hour urinary free cortisol.** A random serum cortisol is of no value.
- **Pseudo-Cushing states** produce genuinely abnormal results: depression, alcohol excess, obesity, poorly controlled diabetes and severe illness. Oestrogen raises cortisol-binding globulin and therefore total cortisol; shift work invalidates late-night sampling.

Then localise — and the pivotal test is the corticotrophin level

Adrenocorticotrophic hormone	Meaning and next step
Suppressed	The lesion is adrenal and is making cortisol autonomously — adenoma, carcinoma or hyperplasia. Proceed to adrenal computed tomography.
Not suppressed or raised	The disease is corticotrophin-dependent. Pituitary magnetic resonance imaging, high-dose dexamethasone and corticotrophin-releasing hormone testing, and bilateral inferior petrosal sinus sampling to separate a pituitary source from an ectopic one. Computed tomography of chest and abdomen for an ectopic tumour.

- **Features suggesting ectopic corticotrophin secretion** — small cell lung carcinoma, bronchial or pancreatic neuroendocrine tumours: rapid onset over weeks, **severe hypokalaemia with metabolic alkalosis**, marked hyperpigmentation, profound myopathy, and **weight loss rather than gain**.

Management

- **Treat the cause:** transsphenoidal surgery for Cushing disease; adrenalectomy for an adrenal tumour; resection of an ectopic source. Medical control with metyrapone, ketoconazole or osilodrostat while awaiting definitive treatment.
- **Manage the consequences actively:** diabetes, hypertension, osteoporosis, psychiatric symptoms, infection risk — and **thromboprophylaxis, because Cushing syndrome is a markedly hypercoagulable state**.
- **After successful treatment, expect adrenal insufficiency.** The remaining axis is suppressed and recovers over months. Replace glucocorticoid, taper slowly, and warn the patient about **glucocorticoid withdrawal syndrome** — aching, fatigue and low mood despite adequate replacement. Issue a steroid card.

2. Adrenal Insufficiency

CLINICAL VIGNETTE — PART TWO

A **32-year-old man** has had eight months of fatigue, anorexia and 9 kg of weight loss, with nausea, dizziness on standing and a **craving for salty food**. His wife has noticed that his skin has darkened, especially the creases of his palms and an old appendicectomy scar. He now presents collapsed with vomiting and abdominal pain three days into an influenza-like illness.

Blood pressure 78/48 mmHg · sodium 122 mmol/L · potassium 6.0 mmol/L · glucose 3.2 mmol/L · urea raised. Buccal mucosa and palmar creases are pigmented.

- **Pigmentation of the palmar creases, buccal mucosa, scars and pressure areas is the sign of primary adrenal failure**, caused by the high corticotrophin level. **It is absent in secondary, pituitary-driven insufficiency** — which is how the two are separated at the bedside.
- **The combination to recognise:** fatigue and weight loss with **hyponatraemia, hyperkalaemia and hypoglycaemia**, and postural hypotension. It is repeatedly mistaken for gastroenteritis, depression or occult malignancy.

Primary — adrenal	Secondary — pituitary or exogenous
Autoimmune adrenalitis, often with other autoimmune disease	Abrupt withdrawal of long-term glucocorticoids — by far the commonest cause of adrenal insufficiency overall
Tuberculosis — historically the leading cause and still important in this region; look for adrenal calcification	Pituitary tumour, surgery or radiotherapy; apoplexy; Sheehan syndrome
Adrenal haemorrhage — meningococcal sepsis, antiphospholipid syndrome; metastases; adrenoleukodystrophy; congenital adrenal hyperplasia	Hypophysitis, including from immune checkpoint inhibitors; infiltrative disease
Drugs — ketoconazole, etomidate, checkpoint inhibitors; fungal infection and human immunodeficiency virus	Aldosterone production is preserved, so hyperkalaemia and salt craving are absent and pigmentation does not occur

Investigation

- **A 9 a.m. cortisol** as the initial test, with **the short synacthen test as the confirmatory one**. **Corticotrophin** — high in primary, low or normal in secondary disease. Renin and aldosterone.
- **21-hydroxylase autoantibodies**; adrenal computed tomography where autoantibodies are negative, looking for **calcification, enlargement or metastases**; tuberculosis assessment.
- Screen for associated autoimmune disease — thyroid, coeliac, pernicious anaemia, type 1 diabetes.

EMERGENCY: ADRENAL CRISIS

Treat first, confirm afterwards. Do not wait for a synacthen test on a hypotensive, hyponatraemic, vomiting patient.

1. Take a sample for cortisol and corticotrophin — one tube, ten seconds.

2. Hydrocortisone 100 mg intravenously immediately, then regularly.

3. Rapid intravenous 0.9% sodium chloride; correct hypoglycaemia.

4. Treat the precipitant — usually infection.

Mineralocorticoid replacement is not needed in the acute phase, because high-dose hydrocortisone has sufficient mineralocorticoid activity. **The commonest fatal error is diagnostic delay while tests are arranged.**

Long-term management — and the education that keeps them alive

- **Hydrocortisone in divided doses** approximating the diurnal rhythm; **fludrocortisone in primary disease only**, titrated against blood pressure, postural drop, sodium and renin.
- **Sick-day rules, taught and written down: double the oral dose during febrile illness, and use parenteral hydrocortisone if vomiting or unable to take tablets.**
- **A steroid emergency card, medical alert identification, and an emergency hydrocortisone injection kit with the patient and a family member trained to use it.**
- **Stress dosing for surgery, procedures and childbirth** — and **steroids must never be omitted before an operation**, which is a recurring and preventable cause of perioperative crisis.

3. Teaching Points and Viva Questions

- Ask about every steroid, including creams, inhalers, injections and traditional remedies.

- The catabolic features separate Cushing syndrome from obesity — myopathy, thin skin, purple striae, fracture.
- Corticotrophin divides the differential: suppressed means adrenal, unsuppressed means pituitary or ectopic.
- Pigmented palmar creases mean primary adrenal failure.
- Hyponatraemia with hyperkalaemia and hypoglycaemia in a tired thin patient is Addison disease.
- Treat adrenal crisis before you confirm it, and never omit steroid before surgery.

Questions you should be able to answer:

- Which of her features would you use to argue that this is not simple obesity?
- Her corticotrophin is undetectable. What is the lesion and what imaging do you request?
- Give three findings that would suggest an ectopic source instead.
- The collapsed man's synacthen test cannot be done until tomorrow. What do you do tonight?
- He is listed for a hernia repair. What must be arranged, and what must not happen?

Case 27 · Lipid and Lipoprotein Disorders

CLINICAL VIGNETTE

A **38-year-old man** is referred after his brother had a myocardial infarction at the age of 41. His father died of a heart attack at 46. He himself has no symptoms, does not smoke, and is of normal weight.

On examination: body mass index 25 kg/m², blood pressure normal. There are **firm nodular thickenings over both Achilles tendons and over the extensor tendons of the hands**, **corneal arcus**, and xanthelasma at both upper eyelids.

Total cholesterol 9.8 mmol/L · low-density lipoprotein cholesterol 7.4 · high-density lipoprotein 1.1 · triglycerides 1.4 · thyroid function, liver function and glucose all normal.

THE PHYSICAL SIGN THAT MAKES THIS DIAGNOSIS

Tendon xanthomata are close to diagnostic of familial hypercholesterolaemia. They are not xanthelasma and not corneal arcus, both of which are common and non-specific — they are firm nodules **within the tendon itself**, classically Achilles and the extensor tendons of the hands, and they move with the tendon.

Feel for them in any patient with a very high cholesterol or a family history of premature coronary disease. **They take fifteen seconds to find and they change the diagnosis, the treatment target, and the management of the entire family.**

1. Exclude Secondary Causes First

A raised cholesterol is not a diagnosis. Before labelling a dyslipidaemia primary, exclude the treatable secondary causes — several of which resolve completely when the underlying problem is corrected.

Cause	Test or question
Hypothyroidism	Thyroid-stimulating hormone — and a common, entirely reversible cause
Nephrotic syndrome and chronic kidney disease	Urine albumin-to-creatinine ratio, creatinine, albumin
Cholestasis	Liver function tests
Poorly controlled diabetes and obesity	Glycated haemoglobin, weight
Alcohol	Quantified intake — particularly for hypertriglyceridaemia
Drugs	Thiazides, corticosteroids, oestrogens, retinoids, antiretrovirals, ciclosporin, some antipsychotics
Pregnancy	Pregnancy test

2. Familial Hypercholesterolaemia

- **Autosomal dominant**, from mutations in the low-density lipoprotein receptor, apolipoprotein B or *PCSK9*, and affecting roughly one person in 250 — which makes it one of the commonest serious inherited disorders, and one of the most under-diagnosed.

A REGIONAL CONSIDERATION

Consanguineous marriage substantially increases the likelihood of homozygous familial hypercholesterolaemia, which is far more severe: it presents in childhood with extensive cutaneous and tendon xanthomata, aortic stenosis and coronary disease in the first two decades, and it requires lipoprotein apheresis and specialist care.

So in this population the **pedigree matters twice over** — for cascade screening of an autosomal dominant condition, and for recognising the homozygous form early enough to treat it.

- **Diagnostic pointers:** low-density lipoprotein cholesterol above about 4.9 mmol/L in an adult; **tendon xanthomata**; corneal arcus or xanthelasma before the age of 45; and **premature coronary disease in the family — under 55 in men, under 65 in women — or unexplained sudden death.**
- Use a validated criteria set — the Simon Broome or Dutch Lipid Clinic Network criteria — and arrange **genetic testing with cascade screening of all first-degree relatives.**

WHAT ACTUALLY SAVES LIVES HERE

Cascade screening is the highest-value intervention in this consultation, and it is not about the patient in front of you. Each first-degree relative has a one-in-two chance of carrying the same mutation. Identifying and treating them **before their first coronary event** is the entire point, and it extends outwards through the family. Where a mutation is found, testing also allows you to **discharge the relatives who did not inherit it** — which is as valuable as finding those who did.

Treatment of affected children generally begins around the age of ten.

3. Severe Hypertriglyceridaemia — a Different Problem

- **Triglycerides above about 10 mmol/L carry a real risk of acute pancreatitis**, which is the immediate concern rather than atherosclerosis.
- Look for **eruptive xanthomata**, lipaemia retinalis, hepatosplenomegaly, and grossly **milky (lipaemic) serum**.
- Causes: familial chylomicronaemia and familial combined hyperlipidaemia, on a background of **alcohol, uncontrolled diabetes, obesity, oestrogens or retinoids** — usually a genetic predisposition unmasked by an acquired factor.
- **Treatment is a fibrate, omega-3 fatty acids, a very low fat diet, strict glycaemic control and complete alcohol abstinence.** A statin lowers cholesterol and does comparatively little for very high triglycerides.
- **Laboratory artefacts to know:** severe hypertriglyceridaemia causes **pseudohyponatraemia** and can interfere with several assays.

4. Investigation and Management

- **A full lipid profile with non-high-density-lipoprotein cholesterol. A fasting sample is not required** for routine assessment. Glycated haemoglobin, thyroid, renal and liver function, urine albumin-to-creatinine ratio, and a baseline creatine kinase.
- **Lipoprotein(a) measured once in a lifetime** in anyone with premature or familial disease — it is an independent, largely genetically determined risk factor.
- A three-generation family history, and formal cardiovascular risk assessment.

A CALCULATION NOT TO MAKE

Cardiovascular risk calculators are not valid in familial hypercholesterolaemia.

They estimate ten-year risk from current risk factors, whereas what harms this patient is **lifetime exposure to a very high cholesterol from birth**. A 38-year-old with familial disease will have a reassuring ten-year score and a severely elevated lifetime risk.

Treat on the diagnosis, not on the calculator.

- **Lifestyle for everyone:** diet, weight, physical activity, alcohol, and smoking cessation — which matters more in this patient than any milligram adjustment.
- **High-intensity statin as the foundation**, aiming for at least a 50% reduction in low-density lipoprotein cholesterol in familial disease, with absolute targets set by risk category.
- **Then add, in sequence: ezetimibe; a PCSK9 inhibitor or inclisiran; bempedoic acid. Lipoprotein apheresis** in homozygous disease and refractory cases.

STATIN INTOLERANCE

Do not accept "statin intolerant" without a structured rechallenge — the alternative is an untreated patient with a lifetime of excess risk.

Check creatine kinase; exclude hypothyroidism, vitamin D deficiency and interacting drugs; then rechallenge with a different statin, at a lower dose, or on alternate days. Most patients who report myalgia can eventually tolerate some statin, and the nocebo effect is well documented.

True rhabdomyolysis is rare and is a different matter entirely — stop the drug and investigate.

- **Stop statins in pregnancy** and manage with diet, with specialist input; plan pregnancies in women on lipid-lowering therapy.

5. Teaching Points and Viva Questions

- Exclude thyroid, renal, hepatic, diabetic, alcohol and drug causes before calling it primary.
- Feel the Achilles tendons. Tendon xanthomata are close to diagnostic.
- Risk calculators do not apply in familial hypercholesterolaemia.
- Cascade-screen the family — that is where the benefit is, and consanguinity makes it matter more.
- Triglycerides above 10 mean pancreatitis risk and a fibrate, not a statin.
- Investigate statin myalgia and rechallenge rather than abandoning treatment.

Questions you should be able to answer:

- Which physical sign here is close to diagnostic, and how does it differ from xanthelasma?
- His ten-year cardiovascular risk score is 4%. How do you interpret that?
- What do you do about his brother, his sister and his children?
- A different patient has triglycerides of 34 mmol/L. What is the immediate risk and the treatment?
- He returns saying the statin gives him aching legs. Set out your approach.

The Nephrology Block

Acute kidney injury, chronic kidney disease, acid–base disorders, hyponatraemia, urinary tract infection and glomerulonephritis.

Cases 28–33 · 8,592 words

This block covers the renal teaching of both internal medicine courses. The **first course** supplies cases 28 and 31; the **second course** supplies cases 32 and 33.

Case	Lecture it serves
System opener: the renal history and examination	History taking in nephrology
Case 28 — Acute kidney injury	Acute kidney injury; acute renal failure seminar
Case 29 — Chronic kidney disease	Chronic kidney disease; approach to the patient with chronic kidney disease
Case 30 — Acid–base disorders	Acid–base disorders
Case 31 — Hyponatraemia	Fluid and electrolyte disorders
Case 32 — Urinary tract infection	Urinary tract infections
Case 33 — Glomerulonephritis	Glomerulonephritis

Hyperkalaemia is taught within the acute kidney injury case, where students will actually meet it, and hypernatraemia within the hyponatraemia case. **Nephrotic syndrome** is covered as Seminar 2 in Part Two, where the approach to generalised oedema can be set out in full.

System Opener · The Renal History and Examination

Kidneys announce themselves late and quietly. Half of renal medicine at the bedside is one skill — **deciding whether the patient is volume-depleted, euvolaemic or overloaded** — and the other half is remembering to look at the urine.

The history

Ask about the urine, in detail

- **Volume.** Oliguria, and specifically **anuria** — complete absence of urine points to obstruction, a vascular catastrophe or severe glomerular disease, and almost never to simple dehydration.
- **Appearance.** Frothy urine suggests heavy proteinuria; red or cola-coloured urine suggests glomerular bleeding; blood only at the start or end of the stream suggests a urethral or bladder source.

- **Nocturia** — an early and underrated symptom of both concentrating failure and obstruction.
- **Obstructive symptoms:** hesitancy, poor stream, terminal dribbling, incomplete emptying. In an older man these three questions may be the whole diagnosis.

Ask about the consequences

- **Oedema, and where it is worst on waking.** Periorbital puffiness in the morning suggests renal disease; ankle swelling worst in the evening suggests cardiac or hypoalbuminaemic causes.
- **Uraemic symptoms:** nausea, anorexia, a metallic taste, hiccups, itch, restless legs, cognitive slowing and easy bruising.

Ask about the causes

- **Drugs and exposures:** non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors and receptor blockers, diuretics, aminoglycosides, iodinated contrast, proton pump inhibitors, chemotherapy, and **herbal or traditional remedies**, which patients seldom classify as medicines.
- **Volume loss:** vomiting, diarrhoea, burns, and **heat exposure with inadequate intake**, which in this climate is a common and entirely preventable cause.
- **Systemic disease:** rash, arthralgia, oral ulceration, sinusitis, **haemoptysis** (the pulmonary–renal syndromes), fever and weight loss.
- **Background:** duration of diabetes and hypertension, stones, childhood urinary infections, obstetric history, family history of polycystic kidney disease or deafness, and consanguinity.

> **THE SINGLE MOST USEFUL PIECE OF INFORMATION**
>
> Before you can call anything "acute", you need to know where the patient started. **Find the previous creatinine** — from old records, another hospital, a pre-operative check, an insurance medical.
>
> A creatinine of 280 µmol/L means something entirely different in a patient whose baseline was 90 than in one whose baseline was 250. Without the baseline you cannot distinguish acute kidney injury from chronic kidney disease, and the management of the two diverges immediately.

The examination

Volume status — the central skill

	Hypovolaemic	Euvolaemic	Hypervolaemic
Jugular venous pressure	Not visible	Normal	Raised
Blood pressure	Low, with a postural drop	Normal	Often raised
Mucous membranes, skin	Dry, reduced turgor	Normal	Normal or oedematous
Peripheries	Cool, delayed capillary refill	Warm	Oedema — ankles if ambulant, sacrum if bedbound
Chest	Clear	Clear	Basal crackles, effusions
Weight and urine output	Falling weight, low output	Stable	Rising weight

Then the rest

- **General:** pallor, sallow uraemic complexion, scratch marks, bruising, uraemic fetor, **asterixis**, and a **pericardial rub** — uraemic pericarditis is an emergency and an indication for dialysis.
- **Arms:** an arteriovenous fistula, felt for a thrill and listened to for a bruit; scars from previous dialysis lines; leuconychia.
- **Abdomen:** ballotable kidneys of polycystic disease, a **transplanted kidney in the iliac fossa** beneath a hockey-stick scar, a peritoneal dialysis catheter, renal bruits, and — always — a **palpable bladder**.
- **Never omit:** blood pressure, **urine dipstick**, and fundoscopy.

THE THREE BEDSIDE STEPS IN EVERY CASE OF ACUTE KIDNEY INJURY

Dipstick the urine. Feel or scan the bladder. Assess the volume status.

Each takes under a minute, none requires the laboratory, and together they identify or exclude the majority of causes. In practice, all three are frequently skipped in favour of waiting for a creatinine that has already been reported.

Case 28 · Acute Kidney Injury

CLINICAL VIGNETTE

A **76-year-old man** is brought in after four days of vomiting and profuse diarrhoea that began after a family gathering. He has been unable to keep fluids down and, for the past 24 hours, has passed only a small amount of dark urine.

He takes ramipril for hypertension, indometacin for knee pain that he buys himself, and gliclazide for type 2 diabetes. He has longstanding prostatic symptoms.

On examination: he is dry with reduced skin turgor. Blood pressure 104/62 mmHg lying, falling to 82/54 mmHg on standing. Heart rate 108/min. The jugular venous pressure is not visible. **The bladder is not palpable, and a bedside scan shows 40 mL.** Urine dipstick is negative for blood, protein, leucocytes and nitrites.

Creatinine 342 µmol/L (baseline 96 eight months ago) · urea 28 mmol/L · potassium 6.4 mmol/L · bicarbonate 16 mmol/L.

1. Stage It, Then Classify It

Acute kidney injury is present if any one of these is met: a rise in creatinine of 26.5 µmol/L or more within 48 hours; a rise to 1.5 times baseline or more within 7 days; or a urine output below 0.5 mL/kg/hour for 6 hours.

Stage	Creatinine	Urine output
1	1.5–1.9 × baseline, or a rise of 26.5 µmol/L	Below 0.5 mL/kg/h for 6–12 hours
2	2.0–2.9 × baseline	Below 0.5 mL/kg/h for 12 hours or more
3	3.0 × baseline or more, or creatinine above 354 µmol/L, or the need for replacement therapy	Below 0.3 mL/kg/h for 24 hours, or anuria for 12 hours

This patient is **stage 3**. But staging is not diagnosis. **"Acute kidney injury" is a syndrome, not an answer** — the task is to say which of the three mechanisms is responsible, because the treatment of each is entirely different.

Mechanism	Causes	What points to it
Pre-renal — the kidney is underperfused but structurally intact	Volume depletion, sepsis, heart failure, cirrhosis, renal artery disease, and drugs that disable autoregulation	Hypovolaemia or hypotension, bland urinalysis, concentrated urine, rapid response to volume replacement
Intrinsic — the kidney itself is damaged	Acute tubular necrosis (ischaemic or toxic); acute interstitial nephritis; glomerulonephritis; vascular disease and thrombotic microangiopathy	Abnormal urinalysis, casts on microscopy, systemic features, no response to volume
Post-renal — the urine cannot get out	Prostatic disease, stones, pelvic or retroperitoneal malignancy, retroperitoneal fibrosis, a blocked catheter	Anuria or fluctuating output, palpable bladder, hydronephrosis on ultrasound. Must obstruct both kidneys, or a single functioning one

2. Focused History

- Quantify the losses and the intake, and establish the urine output — including whether anuria was complete.

- **The drug history is the diagnosis in a large proportion of cases.** This man is taking the classical combination.

> **THE TRIPLE WHAMMY**
> An **angiotensin-converting enzyme inhibitor** dilates the efferent arteriole. A **non-steroidal anti-inflammatory drug** constricts the afferent arteriole. A **diuretic**, or any other cause of volume depletion, removes the perfusion pressure altogether.
> Each alone is usually tolerated. Together, on a day when the patient stops drinking, they dismantle glomerular autoregulation completely. **Ask about drugs bought without prescription**, which is how the anti-inflammatory usually enters the picture.

- **Sepsis:** fever, rigors, localising symptoms. Sepsis is the commonest cause of acute kidney injury in hospital.
- **Obstruction:** prostatic symptoms, known malignancy, previous pelvic surgery or radiotherapy, stones.
- **Intrinsic disease:** rash, arthralgia, haemoptysis, sinusitis, fever with eosinophilia after a new drug, and **muscle pain with dark urine** suggesting rhabdomyolysis.
- Recent iodinated contrast, and any recent hospital admission.

3. Physical Examination

- **Volume status**, using the table in the opener. This decides the first hour.
- **Palpate and scan the bladder in every patient.** Chronic retention is common, easily missed, and reversed by a catheter — the cheapest cure in medicine.
- Assess for sepsis and its source; examine for rash, joints and signs of systemic vasculitis; check for a pericardial rub and for asterixis.
- Perform a rectal examination where prostatic obstruction is suspected, and abdominal examination for masses.

4. Investigations

The urine tells you the mechanism

Urinalysis	What it suggests
Bland — no blood, no protein	Pre-renal disease or acute tubular necrosis
Blood and protein together	Glomerulonephritis — this combination demands urgent nephrology discussion
Leucocytes and nitrites	Urinary tract infection
Leucocytes without infection, with eosinophilia and a recent new drug	Acute interstitial nephritis
Microscopy: red cell casts	Glomerulonephritis
Microscopy: muddy brown granular casts	Acute tubular necrosis

- **Blood:** urea, electrolytes and creatinine, bicarbonate, calcium and phosphate, **creatine kinase** if rhabdomyolysis is possible, liver function, complete blood count with film (fragments suggest thrombotic microangiopathy), C-reactive protein, blood cultures, venous gas and lactate.
- **If intrinsic renal disease is suspected:** antinuclear and antineutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibody, complement, immunoglobulins with protein electrophoresis and serum free light chains, hepatitis B and C, and human immunodeficiency virus serology.
- **Urine protein-to-creatinine ratio** to quantify proteinuria.
- **Renal ultrasound within 24 hours** — immediately if obstruction is suspected or no cause is apparent. It looks for hydronephrosis, and also reports kidney size and cortical thickness: **small echogenic kidneys mean the disease is chronic**, whatever the history says.
- **Electrocardiogram** now, because of the potassium.
- **Renal biopsy** where pre-renal and post-renal causes are excluded and the intrinsic cause is unclear — a nephrology decision, but one students should know exists.

5. Management

EMERGENCY: HYPERKALAEMIA

Treat the potassium before anything else if it is 6.5 mmol/L or above, or if there are electrocardiographic changes at any level.

Electrocardiogram sequence: tall tented T waves → flattened or absent P waves with a prolonged PR interval → broadening QRS → sine wave → arrest.

1. Calcium gluconate 10%, 10 mL intravenously — stabilises the myocardium within minutes. It does **not** lower the potassium, and it must be repeated if changes persist.

2. Insulin with glucose — 10 units of soluble insulin in 25 g of glucose, which shifts potassium into cells over 15–30 minutes. **Monitor for rebound hypoglycaemia for several hours.**

3. Nebulised salbutamol, 10–20 mg, as an additional shifting agent.

4. Then remove potassium from the body: stop all contributing drugs, treat the cause, give a potassium binder, and refer for dialysis if the level is refractory.

Sodium bicarbonate is not part of routine treatment.

Then treat the kidney injury

- **Restore perfusion.** In a hypovolaemic patient give balanced crystalloid and reassess repeatedly — clinically, not by a single number. **Do not give unmeasured fluid to an anuric, overloaded patient**; that produces pulmonary oedema without producing urine.
- **Stop the nephrotoxic drugs:** the anti-inflammatory permanently, the angiotensin-converting enzyme inhibitor temporarily. **Review every drug for renal clearance** — metformin, sulfonylureas, direct oral anticoagulants, opioids, and many antibiotics need adjustment or suspension.
- **Relieve obstruction** — catheterise for bladder outflow obstruction, and arrange nephrostomy or stenting for upper tract obstruction. Anticipate a **post-obstructive diuresis** and replace the losses.
- **Treat sepsis** with source control and appropriate antibiotics at renally adjusted doses.

- **Monitor:** hourly urine output, daily weight, daily electrolytes, and a fluid balance chart that someone actually completes.
- Avoid further contrast where possible, and avoid nephrotoxic antibiotics where an alternative exists.

Urgent dialysis — the indications	Detail
A cidosis	Severe metabolic acidosis refractory to medical treatment
E lectrolytes	Hyperkalaemia refractory to medical treatment
I ntoxication	Lithium, salicylate, toxic alcohols, metformin-associated lactic acidosis
O verload	Pulmonary oedema unresponsive to diuretics
U raemia	Uraemic pericarditis or encephalopathy

After the episode

- **An episode of acute kidney injury predicts chronic kidney disease.** Document it clearly in the discharge summary, arrange follow-up of the creatinine, and specify **when and how the suspended drugs should be restarted, and by whom**.
- Give **sick-day rules**: patients taking angiotensin-converting enzyme inhibitors or receptor blockers, diuretics, metformin, sodium–glucose co-transporter 2 inhibitors or anti-inflammatory drugs should hold them during vomiting, diarrhoea or fever, and seek advice.

6. Teaching Points and Viva Questions

- Dipstick, bladder, volume status. Three bedside steps, one minute, most of the diagnosis.
- Find the baseline creatinine before you call anything acute.
- Blood and protein on the dipstick changes the whole problem — that is glomerular disease and it needs a nephrologist today.
- The commonest reversible causes are a drug you can stop and a bladder you can drain.
- A patient can die of hyperkalaemia while the team is discussing the creatinine.

Questions you should be able to answer:

- Classify this man's injury and justify it from the findings given.
- Explain, at the level of the arteriole, how his three drugs interacted.
- His potassium is 6.4 with tented T waves. Give your first three actions in order, and say what each achieves.
- The urine now shows blood and protein. How does your plan change?
- When would you refer for urgent dialysis?

Case 29 · Chronic Kidney Disease

CLINICAL VIGNETTE

A **62-year-old woman** with type 2 diabetes of 15 years and longstanding hypertension is referred from the diabetes clinic. She has been increasingly tired for a year, itches at night, gets up three times to pass urine, and has noticed her ankles swelling.

Estimated glomerular filtration rate 24 mL/min/1.73 m² (48 two years ago) · **urine albumin-to-creatinine ratio 180 mg/mmol** · haemoglobin 94 g/L · phosphate raised · corrected calcium low-normal · parathyroid hormone markedly raised · bicarbonate 19 mmol/L.

Ultrasound shows two small, echogenic kidneys with thinned cortex and no hydronephrosis.

1. Staging — Two Axes, Not One

Students learn the estimated filtration rate and stop there. **Albuminuria carries at least as much prognostic weight**, and the two together define risk far better than either alone.

Filtration rate (mL/min/1.73 m²)	Albuminuria (mg/mmol)
G1 90 or above · G2 60–89	A1 below 3 — normal to mildly increased
G3a 45–59 · G3b 30–44	A2 3–30 — moderately increased
G4 15–29 · G5 below 15	A3 above 30 — severely increased

This patient is **G4 A3** — among the highest risk categories for both progression to end-stage disease and for cardiovascular death. Chronic kidney disease also requires that the abnormality has been present for **more than three months**.

Is it chronic, or acute, or both?

Favours chronic	But be careful
Previous abnormal results over months or years	A single old result may itself have been an acute episode
Small, echogenic kidneys with thinned cortex	Kidneys stay large in diabetic nephropathy, polycystic disease, amyloidosis, myeloma and human immunodeficiency virus nephropathy
Normocytic anaemia, raised phosphate with raised parathyroid hormone, renal bone disease	Anaemia and hyperphosphataemia can develop within weeks in severe acute injury
Absence of any acute precipitant	Chronic disease very commonly presents with acute-on-chronic deterioration

2. Focused History

- **The trajectory.** Collect every previous creatinine you can find and plot them. A gradual decline over years, a sudden step, or a recent acceleration each mean something different.
- **Establish the cause.** Duration and control of diabetes and hypertension; previous proteinuria or haematuria; recurrent childhood urinary infection or reflux; stones; obstetric history; family history of polycystic disease or of deafness with renal failure; long-term drug and analgesic use, including traditional remedies.

- **Symptoms of complications:** fatigue and breathlessness (anaemia), bone and joint pain, itch, cramps and restless legs, nausea and anorexia, and cognitive change.
- **Cardiovascular history**, since that is what is most likely to kill her.
- **Function, support and preferences** — because planning for renal replacement, or for conservative care, has to begin long before it is needed.

3. Physical Examination

- Blood pressure, including standing; volume status; weight.
- Pallor, scratch marks, bruising, sallow complexion; **asterixis and a pericardial rub** in advanced disease.
- Signs of the underlying cause: diabetic retinopathy on fundoscopy, ballotable kidneys, bruits.
- **Diabetic foot examination** and peripheral pulses. Assess the forearm veins — see below.

4. Investigations

- Urea, electrolytes, creatinine and estimated filtration rate, with the **trend** rather than the single value; bicarbonate.
- **Urine albumin-to-creatinine ratio** on an early morning sample, with urinalysis and microscopy. Blood and protein together still means glomerular disease and still needs investigation, even in a known diabetic.
- **Ultrasound** for size, symmetry, cortical thickness, cysts and obstruction.
- **Complete blood count with full haematinics — iron studies, ferritin, transferrin saturation, vitamin B12 and folate.** Do not label anaemia as renal until iron deficiency has been excluded and corrected.
- **Bone profile:** calcium, phosphate, alkaline phosphatase, parathyroid hormone and 25-hydroxyvitamin D.
- Lipids, glycated haemoglobin, and where the cause is unclear an immunological and myeloma screen. Hepatitis B and C and human immunodeficiency virus serology when replacement therapy is anticipated.

5. Management

Management has four separate aims. Students usually remember the third and forget the first.

Aim 1 — Reduce cardiovascular risk

- **Most patients with chronic kidney disease die of cardiovascular disease before they ever reach dialysis.** Blood pressure control, statin therapy, smoking cessation and glycaemic control are therefore not peripheral to renal care; they are the largest part of it.

Aim 2 — Slow progression

- **Blood pressure** below 130/80 mmHg where albuminuria is present.

- **An angiotensin-converting enzyme inhibitor or receptor blocker**, titrated to the maximum tolerated dose, in anyone with significant albuminuria.
- **A sodium–glucose co-transporter 2 inhibitor**, which now has clear evidence for slowing progression in albuminuric chronic kidney disease, in diabetic and non-diabetic patients alike.
- Glycaemic control; consideration of a non-steroidal mineralocorticoid receptor antagonist in diabetic kidney disease; dietary sodium restriction; avoidance of nephrotoxins; treatment of obesity.

DO NOT STOP THE DRUG FOR THE EXPECTED RISE

When you start or increase one of these drugs, **the creatinine will rise and the potassium may rise**. That is the expected haemodynamic consequence of reducing intraglomerular pressure — which is precisely the mechanism by which the drug protects the kidney.

Accept a creatinine rise of up to about 30% and a modest potassium rise, and continue. Recheck at one to two weeks. Stop only if the rise exceeds that, or if potassium cannot be controlled.

Stopping these drugs at the first small rise is one of the commonest errors in chronic kidney disease, and it deprives the patient of the single most effective renal protection available.

Aim 3 — Treat the complications

Complication	Management
Anaemia	Correct iron deficiency first, usually intravenously in advanced disease. Then erythropoiesis-stimulating agents, targeting a haemoglobin of roughly 100–120 g/L — deliberately not normal, because normalising it increases stroke and thrombotic risk.
Mineral and bone disorder	Dietary phosphate restriction and phosphate binders taken with food; activated vitamin D; control of parathyroid hormone. Treat the phosphate and the parathyroid hormone rather than chasing the calcium.
Metabolic acidosis	Oral sodium bicarbonate when the serum bicarbonate falls below about 22 mmol/L — it reduces muscle catabolism and may slow progression.
Fluid overload	Dietary salt restriction and a loop diuretic, which needs higher doses as filtration falls.
Hyperkalaemia	Dietary advice and a potassium binder — used specifically so that renin–angiotensin blockade can be continued.
Other	Vaccination, including hepatitis B early; avoidance of non-steroidal anti-inflammatory drugs; medication review at every visit.

Aim 4 — Prepare for what comes next

- **Refer to nephrology** when the filtration rate falls below 30, when decline is rapid, when albuminuria is heavy, when there is unexplained haematuria with proteinuria, or when the cause is unclear.
- Discuss the options honestly and early: haemodialysis, peritoneal dialysis, **transplantation — including pre-emptive transplantation before dialysis is ever needed** — and conservative kidney management, which is a legitimate and sometimes better choice in a frail patient.
- **Create arteriovenous access around six months before dialysis is anticipated**, since a fistula needs time to mature.

SAVE THE VEINS

From the moment dialysis becomes a possibility, **the veins of the non-dominant forearm are the patient's future lifeline.** No cannulas, no venepuncture, no blood pressure cuffs, no peripherally inserted central catheters in that arm. Put a sign above the bed. A fistula that cannot be created because the veins were used for routine blood tests is an avoidable harm, and it is usually caused by a junior doctor who did not know.

6. Teaching Points and Viva Questions

- Stage on two axes. Albuminuria predicts outcome as powerfully as the filtration rate.
- Small echogenic kidneys mean chronic disease — but diabetic, polycystic and infiltrated kidneys stay large.
- Check the iron before you call it renal anaemia, and do not aim for a normal haemoglobin.
- A creatinine rise after starting an angiotensin blocker is the drug working, not the drug failing.
- Protect the forearm veins from the day dialysis becomes conceivable.

Questions you should be able to answer:

- Stage this patient and explain what each axis contributes to her prognosis.
- Her creatinine rises 22% two weeks after you increase the ramipril. What do you do?
- Why is the haemoglobin target below the normal range?
- Which features would make you doubt that this is simply diabetic nephropathy?
- She asks whether she must have dialysis. What options do you set out?

Case 30 · Acid–Base Disorders

CLINICAL VIGNETTE

A **24-year-old woman** presents after five days of persistent vomiting. She has a long history of dyspepsia and now vomits undigested food several hours after eating. She feels weak, has cramps in her hands, and describes tingling around her mouth.

On examination: dry mucous membranes, heart rate 112/min, blood pressure 98/60 mmHg with a postural drop.

First arterial blood gas and biochemistry: pH 7.51 · carbon dioxide 6.2 kPa · bicarbonate 38 mmol/L · sodium 133 · chloride 88 · potassium 2.6 mmol/L · **urine chloride 8 mmol/L**.

Thirty-six hours later she aspirates and becomes septic. **Repeat gas:** pH 7.33 · carbon dioxide 4.4 kPa · bicarbonate 22 mmol/L · sodium 136 · chloride 92 · lactate 5.1 mmol/L.

1. The Five-Step Method

Apply the same five steps to every gas, in the same order, every time. The method matters more than the memorised lists, because it will get you through gases you have never seen before.

Step	What to do
1. Look at the pH	Acidaemia below 7.35, alkalaemia above 7.45. Even in a mixed disorder, the pH tells you which process is winning.
2. Identify the primary disorder	Which value — carbon dioxide or bicarbonate — has moved in the direction that explains the pH? A low bicarbonate with acidaemia is a metabolic acidosis; a high carbon dioxide with acidaemia is a respiratory acidosis.
3. Check whether compensation is appropriate	Use the rules below. Compensation never fully corrects the pH and never overshoots. If it appears to, there is a second disorder.
4. Calculate the anion gap	In every metabolic acidosis. Anion gap = sodium − (chloride + bicarbonate), normal 8–16 mmol/L.
5. If the gap is raised, check the delta ratio	To reveal a second metabolic process hiding behind a normal-looking bicarbonate.

Expected compensation

Primary disorder	Expected compensation
Metabolic acidosis	Carbon dioxide falls. Winter formula: expected carbon dioxide (mmHg) = 1.5 × bicarbonate + 8, ± 2. In kilopascals, roughly 0.2 × bicarbonate + 1.1.
Metabolic alkalosis	Carbon dioxide rises by about 0.7 mmHg for each 1 mmol/L rise in bicarbonate.
Acute respiratory acidosis	Bicarbonate rises 1 mmol/L for each 10 mmHg rise in carbon dioxide.
Chronic respiratory acidosis	Bicarbonate rises 4 mmol/L for each 10 mmHg rise — which is why the bicarbonate dates the disorder.
Acute respiratory alkalosis	Bicarbonate falls 2 mmol/L for each 10 mmHg fall.
Chronic respiratory alkalosis	Bicarbonate falls 5 mmol/L for each 10 mmHg fall.

THE CORRECTION ALMOST EVERYONE FORGETS

Correct the anion gap for albumin. Albumin is itself an unmeasured anion, so a hypoalbuminaemic patient has a lower baseline gap and a significant acidosis can hide within an apparently normal number.

Add 2.5 mmol/L to the expected gap for every 10 g/L that albumin falls below 40 g/L. In a critically ill patient with an albumin of 20 g/L, a "normal" gap of 14 is in fact substantially raised.

2. The Causes

Metabolic acidosis with a raised anion gap

- **Lactate** — tissue hypoperfusion, sepsis, ischaemic bowel, metformin accumulation, severe hypoxaemia.
- **Ketones** — diabetic, alcoholic and starvation ketoacidosis.
- **Renal failure** — retained sulfate, phosphate and urate.
- **Toxins** — methanol, ethylene glycol, salicylate, and 5-oxoproline with chronic paracetamol use. **Calculate the osmolar gap:** measured minus calculated osmolality above 10 mosmol/kg points to a toxic alcohol.

Metabolic acidosis with a normal anion gap (hyperchloraemic)

- Gastrointestinal bicarbonate loss — **diarrhoea**, and pancreatic or biliary fistula.
- **Renal tubular acidosis.** Carbonic anhydrase inhibitors, ureteric diversion, large-volume saline infusion, and adrenal insufficiency.
- **Distinguish renal from gastrointestinal loss with the urinary anion gap** (urine sodium + potassium − chloride): **negative** means the kidney is excreting ammonium appropriately, so the loss is from the gut; **positive** means the kidney is at fault.

Renal tubular acidosis	Potassium	Urine pH	Features
Type 1 — distal	Low	Above 5.5 despite acidosis	Nephrocalcinosis and stones; associated with autoimmune disease
Type 2 — proximal	Low	Variable, may be below 5.5	Part of Fanconi syndrome with glycosuria, phosphaturia and aminoaciduria
Type 4	High	Below 5.5	Hypoaldosteronism — diabetes, renal disease, and drugs including angiotensin blockers

Metabolic alkalosis — and the test that splits it

Measure the urine chloride. It divides metabolic alkalosis into two groups that are managed in opposite ways, and it is the reason this patient's urine chloride was requested.

Chloride-responsive — urine chloride below 20 mmol/L	Chloride-resistant — urine chloride above 20 mmol/L
Vomiting and nasogastric aspiration	Primary hyperaldosteronism, Cushing syndrome
Diuretic therapy (after the drug has worn off)	Bartter and Gitelman syndromes
Post-hypercapnic alkalosis	Severe potassium depletion, liquorice ingestion
Treatment: sodium chloride and potassium	Treatment: address the underlying cause; saline will not correct it

3. Working Through This Patient

The first gas

- **Step 1:** pH 7.51 — alkalaemia.
- **Step 2:** bicarbonate is high at 38, which explains the alkalaemia — a **primary metabolic alkalosis**.
- **Step 3:** carbon dioxide has risen to 6.2 kPa, which is appropriate respiratory compensation for a bicarbonate of 38.
- **The cause:** loss of hydrogen and chloride in gastric contents, compounded by volume depletion and profound hypokalaemia. **The urine chloride of 8 confirms it is chloride-responsive.**
- **Her tingling and cramps** are from the fall in ionised calcium that alkalaemia produces, not from hypocalcaemia as such.

The second gas — and the trap

- **Bicarbonate is now 22 — apparently normal.** A student who stops there will report that the acid–base disturbance has resolved.
- **Calculate the anion gap:** 136 − (92 + 22) = **22**, which is clearly raised. She has developed a **lactic acidosis** from sepsis, superimposed on her existing metabolic alkalosis.
- The two disorders have moved the bicarbonate in opposite directions and it has landed in the normal range. **A normal bicarbonate does not mean normal acid–base status** — the anion gap is what exposes the second process.
- **The delta ratio** — (anion gap − 12) divided by (24 − bicarbonate) — is 10 divided by 2, which is 5. A ratio above 2 confirms a coexisting metabolic alkalosis.

Delta ratio	Interpretation
Below 0.4	Pure normal anion gap acidosis
0.4–0.8	Mixed high and normal anion gap acidosis
1 to 2	Pure high anion gap acidosis
Above 2	High anion gap acidosis plus a coexisting metabolic alkalosis, or a chronic respiratory acidosis

4. Management Principles

- **Treat the cause, not the number.** Acid–base derangement is a signal, not usually a target.
- For this patient: **sodium chloride 0.9% with generous potassium replacement.** Chloride and volume repletion allow the kidney to excrete the excess bicarbonate; potassium must be corrected because hypokalaemia and alkalosis sustain each other. Then treat the gastric outlet obstruction and, subsequently, the sepsis and its source.
- **Bicarbonate therapy is rarely indicated** and is reserved for severe acidaemia in specific situations, always with senior involvement.
- In renal tubular acidosis, give oral alkali and replace potassium in types 1 and 2. In toxic alcohol or salicylate poisoning, specific antidotes and dialysis are needed urgently.

5. Teaching Points and Viva Questions

- Use the five steps in the same order every time, even when the answer looks obvious.
- A normal bicarbonate can conceal two large opposing disorders. Calculate the anion gap regardless.
- Correct the anion gap for albumin in any sick patient.
- Compensation never overshoots. If it appears to, look for a second primary disorder.
- The urine chloride separates the metabolic alkaloses, and the urinary anion gap separates the normal-gap acidoses.

Questions you should be able to answer:

- Work through both of her gases using the five steps aloud.
- Why did her bicarbonate return to normal while she got sicker?
- A patient has pH 7.30, carbon dioxide 9.0 kPa and bicarbonate 32. Is this acute or chronic, and how do you know?
- Explain why she has perioral tingling with a normal total calcium.
- How would you distinguish diarrhoea from renal tubular acidosis as a cause of a normal-gap acidosis?

Case 31 · Hyponatraemia

CLINICAL VIGNETTE

A **68-year-old man** is brought in with three days of confusion and unsteadiness. In the department he has a generalised seizure lasting 90 seconds.

A thiazide diuretic was started three weeks ago for hypertension. He is a lifelong smoker and mentions a cough and 5 kg of weight loss over four months.

On examination: he is drowsy and disorientated. Clinically **euvolaemic** — the jugular venous pressure is normal, mucous membranes are moist, there is no postural drop and no oedema.

Sodium 112 mmol/L · serum osmolality 240 mosmol/kg · urine osmolality 480 mosmol/kg · urine sodium 62 mmol/L · potassium 3.2 · normal thyroid function · morning cortisol pending.

1. The Diagnostic Sequence

THE ORDER THAT MATTERS

Take the diagnostic samples before you give any fluid. Serum osmolality, urine osmolality and urine sodium, drawn on arrival, will give you the answer. Once a litre of saline has gone in, they become uninterpretable and the cause may never be established.

- **Step 1 — Confirm it is truly hypotonic.** Measure the serum osmolality. A **normal** osmolality means pseudohyponatraemia from severe hyperlipidaemia or paraproteinaemia. A **high** osmolality means a translocational cause — hyperglycaemia or mannitol — where water has been drawn into the vascular space. Only a **low** osmolality is true hypotonic hyponatraemia.
- **Step 2 — Measure the urine osmolality.** Below 100 mosmol/kg means antidiuretic hormone is appropriately switched off, and the problem is water intake exceeding excretory capacity: primary polydipsia, or a **low-solute diet** such as beer potomania or a tea-and-toast diet. Above 100 means the hormone is acting when it should not be.
- **Step 3 — Measure the urine sodium.** Below 30 mmol/L indicates a low effective circulating volume — true hypovolaemia, heart failure or cirrhosis. Above 30 with clinical euvolaemia points to the syndrome of inappropriate antidiuresis, adrenal insufficiency, or salt loss from diuretics or renal disease. **The urine sodium is unreliable while a diuretic is acting.**
- **Step 4 — Assess the volume status clinically**, using the table in the system opener. This is the step most often done badly, and the whole algorithm depends on it.
- **Step 5 — Exclude hypothyroidism and adrenal insufficiency** before diagnosing the syndrome of inappropriate antidiuresis. Both mimic it exactly, and one of them is fatal if missed.

Volume state	Causes
Hypovolaemic	Vomiting, diarrhoea, burns, excessive sweating, diuretics, adrenal insufficiency, salt-wasting nephropathy
Euvolaemic	Syndrome of inappropriate antidiuresis, hypothyroidism, adrenal insufficiency, primary polydipsia, low solute intake
Hypervolaemic	Heart failure, cirrhosis, nephrotic syndrome, advanced kidney disease

The syndrome of inappropriate antidiuresis

- **Diagnostic criteria:** hypotonic hyponatraemia; urine osmolality above 100; urine sodium above 30; clinical euvolaemia; normal thyroid, adrenal and renal function; and no diuretic in use.
- **Causes:** malignancy — above all **small cell lung cancer**, which this patient's smoking history and weight loss should raise; central nervous system disease; pulmonary disease including pneumonia and tuberculosis; **drugs** — selective serotonin reuptake inhibitors, carbamazepine, antipsychotics, proton pump inhibitors, desmopressin, ecstasy; and pain, nausea and the postoperative state.

2. Focused History and Examination

- **Speed of onset is the most important historical point**, because it governs how fast you may correct. Acute hyponatraemia, developing within 48 hours, is dangerous in itself and tolerates faster correction. Chronic hyponatraemia has allowed the brain to adapt, and rapid correction is what harms.
- Symptoms: nausea and headache early; then confusion, unsteadiness, drowsiness; then seizures and coma.
- Fluid intake including water, beer and any recent endurance exercise; every drug, with **thiazides the commonest culprit**; vomiting and diarrhoea; cardiac, hepatic and renal history; respiratory symptoms and weight loss; head injury or intracranial disease; features of adrenal insufficiency including pigmentation and postural hypotension.
- Examination is directed at volume status, at the neurological state, and at a search for an underlying malignancy or chest disease.

3. Management

SEVERE SYMPTOMS COME FIRST

This man is fitting. **The seizure is treated before the algorithm is completed.**

Hypertonic saline 3%, 100–150 mL over 10–20 minutes, repeated up to three times if seizures continue, aiming for a **prompt rise of about 5 mmol/L** — which is enough to reduce cerebral oedema and stop the fitting.

This is one of the few situations in medicine where rapid correction of sodium is not only permitted but required. It applies at any sodium concentration if the symptoms are severe.

Then the correction limit

- **No more than 8–10 mmol/L in the first 24 hours**, and no more than 8 mmol/L in each subsequent 24 hours. Use a lower limit, around 6–8 mmol/L, in patients at high risk.
- **Osmotic demyelination syndrome** is the consequence of exceeding this. It appears days later as dysarthria, dysphagia, quadriparesis and altered consciousness, and it is frequently irreversible. **Highest risk:** chronic hyponatraemia, alcohol use, malnutrition, liver disease, hypokalaemia and a sodium below 105.
- Measure the sodium **every 4 to 6 hours** during active correction. This is not a once-daily test.

THE OVERCORRECTION TRAP

The moment the cause of the antidiuretic drive is removed — fluid given to a hypovolaemic patient, a thiazide stopped, desmopressin withheld, cortisol replaced — the hormone switches off and the kidney produces **a large volume of dilute urine very suddenly**. The sodium can then rise far faster than intended, straight through the safe limit.

Watch for a rising urine output. If the sodium is climbing too quickly, **give 5% dextrose, and desmopressin if necessary, to bring it back down** — relowering the sodium is legitimate and is safer than allowing the overshoot to stand.

Treatment by cause

- **Hypovolaemic:** isotonic saline, and the sodium will correct as the antidiuretic stimulus resolves — with close monitoring for exactly the overshoot described above.
- **Syndrome of inappropriate antidiuresis:** fluid restriction to 800–1000 mL daily, treatment of the underlying cause, and where restriction fails, oral urea, increased solute intake or a vasopressin receptor antagonist.
- **Hypervolaemic:** fluid and sodium restriction with a loop diuretic, and treatment of the heart or liver disease. Saline will make these patients worse.
- **Drug-induced:** stop the drug — here, the thiazide — and do not restart it.
- **Correct hypokalaemia**, remembering that potassium replacement itself **raises the sodium** and must be counted within the daily correction allowance.
- For this patient, once stable: computed tomography of the chest for the suspected lung primary, and a short synacthen test if the cortisol is equivocal.

THE OTHER DIRECTION: HYPERNATRAEMIA

Almost always a **water deficit** rather than salt excess, and almost always in someone who could not get to water — the elderly, the confused, the intubated, the very young. Also consider diabetes insipidus where the urine is inappropriately dilute.

Correct slowly: no more than 10–12 mmol/L in 24 hours, replacing the deficit over 48 hours, because rapid correction of chronic hypernatraemia causes cerebral oedema. Give water enterally where possible, otherwise 5% dextrose or 0.45% saline, after restoring circulating volume with isotonic fluid if the patient is shocked.

4. Teaching Points and Viva Questions

- Take the diagnostic bloods and urine before the first bag of fluid, or you lose the diagnosis.
- Confirm the hyponatraemia is hypotonic before doing anything else.
- Treat severe symptoms fast with hypertonic saline; treat everything else slowly.
- Exclude adrenal insufficiency and hypothyroidism before diagnosing inappropriate antidiuresis.
- When the cause is removed, expect an abrupt aquaresis and be ready to relower the sodium.
- Thiazides are the commonest drug cause, and the drug is usually recently started.

Questions you should be able to answer:

- Work through the five diagnostic steps on this patient and state your conclusion.
- He is fitting with a sodium of 112. What exactly do you give, and how much?
- By how much may his sodium rise in 24 hours, and what happens if it rises by 18?
- Six hours after stopping the thiazide his urine output is 400 mL/hour. What is happening and what do you do?
- What single further investigation does his smoking history and weight loss demand?

Case 32 · Urinary Tract Infection

CLINICAL VIGNETTE

A **68-year-old woman** with type 2 diabetes has had two days of burning on passing urine with frequency and urgency. Since this morning she has had **right loin pain, rigors and vomiting**, and her daughter says she has become confused. She has had four urinary infections in the past year and took ciprofloxacin two months ago.

On examination: temperature 38.9 °C, heart rate 112/min, blood pressure 96/58 mmHg, respiratory rate 22/min. **There is marked right loin tenderness on percussion.** The bladder is not palpable. Urine dipstick: leucocytes +++, nitrites positive, blood +.

Creatinine 148 µmol/L (baseline 82) · lactate 3.2 mmol/L · white cells 17.8 × 10^9/L · glucose 16.4 mmol/L.

1. Classify It — the Classification Decides the Management

Category	Definition and consequence
Uncomplicated cystitis	A non-pregnant woman with a structurally and functionally normal tract and no systemic features. Short-course oral antibiotic; culture not routinely needed.
Complicated urinary infection	Male sex · pregnancy · structural or functional abnormality · stones · catheter · diabetes · immunosuppression · renal impairment · recent instrumentation. Always culture, treat longer, and consider imaging.
Acute pyelonephritis	Fever, rigors, loin pain and vomiting. Culture, blood cultures, and a low threshold for imaging and admission.
Urosepsis	With organ dysfunction — as here. Sepsis bundle, and look for obstruction.
Asymptomatic bacteriuria	Bacteria in the urine with no urinary symptoms. Not an infection and, with two exceptions, not treated.

THE MOST IMPORTANT POINT IN THIS CASE

Do not treat asymptomatic bacteriuria. The only established exceptions are **pregnancy** and **before a urological procedure that will breach the mucosa**. Treating it elsewhere produces resistance, *Clostridioides difficile* infection and adverse drug reactions, with no benefit at all.

And in an older patient, a positive dipstick plus confusion is not a diagnosis of urinary infection. Asymptomatic bacteriuria is present in a large proportion of elderly women and in almost all long-term catheterised patients, and leucocyte esterase is frequently positive in both. **Dipsticks are therefore unreliable over the age of 65 and in catheterised patients.**

Diagnose a urinary infection in an older confused patient only where there are **urinary symptoms or systemic features of infection** — and look properly for another source before settling on the urine. This is the single commonest reason antibiotics are given unnecessarily in hospital medicine.

2. Focused History

- **Lower tract:** dysuria, frequency, urgency, suprapubic pain, haematuria, offensive urine. **Upper tract:** fever, rigors, loin pain, nausea and vomiting.
- **Complicating factors**, as in the table above — and in men, **prostatic symptoms**, since obstruction and prostatitis change the treatment.
- **Previous cultures and recent antibiotic exposure.** In a patient with four infections in a year and recent ciprofloxacin, the likely organism and its resistance pattern can be predicted, and empirical therapy

should be chosen accordingly rather than by habit.

- **Red flags for a complication:** anuria, severe unilateral pain, and **failure to improve after 48 to 72 hours of appropriate antibiotics** — which means obstruction, abscess or the wrong organism.
- **In recurrent infection in women:** sexual activity and new partners, spermicide or diaphragm use, postmenopausal status, incomplete bladder emptying, constipation, fluid intake, and previous stones or surgery.
- **The differential of dysuria, which is not all infection:** candidal or atrophic vaginitis, sexually transmitted urethritis and cervicitis, bladder pain syndrome, prostatitis, stones, and bladder cancer.

3. Physical Examination

- Vital signs and a formal sepsis assessment; capillary glucose.
- **Loin tenderness on percussion**; suprapubic tenderness; and **palpate or scan the bladder for retention**, because an obstructed bladder in a septic patient needs a catheter now.
- Prostate examination in men; pelvic examination where there are vaginal symptoms; and a search for an alternative source of sepsis — chest, skin, abdomen, lines.

4. Investigations

- **Urine culture before antibiotics** in all complicated infection, pyelonephritis, men, pregnancy, recurrence and treatment failure. It is **not** required in a young woman with typical uncomplicated cystitis.
- Complete blood count, C-reactive protein, urea and electrolytes, glucose, lactate, and **blood cultures** in any febrile or septic patient.

WHEN TO IMAGE, AND THE TWO DIAGNOSES THAT REQUIRE DRAINAGE

Arrange renal tract ultrasound within 24 hours if the patient is septic, is male, fails to respond within 48–72 hours, or if stones or obstruction are suspected.

You are looking for **hydronephrosis, a stone, a renal or perinephric abscess, or an obstructed infected system.** Computed tomography where an abscess or gas is suspected.

Two findings must be recognised because antibiotics alone will not treat either:

Pyonephrosis — an obstructed, infected kidney. Fever and loin pain with hydronephrosis. **The system must be drained urgently by nephrostomy or ureteric stent.** A septic patient with an obstructed kidney will not improve, and may die, on antibiotics alone.

Emphysematous pyelonephritis — gas within the renal parenchyma, almost always in poorly controlled diabetes, with a high mortality. Urgent urological involvement and consideration of drainage or nephrectomy.

5. Management

- **This patient:** sepsis bundle — cultures, fluid resuscitation, intravenous antibiotics guided by local resistance and her previous isolates, hourly urine output, lactate monitoring — plus **urgent ultrasound**, glycaemic control, and review of her diabetes therapy in the context of acute kidney injury.

Situation	Treatment
Uncomplicated cystitis, non-pregnant woman	A short course — often three days — of nitrofurantoin, trimethoprim, pivmecillinam or fosfomycin according to local resistance. Avoid fluoroquinolones for uncomplicated cystitis given their adverse effect profile and collateral resistance.
Acute pyelonephritis	Intravenous therapy if septic or vomiting, then oral switch; 7 to 10 days in total, longer in men and in complicated disease. Reassess at 48–72 hours and image if not improving.
Men	7 to 14 days, with an agent that penetrates the prostate if prostatitis is suspected. Recurrent infection in a man warrants urological assessment — it is not simply bad luck.
Catheter-associated	Treat only symptomatic infection, and change or remove the catheter as part of treatment. Never treat a positive catheter specimen in an asymptomatic patient.
Pregnancy	Treat, including asymptomatic bacteriuria. Avoid trimethoprim in the first trimester and nitrofurantoin at term. Low threshold for admission.

Recurrent infection in women — what actually helps

- Exclude a treatable cause: stones, obstruction, **incomplete bladder emptying** (measure a post-void residual), and diabetes.
- Behavioural measures: adequate fluid intake, voiding after intercourse, avoiding spermicide and diaphragms, and treating constipation.
- **Vaginal oestrogen in postmenopausal women is effective and substantially under-prescribed** — it restores the vaginal flora and reduces recurrence, and it is a better first step than long-term antibiotics.
- Methenamine hippurate or D-mannose as non-antibiotic options; **antibiotic prophylaxis — post-coital or continuous — only as a later resort, with a documented plan to review and stop it.**

6. Teaching Points and Viva Questions

- Do not treat asymptomatic bacteriuria, except in pregnancy and before urological instrumentation.
- A positive dipstick in a confused elderly patient is not a diagnosis. Look for another source.
- Recent antibiotic exposure predicts resistance — read the old cultures before choosing a drug.
- If there is no improvement in 48 to 72 hours, image the kidneys.
- An obstructed infected kidney needs a drain, not a stronger antibiotic.
- Recurrent infection in a man is a urological referral.
- Vaginal oestrogen before long-term prophylaxis in postmenopausal women.

Questions you should be able to answer:

- Why does her recent ciprofloxacin course change your empirical choice?
- She is still febrile after 60 hours of appropriate intravenous antibiotics. What do you do?

- A catheterised nursing home resident has a positive dipstick and no symptoms. What is your management?
- A 72-year-old man has had three urinary infections this year. What must be arranged?
- The ultrasound shows a dilated right renal pelvis. What is the diagnosis and what is the treatment?

Case 33 · Glomerulonephritis

CLINICAL VIGNETTE

A **24-year-old man** presents with ten days of dark, **cola-coloured urine**. He noticed puffiness around his eyes on waking, and his ankles have begun to swell. He has a headache. He had a severe sore throat **about two and a half weeks ago**, which was not treated.

On examination: blood pressure 168/104 mmHg. Periorbital oedema and pitting ankle oedema. Chest clear. No rash, no joint swelling, no nasal crusting.

Urine dipstick: blood +++, protein ++. Microscopy: dysmorphic red cells and red cell casts. Creatinine 168 µmol/L · albumin-to-creatinine ratio 180 mg/mmol · **C3 low, C4 normal** · antistreptolysin O titre raised · antineutrophil cytoplasmic and anti-glomerular basement membrane antibodies negative.

THE FINDING THAT MAKES THIS DIAGNOSIS

Dysmorphic red cells and red cell casts on urine microscopy mean the bleeding is coming from the glomerulus.

That single finding separates glomerular disease from urological haematuria — stones, tumour, infection — and it redirects the entire investigation from a cystoscopy to an immunology panel and a renal biopsy. It takes minutes, requires a microscope rather than a machine, and it is very often not done.

Blood and protein together on the dipstick should always prompt microscopy and a same-day conversation with a nephrologist.

1. Think First — Two Syndromes and One Emergency

	Nephritic syndrome	Nephrotic syndrome
The glomerulus is	Inflamed	Leaky
Urine	Haematuria with dysmorphic red cells and red cell casts; proteinuria usually under 3 g	Heavy proteinuria, over 3.5 g; bland microscopy
Blood pressure	Raised	Often normal
Other	Oliguria, rising creatinine, oedema	Hypoalbuminaemia, hyperlipidaemia, thrombotic risk
Covered in	This case	Seminar 2

THE PRESENTATION THAT MUST NOT BE MISSED

A nephritic urine with a creatinine that is rising over days to weeks is rapidly progressive glomerulonephritis, and it is a medical emergency.

The biopsy shows crescents. **Every day of delay converts recoverable nephrons into permanent scar**, and patients arrive dialysis-dependent because a urine dipstick was filed and a creatinine was rechecked "next week".

Action: same-day nephrology referral · urgent antineutrophil cytoplasmic antibody, anti-glomerular basement membrane antibody and complement · urgent renal biopsy. Where suspicion is high, **immunosuppression is started before the biopsy result** — high-dose corticosteroid with cyclophosphamide or rituximab, and **plasma exchange for anti-glomerular basement membrane disease or severe pulmonary haemorrhage**.

2. The Causes — and How to Tell Them Apart

Cause	The discriminating feature
Post-streptococcal glomerulonephritis	Haematuria 1–3 weeks after pharyngitis, or 3–6 weeks after a skin infection. Low C3 with a normal C4; raised antistreptolysin O or anti-DNase B. This patient.
IgA nephropathy	Haematuria during the infection, not two weeks after it — "synpharyngitic". Normal complement. The commonest primary glomerulonephritis. The timing is the whole discriminator from post-streptococcal disease.
IgA vasculitis	Palpable purpura on the buttocks and legs, arthralgia, abdominal pain.
Lupus nephritis	Low C3 *and* C4; positive antinuclear and anti-double-stranded DNA antibodies; multisystem features (Case 59).
ANCA-associated vasculitis	Nasal crusting, epistaxis, sinusitis, deafness, haemoptysis, weight loss; positive myeloperoxidase or proteinase-3 antibodies; normal complement.
Anti-glomerular basement membrane (Goodpasture) disease	Pulmonary haemorrhage with haemoptysis plus nephritis; anti-glomerular basement membrane antibody.
Membranoproliferative disease, C3 glomerulopathy, cryoglobulinaemia	Low complement; hepatitis C; a paraprotein.
Endocarditis-associated nephritis	Fever with a murmur — take blood cultures (Case 13).
Thin basement membrane disease and Alport syndrome	Isolated persistent haematuria, family history, sensorineural deafness in Alport.

THE COMPLEMENT PATTERN NARROWS THE LIST

Low C3 with a normal C4 — post-streptococcal glomerulonephritis, C3 glomerulopathy.

Low C3 and low C4 — lupus nephritis, cryoglobulinaemia, membranoproliferative disease, endocarditis.

Normal complement — IgA nephropathy, ANCA-associated vasculitis, anti-glomerular basement membrane disease, thin basement membrane disease.

Two cheap tests that divide a long differential into three short ones.

- **Pulmonary–renal syndrome — haemoptysis with nephritis — has a short and urgent differential:** ANCA-associated vasculitis, anti-glomerular basement membrane disease, lupus and cryoglobulinaemia. Send the antibodies the same day and involve nephrology immediately.

3. Focused History

- **The timing of the haematuria relative to any infection** — the single most useful question, as above.
- Sore throat or skin infection; rash; joint pain; **nasal crusting, epistaxis, sinusitis or hearing loss**; **haemoptysis**; fever and weight loss.
- **Drugs** — non-steroidal anti-inflammatory drugs, penicillamine, gold, anti-tumour-necrosis-factor agents, hydralazine; and any herbal or traditional preparation.
- Hepatitis B and C and human immunodeficiency virus risk; **family history of renal failure or deafness**; travel and exposure to malaria or schistosomiasis; and **any previous urinalysis result**, which may date the disease.

4. Examination and Investigation

- **Blood pressure, volume status, and urinalysis performed yourself.** Periorbital and peripheral oedema.
- **Look for the systemic disease:** purpuric or vasculitic rash, synovitis, nasal bridge and septum, chest for haemorrhage or crackles, eyes for uveitis and scleritis, and a neurological examination for mononeuritis multiplex.
- **Urine microscopy** and quantification of proteinuria; creatinine **with its trend**, which is the number that determines urgency.
- **The immunology panel, sent urgently:** antinuclear and anti-double-stranded DNA antibodies, **complement C3 and C4**, **antineutrophil cytoplasmic antibodies (myeloperoxidase and proteinase-3)**, **anti-glomerular basement membrane antibody**, immunoglobulins with electrophoresis, cryoglobulins; antistreptolysin O and anti-DNase B; hepatitis B and C and human immunodeficiency virus serology; blood cultures where endocarditis is possible.
- Renal ultrasound for size, obstruction and suitability for biopsy; chest radiograph for pulmonary involvement.
- **Renal biopsy is the definitive investigation, and the threshold for it should be low.** It gives the diagnosis, distinguishes active inflammation from established scarring, and determines the treatment. It is **urgent** in suspected rapidly progressive disease.

5. Management

Supportive, for every patient

- **Blood pressure control**, with an angiotensin-converting enzyme inhibitor or receptor blocker once the acute phase has stabilised, to reduce proteinuria; salt restriction; a loop diuretic for oedema.
- Avoid nephrotoxins; statin therapy; **thromboprophylaxis where the picture is nephrotic**; vaccination; and dietary advice.

Specific to the cause

- **Post-streptococcal glomerulonephritis — this patient — is treated supportively**, with antibiotics to eradicate the organism. Expect recovery: **haematuria may persist for months and proteinuria for up to a year**, and the patient should be told so and monitored rather than re-investigated at every visit. The prognosis is excellent in children and somewhat less so in adults.
- **IgA nephropathy:** blood pressure and proteinuria control with a renin–angiotensin blocker and a sodium–glucose co-transporter 2 inhibitor; immunosuppression only in selected progressive disease.
- **Lupus nephritis:** induction with mycophenolate or cyclophosphamide plus corticosteroid, then maintenance (Case 59).
- **ANCA-associated vasculitis and anti-glomerular basement membrane disease:** urgent immunosuppression as above, with plasma exchange where indicated.
- **Membranous nephropathy:** risk-stratified, with rituximab-based therapy in higher-risk disease — and **screen for malignancy, hepatitis B and drugs as secondary causes**.

- **Minimal change disease:** corticosteroids, with a good response expected.
- Follow up for progression to chronic kidney disease (Case 29), with dialysis and transplant planning where the course is unfavourable.

6. Teaching Points and Viva Questions

- Blood and protein together means microscopy, and red cell casts mean the glomerulus.
- The timing of haematuria after a sore throat separates IgA nephropathy from post-streptococcal disease.
- Complement divides the differential into three.
- A creatinine rising over days is an emergency, and treatment may legitimately precede the biopsy.
- Haemoptysis with nephritis is a short, urgent list.
- Persistent haematuria for months after post-streptococcal disease is expected, not a treatment failure.

Questions you should be able to answer:

- What do red cell casts tell you, and how do they change your investigation?
- His sore throat was two weeks ago. How would the diagnosis differ if the haematuria had begun during the sore throat?
- Interpret a low C3 with a normal C4, and then a low C3 with a low C4.
- His creatinine rises from 168 to 320 over four days. What is the diagnosis and what happens today?
- He still has microscopic haematuria at four months. Does that concern you?

The Gastroenterology Block

Peptic ulcer disease, acute and chronic viral hepatitis, decompensated cirrhosis, upper GI bleeding, inflammatory bowel disease and hepatocellular carcinoma.

Cases 34–40 · 9,176 words

This block covers the gastrointestinal and hepatological teaching of both internal medicine courses. The **first course** supplies cases 34 and 38; the **second course** supplies cases 39 and 40.

Case	Lecture it serves
System opener: the gastrointestinal history and examination	History taking in gastrointestinal; physical examination of the gastrointestinal system
Case 34 — Dyspepsia, reflux and peptic ulcer disease	Gastro-oesophageal reflux disease and peptic ulcer disease
Case 35 — Acute viral hepatitis	Hepatitis (acute)
Case 36 — Chronic viral hepatitis	Hepatitis (chronic)
Case 37 — Decompensated cirrhosis and portal hypertension	Cirrhosis and portal hypertension; hepatocellular failure and ascites seminars
Case 38 — Upper gastrointestinal bleeding	Gastrointestinal bleeding
Case 39 — Inflammatory bowel disease	Inflammatory bowel disease; approach to chronic diarrhoea
Case 40 — Hepatocellular carcinoma	Malignancies of the liver

System Opener · The Gastrointestinal History and Examination

The history

Characterise the cardinal symptoms

Symptom	What to establish
Abdominal pain	Site, character, radiation and relation to food. Epigastric pain related to meals suggests peptic disease; right upper quadrant pain radiating to the back or shoulder tip suggests biliary disease; epigastric pain boring through to the back and eased by sitting forward suggests pancreatic disease.
Dysphagia	Solids first, then liquids, progressively means a mechanical obstruction — stricture or carcinoma. Both from the outset suggests a motility disorder such as achalasia. Painful swallowing is odynophagia. Ask the patient to point to the level at which food sticks.
Dyspepsia and reflux	Heartburn, acid regurgitation, waterbrash; relation to meals, to lying flat and to bending. Ask also about cough, hoarseness and dental erosion, which are the extra-oesophageal manifestations.
Vomiting	Timing, volume and content. Vomiting of undigested food several hours after eating indicates gastric outlet obstruction. Bile, blood or coffee grounds each mean something different.
Change in bowel habit	Frequency and stool consistency; blood mixed through the stool, on its surface, or only on the paper; mucus; tenesmus; and nocturnal diarrhoea, which points to organic rather than functional disease.
Steatorrhoea	Pale, bulky, offensive stool that floats and is difficult to flush — malabsorption.
Jaundice	With pale stools, dark urine and itching, indicating cholestasis. Painless progressive jaundice with weight loss is malignancy until proved otherwise.

THE ALARM FEATURES

The presence of any one of these changes a case of dyspepsia into a case requiring urgent endoscopy:

Dysphagia · unintentional weight loss · anaemia · overt gastrointestinal bleeding · persistent vomiting · an abdominal or epigastric mass · new symptoms above the age threshold · a family history of upper gastrointestinal cancer.

Every dyspepsia consultation in this book, and on the ward, begins by asking about these.

Then the exposures

- **Alcohol, quantified in units per week** and over how many years — not "socially". **Non-steroidal anti-inflammatory drugs and aspirin**, including those bought without prescription. Smoking.
- **Liver risk:** blood transfusion before screening, tattoos and unsterile procedures, injecting drug use, needle-stick injury, sexual history, family history of hepatitis, and country of birth.
- **Travel, food and water exposure**, shellfish, and **unpasteurised dairy and animal contact** — brucellosis presents with hepatitis and fever in this region.
- **Drugs that damage the liver:** paracetamol, antituberculous therapy, methotrexate, anabolic steroids, and **herbal and traditional preparations**, which patients rarely mention unless asked directly.
- Family history of inflammatory bowel disease, coeliac disease, colorectal cancer and liver disease.

The examination

Before the abdomen

- **General:** cachexia and muscle wasting, **jaundice examined in the sclerae in natural light**, pallor, hydration, and mental state — a drowsy or disinhibited patient with liver disease has encephalopathy until proved otherwise.
- **Hands:** clubbing, leuconychia, koilonychia, palmar erythema, Dupuytren contracture, and **asterixis** — ask the patient to hold the wrists extended for thirty seconds.
- **Arms and chest: spider naevi** — more than five is abnormal, they occur in the distribution of the superior vena cava, and they fill from the centre outwards after blanching; bruising, scratch marks, gynaecomastia, loss of body hair, tattoos.
- **Face and mouth:** xanthelasma, parotid enlargement, fetor hepaticus, angular stomatitis, glossitis, aphthous ulceration, telangiectasia.
- **Neck:** the left supraclavicular node of Troisier, which points to an intra-abdominal malignancy.

The abdomen

- **Inspect** for distension, scars, caput medusae, striae, visible peristalsis and hernias, with the patient lying flat and the abdomen fully exposed from nipples to knees.
- **Palpate** lightly through all regions watching the patient's face, then deeply. **Liver:** begin in the right iliac fossa and move up towards the costal margin, asking the patient to breathe in; measure the extent below the costal margin and describe the edge, consistency, tenderness and any pulsatility. **Spleen:** begin in the right iliac fossa and move towards the left costal margin; if not felt, roll the patient into the right lateral position. A spleen has a notch, you cannot get above it, it moves with respiration and it is dull to percussion — a kidney is none of these things.
- **Percuss** the liver span, the Traube space, and for **shifting dullness**; test for a fluid thrill if the ascites is tense.
- **Auscultate** for bowel sounds and for bruits.
- **Complete the examination:** hernial orifices, external genitalia, **rectal examination**, and urinalysis. In an examination you may offer these; on the ward you perform them.

Stigmata of chronic liver disease	Signs of portal hypertension	Signs of decompensation
Spider naevi, palmar erythema, leuconychia, clubbing	Splenomegaly	Jaundice
Gynaecomastia, testicular atrophy, loss of body hair	Ascites	Ascites
Dupuytren contracture, parotid enlargement	Caput medusae, dilated abdominal veins	Encephalopathy — asterixis, altered sleep pattern, confusion
Bruising, scratch marks	Varices — not visible externally	Variceal bleeding

The distinction matters. Stigmata tell you the liver is chronically diseased. Signs of decompensation tell you it is failing now, and it is decompensation — not the stigmata — that determines admission, prognosis and the need for transplant assessment.

Case 34 · Dyspepsia, Reflux and Peptic Ulcer Disease

CLINICAL VIGNETTE

A **38-year-old man** describes four months of burning discomfort behind the sternum, worse at night and when he lies flat, sometimes waking him with a sour taste at the back of his throat. Separately, he describes a gnawing epigastric pain that comes on two to three hours after meals and is **relieved by eating**.

He takes ibuprofen most days for back pain, bought from the pharmacy. He smokes 15 cigarettes daily and drinks strong coffee through the day.

He has lost no weight, swallows normally, has never vomited blood and has no family history of gastric cancer.

On examination: body mass index 29 kg/m^2, mild epigastric tenderness, no mass, no lymphadenopathy. **Stool antigen for *Helicobacter pylori* is positive.**

1. Focused History

- **Separate the two symptom patterns**, because he has both. Retrosternal burning worse on lying flat is reflux. Epigastric gnawing pain with a clear relation to meals is peptic ulceration — classically **relieved by food in duodenal ulcer** and **provoked by food in gastric ulcer**, although the distinction is far from reliable in practice.
- **Screen for every alarm feature** listed in the system opener. Their absence in a man under the age threshold is what permits a non-invasive approach.
- **Drugs:** non-steroidal anti-inflammatory drugs and aspirin, corticosteroids, anticoagulants, bisphosphonates, and potassium supplements. Ask about what is bought over the counter — that is where the anti-inflammatory almost always comes from.
- Alcohol, smoking, caffeine, late meals, and weight. Previous eradication therapy and whether it was completed.
- **Extra-oesophageal reflux symptoms:** chronic cough, hoarseness, sore throat, worsening asthma, dental erosion.

2. Differential Diagnosis

Diagnosis	The feature that discriminates it
Functional dyspepsia	The commonest cause overall. Normal endoscopy, no alarm features, often with other functional symptoms. A positive diagnosis after exclusion, not a shrug.
Gastro-oesophageal reflux disease	Retrosternal burning, regurgitation, worse lying flat and bending, relieved by antacids.
Peptic ulcer disease	Epigastric pain with a meal relationship; *Helicobacter pylori* or anti-inflammatory drug exposure.
Gastric carcinoma	Alarm features — weight loss, anaemia, vomiting, mass, dysphagia. This is the reason the alarm list exists.
Biliary colic	Severe right upper quadrant pain in discrete episodes lasting hours, often nocturnal, radiating to the back.
Chronic pancreatitis	Boring epigastric pain to the back, steatorrhoea, weight loss, alcohol history.
Myocardial ischaemia	Epigastric discomfort with exertion, sweating or radiation. Always consider it in an older patient with vascular risk factors — patients with infarction are routinely treated for indigestion.

3. Investigations

THE DECISION THAT STRUCTURES THE WHOLE CONSULTATION

Under the age threshold and with no alarm features: test non-invasively for *Helicobacter pylori* and treat if positive. Endoscopy is not required.

Any alarm feature, new symptoms above the age threshold, or failure of treatment: endoscopy.

- **Urea breath test or stool antigen** are the tests of choice — both detect **active** infection. **Serology cannot distinguish current from past infection** and is of little use where prevalence is high.

THE PRACTICAL POINT STUDENTS GET WRONG

Stop proton pump inhibitors for two weeks and antibiotics and bismuth for four weeks before testing — for both the initial test and the test of cure.

Acid suppression suppresses the organism as well as the acid, and produces false negative breath and stool tests. A patient sent for a breath test while taking omeprazole has had a wasted test, and will be told they do not have an infection that they do have.

- **At endoscopy:** biopsy for a rapid urease test and histology. **Every gastric ulcer must be biopsied**, because gastric ulcers may be malignant.
- **Repeat endoscopy after 6–8 weeks to confirm healing of a gastric ulcer.** Duodenal ulcers do not require this — they do not become malignant. This asymmetry is a favourite examination question.
- **Confirm eradication** with a urea breath test at least four weeks after completing therapy, in complicated ulcer disease, persistent symptoms or a bleeding ulcer.
- Complete blood count and ferritin for iron deficiency, coeliac serology where the picture fits, liver function and an ultrasound if biliary disease is possible.

- **Fasting gastrin** where ulcers are multiple, distal to the duodenal bulb, refractory or recurrent — the Zollinger–Ellison syndrome.

4. Management

Address the causes

- **Stop the ibuprofen.** If an anti-inflammatory is genuinely necessary, use the lowest effective dose with proton pump inhibitor cover, and reconsider the underlying back problem.
- Smoking cessation, weight reduction, avoiding meals within three hours of lying down, elevating the head of the bed, and reducing alcohol and caffeine.

Eradicate the organism

- Standard first-line therapy is a **proton pump inhibitor with amoxicillin and clarithromycin for 14 days**. Where clarithromycin resistance is high — and it is high in much of this region — **bismuth-based quadruple therapy or a levofloxacin-containing regimen** is preferred. **Follow local resistance data rather than the textbook default.**
- Emphasise completing the full course; failure is usually a failure of adherence.

Acid suppression

- A proton pump inhibitor for 4–8 weeks for reflux or ulcer healing, then **step down to the lowest effective dose or on-demand use**.
- **Review long-term proton pump inhibitor use annually.** Prolonged therapy is associated with vitamin B12 and magnesium deficiency, enteric infection including *Clostridioides difficile*, and fracture. Many patients continue them for years without anyone reconsidering the indication.

When it does not settle

- Reconsider the diagnosis, confirm eradication, and check adherence. Then oesophageal pH studies and manometry, and consideration of anti-reflux surgery in carefully selected patients.
- **Complications to know:** bleeding, perforation, gastric outlet obstruction, and **Barrett oesophagus** — intestinal metaplasia of the lower oesophagus which carries a risk of adenocarcinoma and enters a surveillance programme.

5. Teaching Points and Viva Questions

- The alarm features decide whether this is a prescription or an endoscopy.
- Stop the acid suppression before testing for *Helicobacter pylori*, or the result is worthless.
- Biopsy and re-scope gastric ulcers. Duodenal ulcers need neither.
- The anti-inflammatory drug is almost always bought, not prescribed, so it will not be on the medication list.
- Epigastric pain in an older patient with vascular risk factors deserves an electrocardiogram before an antacid.

Questions you should be able to answer:

- List the alarm features and explain what each one is a marker for.
- He has been taking omeprazole for three weeks. How does that affect your testing?
- Why must a gastric ulcer be re-scoped but not a duodenal one?
- Eradication fails and he remains positive. What are the three explanations, in order of likelihood?
- What are the risks of leaving him on a proton pump inhibitor for ten years?

Case 35 · Acute Viral Hepatitis

CLINICAL VIGNETTE

A **22-year-old student** presents with ten days of malaise, anorexia, nausea and a low-grade fever. He describes a striking aversion to cigarettes, which he previously smoked daily. Three days ago his urine turned dark, his stools became pale, and his family noticed he was yellow. He has a dull ache under the right ribs.

He returned three weeks ago from a trip during which he ate frequently from street stalls. He has had no tattoos, injections or transfusions, and takes no regular medication.

On examination: clearly jaundiced. Temperature 37.6 °C. The liver is **palpable 3 cm below the costal margin and tender**. There is no splenomegaly, no ascites, and **no spider naevi, palmar erythema or clubbing**. He is fully alert with no asterixis.

Alanine aminotransferase 1840 U/L · aspartate aminotransferase 1320 · bilirubin 180 µmol/L · alkaline phosphatase 160 · albumin 40 g/L · INR 1.1.

1. Read the Liver Tests First

Before any serology, decide which of three patterns you are looking at. It narrows the differential more than anything else you will do.

Pattern	Definition	Points to
Hepatitic	Aminotransferases raised far out of proportion to alkaline phosphatase	Viral hepatitis, drugs and toxins, autoimmune hepatitis, ischaemia
Cholestatic	Alkaline phosphatase and gamma-glutamyl transferase raised out of proportion	Biliary obstruction — stones, tumour, stricture — or intrahepatic cholestasis
Mixed	Both raised comparably	Drug reactions, infiltration, sepsis

WHEN THE AMINOTRANSFERASE IS ABOVE 1000

An alanine aminotransferase above 1000 U/L has a **short** differential, and you should be able to recite it:

Acute viral hepatitis · drugs and toxins, above all paracetamol · ischaemic hepatitis, the "shock liver" · autoimmune hepatitis · acute biliary obstruction from a passing stone · acute Budd–Chiari syndrome · Wilson disease in a young patient.

2. Focused History

- **The prodrome** — malaise, anorexia, nausea, fever, and the characteristic **aversion to cigarettes** — followed by jaundice, at which point the patient often begins to feel better.
- **Route of exposure, matched to the virus:** hepatitis **A and E** are faecal–oral, from contaminated food and water, shellfish, and for E also undercooked meat; hepatitis **B, C and D** are parenteral, sexual and vertical.
- **Every drug, including herbal, traditional and slimming preparations, and anabolic steroids.** Ask specifically about paracetamol — total dose and over how many days, including staggered overdose and therapeutic excess in a malnourished patient.
- Alcohol; mushroom ingestion; occupational exposure; contacts with similar illness; vaccination status; and, in a woman, pregnancy.

WHAT TO LOOK FOR, AND WHAT ITS ABSENCE MEANS

The absence of ascites and of chronic stigmata in this patient is a positive finding, not merely a negative one. It tells you this is acute disease in a previously normal liver, rather than an acute deterioration on a background of cirrhosis — which has a different management and a far worse prognosis.

Red flags for acute liver failure: confusion, altered sleep pattern or any change in personality; persistent vomiting; bleeding or bruising; a **shrinking liver**; hypoglycaemia; and a **rising prothrombin time**.

3. Physical Examination

- Depth of jaundice; a tender smooth hepatomegaly; **splenomegaly and lymphadenopathy**, which suggest Epstein–Barr or cytomegalovirus infection rather than a hepatitis virus.
- A deliberate search for **stigmata of chronic liver disease** and for ascites, as above.
- **Mental state and asterixis, formally assessed and repeated.** Encephalopathy is what converts acute hepatitis into acute liver failure, and it is a clinical diagnosis.
- Bruising and bleeding from puncture sites.

4. Investigations

THE DISTINCTION THAT DECIDES WHO IS IN DANGER

Bilirubin and aminotransferases measure **damage**. They tell you cells are dying; they do not tell you how much liver is working, and a falling aminotransferase in a deteriorating patient is a bad sign, not a good one.

The tests of liver function, and therefore of severity, are: the prothrombin time or INR, the blood glucose, and the mental state. Check all three, and repeat them.

- **Viral serology:** hepatitis A IgM; hepatitis B surface antigen with **core IgM**; hepatitis C antibody **and HCV RNA**, since the antibody may still be negative in early infection; hepatitis E IgM; Epstein–Barr and cytomegalovirus serology.
- **Paracetamol level in every patient**, whatever the history says.
- Autoimmune screen — antinuclear and anti-smooth muscle antibodies, immunoglobulin G. **Caeruloplasmin and copper studies in any patient under 40.**
- **Brucella serology** where there has been exposure to unpasteurised dairy or livestock, which is a realistic cause of fever with hepatitis in this region.
- Complete blood count, renal function, glucose, INR repeated at least daily, and **ultrasound with Doppler** to exclude biliary obstruction and hepatic vein thrombosis.

5. Management

- **Supportive care is the treatment for uncomplicated acute viral hepatitis.** Rest, hydration, adequate nutrition, and avoidance of alcohol and hepatotoxic drugs.
- **Monitor INR, glucose, creatinine and mental state.** Deterioration in any of these changes the plan entirely.

- **N-acetylcysteine** for paracetamol toxicity, and it is also used in non-paracetamol acute liver failure.
- **Notify public health.** Advise on hand hygiene and food handling for hepatitis A; vaccinate close contacts; test and vaccinate contacts where hepatitis B is found. Advise abstaining from unprotected sex and from donating blood.

WHEN TO REFER TO A LIVER UNIT

Discuss with a transplant centre early — before the patient is critically ill, not after.

Transfer for **any degree of encephalopathy**, a rising INR, hypoglycaemia, metabolic acidosis, or renal impairment.

King's College criteria — paracetamol: arterial pH below 7.3 after adequate resuscitation, **or** the combination of INR above 6.5, creatinine above 300 µmol/L and grade 3–4 encephalopathy.

Non-paracetamol: INR above 6.5 alone, or three of — unfavourable aetiology, age under 10 or over 40, jaundice for more than 7 days before encephalopathy, INR above 3.5, bilirubin above 300 µmol/L.

6. Outcome by Virus

Virus	Course
A	Self-limiting, never chronic. More severe with increasing age. Vaccine available.
E	Usually self-limiting, but carries a mortality of up to one in five in pregnancy, particularly in the third trimester. Can be chronic in the immunosuppressed.
B	Becomes chronic in about 5% of infected adults but in around 90% of infected neonates — which is why perinatal prevention matters so much. Vaccine available.
C	Becomes chronic in around three-quarters. Now curable with oral antiviral therapy.
D	Only in the presence of hepatitis B; co-infection or superinfection, and it worsens the course.

7. Teaching Points and Viva Questions

- Measure liver function with the INR, the glucose and the mental state — not with the bilirubin.
- A falling aminotransferase in a patient who is getting worse means there is little liver left to leak enzymes.
- Check a paracetamol level in every jaundiced patient regardless of the history.
- Chronic stigmata in an apparently acute hepatitis means the liver was already diseased.
- Hepatitis E in pregnancy is a genuine obstetric emergency.

Questions you should be able to answer:

- Give the differential for an alanine aminotransferase of 1840.
- Which three measurements tell you how sick he is, and why those three?
- His INR rises to 2.4 on day three and he seems muddled. What do you do?
- Why does the absence of spider naevi matter here?

- His sister is pregnant and has been exposed. What is your concern?

Case 36 · Chronic Viral Hepatitis

CLINICAL VIGNETTE

A **45-year-old man** is found to be **hepatitis B surface antigen positive** at a pre-employment screening. He feels entirely well and has never been jaundiced. He was born in a country with high endemic prevalence; his mother died of liver disease in her fifties and a brother has "a liver problem".

He drinks no alcohol. Body mass index 31 kg/m^2.

Alanine aminotransferase 68 U/L · bilirubin normal · albumin 41 g/L · INR 1.0 · platelets 138 × 10^9/L · hepatitis B e antigen negative, anti-HBe positive · hepatitis B DNA 24,000 IU/mL.

1. Reading the Hepatitis B Panel

Students find this confusing because they try to memorise combinations. Learn instead what each marker **means**, and the combinations decode themselves.

Marker	What it means
HBsAg — surface antigen	The virus is present now. Present for more than six months means chronic infection.
Anti-HBs — surface antibody	Immunity. Alone, it means vaccination.
Anti-HBc IgG — core antibody	The patient has met the real virus at some point. Vaccination does not produce this, which is how you distinguish vaccination from past infection.
Anti-HBc IgM	Recent infection, or a flare of chronic infection.
HBeAg — e antigen	High viral replication and high infectivity.
Anti-HBe	Lower replication — but not necessarily inactive disease, because e-antigen-negative chronic hepatitis exists and is common in this part of the world.
HBV DNA	The actual viral load, and the number that drives treatment decisions.

Combination	Interpretation
Anti-HBs positive alone	Vaccinated
Anti-HBs positive with anti-HBc IgG positive	Past infection, resolved, immune
HBsAg positive, anti-HBc IgM positive	Acute infection
HBsAg positive for over 6 months, anti-HBc IgG positive	Chronic infection — then define the phase
Anti-HBc IgG positive alone	Occult infection, remote infection with waning antibody, or the window period. Matters because immunosuppression can reactivate it.

Chronic infection is not one disease but a sequence of phases — immune tolerant, immune active, inactive carrier, and e-antigen-negative chronic hepatitis. **Treatment depends on the phase, not on the positive test**, which is why a positive surface antigen is the beginning of the assessment rather than the end of it.

2. Focused History

- **Probable route and duration:** birth in an endemic area and a mother with liver disease strongly suggest **vertical transmission in infancy**, which means decades of infection and a much higher lifetime risk of cirrhosis and liver cancer.
- **Family history of hepatitis and of hepatocellular carcinoma** — the latter independently raises his own risk and lowers the threshold for surveillance.
- **Cofactors that accelerate fibrosis:** alcohol, obesity, diabetes and fatty liver, and co-infection with hepatitis C, D or human immunodeficiency virus.
- Previous treatment; symptoms suggesting established cirrhosis; and — critically — **any planned or current immunosuppression, chemotherapy or biologic therapy**.
- Household and sexual contacts, and their vaccination status. In a woman, pregnancy plans.

3. Investigations

- Liver enzymes, **albumin, INR and platelet count**. A **falling platelet count is often the earliest laboratory clue to portal hypertension**, appearing long before ascites or varices, and it is easy to overlook on a routine blood count.
- **HBV DNA and e-antigen status**; hepatitis D serology in every surface-antigen-positive patient; hepatitis C, human immunodeficiency virus, and hepatitis A immunity.
- **Assess fibrosis non-invasively.** Transient elastography where available; otherwise the **FIB-4 and APRI scores**, which are calculated from age, aminotransferases and platelet count and therefore cost nothing. Liver biopsy is now reserved for uncertain cases.
- Ultrasound of the liver, alpha-fetoprotein, and cross-sectional imaging for any nodule.
- **Hepatitis C:** the antibody is the screening test, but **HCV RNA is required to confirm active infection**, since the antibody persists after clearance.

4. Management

Hepatitis B

- **Nucleoside or nucleotide analogues — tenofovir or entecavir — suppress the virus but do not cure it**, and are usually continued long term. Treatment is indicated according to a combination of viral load, aminotransferase level, fibrosis stage, family history of liver cancer and extrahepatic disease.
- **Counsel that suppression is not cure**, so that adherence does not lapse when the patient feels well and the tests normalise.

THE SCREENING STEP THAT PREVENTS DEATHS

Screen for hepatitis B before starting any significant immunosuppression — chemotherapy, rituximab in particular, high-dose or prolonged corticosteroids, biologic agents, transplantation.

Reactivation in an unprotected patient can cause fulminant hepatic failure and death. It is entirely preventable with prophylactic antiviral therapy. **This applies to patients who are core-antibody positive with a negative surface antigen as well**, not only to those with active infection.

This is one of the few places in medicine where a routine blood test taken before treatment prevents a death, and it is frequently omitted.

- **In pregnancy:** antiviral therapy in the third trimester where the viral load is high, plus **hepatitis B immunoglobulin and vaccination for the neonate at birth** — together these reduce vertical transmission to near zero. Given that neonatal infection becomes chronic in around nine of ten cases, this is among the highest-value interventions in hepatology.

Hepatitis C

- **Direct-acting antiviral therapy cures over 95% of patients with 8–12 weeks of oral treatment**, with few side effects. This has transformed the disease within a decade. Check for drug interactions before prescribing.
- **Cure does not abolish the risk of hepatocellular carcinoma in a patient who already has cirrhosis.** Surveillance continues after successful treatment, which surprises patients and must be explained.

For both

- Complete alcohol avoidance; weight and metabolic control; vaccination against hepatitis A and B as appropriate; screening and vaccination of household and sexual contacts.
- **Six-monthly ultrasound surveillance for hepatocellular carcinoma** in all patients with cirrhosis, and in hepatitis B also in selected patients without cirrhosis on the basis of age, family history and origin.
- **Screening endoscopy for varices** once cirrhosis is established.

5. Teaching Points and Viva Questions

- Interpret the panel, not the single test. Anti-HBc separates vaccination from past infection.
- A normal aminotransferase does not mean absent disease, and e-antigen-negative chronic hepatitis is common here.
- The platelet count is the cheapest early marker of portal hypertension.
- Screen for hepatitis B before immunosuppression, including in core-antibody-positive patients.
- Cure of hepatitis C does not end cancer surveillance once cirrhosis exists.

Questions you should be able to answer:

- A patient is anti-HBs positive and anti-HBc negative. Explain.
- Why does this man's platelet count of 138 concern you?

- He is about to start rituximab for lymphoma. What must be done?
- His wife is pregnant and also surface antigen positive. What are the steps to protect the baby?
- How would you assess his fibrosis without a biopsy or elastography?

Case 37 · Decompensated Cirrhosis and Portal Hypertension

CLINICAL VIGNETTE

A **54-year-old man** with cirrhosis presents with three weeks of increasing abdominal distension and ankle swelling. For the past two days his family report that he has been sleeping through the day, awake and restless at night, and confused about where he is.

He takes spironolactone and furosemide, and bought ibuprofen last week for backache.

On examination: jaundiced, with spider naevi, palmar erythema, gynaecomastia and multiple bruises. Temperature 37.6 °C, blood pressure 98/58 mmHg, heart rate 96/min. **Asterixis is present** and he is disorientated in time. The abdomen is distended with **shifting dullness**; there is mild generalised tenderness. The spleen is palpable. There is pitting oedema to the thighs.

Sodium 128 · creatinine 132 µmol/L (baseline 78) · bilirubin 78 µmol/L · albumin 24 g/L · INR 1.8 · platelets 78 × 10^9/L.

1. Focused History — Find the Precipitant

A patient with compensated cirrhosis does not decompensate spontaneously. **Something did this**, and the something is usually treatable while the cirrhosis is not.

Precipitant	How to find it
Infection, especially spontaneous bacterial peritonitis	Often with no fever and no abdominal pain. The only way to find it is to tap the ascites.
Gastrointestinal bleeding	Melaena, haematemesis, or a haemoglobin drop. Blood in the gut is a large protein load.
Constipation	Simple, common, and easily corrected.
Dehydration and over-diuresis	Weight loss, rising creatinine, low sodium.
Drugs	Sedatives and opioids; and non-steroidal anti-inflammatory drugs, which this patient has taken and which precipitate both renal failure and fluid retention.
Electrolyte disturbance, alcohol, portal vein thrombosis, hepatocellular carcinoma	Biochemistry, history, imaging with Doppler and alpha-fetoprotein.

- Also establish: the cause of the cirrhosis; previous variceal bleeding or banding; **previous spontaneous bacterial peritonitis**, which mandates lifelong prophylaxis; previous paracentesis; nutritional state; ongoing alcohol use; and whether transplantation has ever been discussed.

2. Physical Examination

- Full stigmata, as set out in the system opener, and **grade the ascites and the encephalopathy** rather than merely noting their presence.
- **Grades of encephalopathy:** I — altered sleep pattern, mild confusion, reversed day and night; II — lethargy, disorientation, obvious asterixis; III — somnolent but rousable, gross disorientation; IV — coma.
- Search deliberately for infection: chest, urine, skin, and the abdomen — remembering that **peritonitis in cirrhosis is frequently silent**.
- Assess **nutrition and muscle bulk**. Sarcopenia is common, is a strong adverse prognostic marker, and is routinely ignored.

- Examine for a hard nodular liver or a hepatic bruit suggesting hepatocellular carcinoma, and for hernias, which are common with tense ascites.

3. Investigations

THE INVESTIGATION THAT MUST NOT BE SKIPPED

Every patient admitted with ascites has a diagnostic tap, whether or not infection is suspected. Spontaneous bacterial peritonitis is present in around one in ten such admissions and is frequently asymptomatic.

Send: cell count and differential, **culture in blood culture bottles inoculated at the bedside**, albumin, total protein, glucose, lactate dehydrogenase, cytology, and acid-fast staining where tuberculosis is a possibility.

The diagnosis is made on the neutrophil count: 250 cells/mm^3 or more is spontaneous bacterial peritonitis, whether or not the culture grows anything, and whether or not the patient has fever or pain.

- **Serum-ascites albumin gradient** — serum albumin minus ascitic albumin. **A gradient of 11 g/L or more indicates portal hypertension** (cirrhosis, heart failure, Budd–Chiari). Below 11 points elsewhere — peritoneal malignancy, tuberculous peritonitis, pancreatitis, nephrotic syndrome.
- Full biochemistry, complete blood count, C-reactive protein, blood and urine cultures, chest radiograph, glucose.
- **Ammonia is of limited value.** Do not use it to diagnose or to exclude encephalopathy, which is a clinical diagnosis. A normal level in a confused cirrhotic patient does not let you off finding the cause.
- **Ultrasound with Doppler:** liver texture and nodules, **portal vein patency**, spleen size and ascites volume. Alpha-fetoprotein; cross-sectional imaging for any nodule.
- Endoscopy for varices. Score severity with **Child–Pugh** (bilirubin, albumin, INR, ascites, encephalopathy) and **MELD**, which also drives transplant prioritisation.

4. Management — One Problem at a Time

Ascites

- **Dietary sodium restriction** to about 2 g of sodium daily, which is the single most important measure and the one most often not explained properly.
- **Spironolactone with furosemide**, conventionally in a 100 mg to 40 mg ratio. **Daily weights** — aim for 0.5 kg loss per day without peripheral oedema, up to 1 kg with oedema. Monitor sodium, potassium and creatinine.
- **Large-volume paracentesis for tense ascites, with intravenous albumin replacement of 6–8 g for every litre removed**, to prevent post-paracentesis circulatory dysfunction.
- **Refractory ascites:** consider a transjugular intrahepatic portosystemic shunt, and refer for transplant assessment.
- **Avoid absolutely: non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors and receptor blockers, and aminoglycosides.**

Spontaneous bacterial peritonitis

- A third-generation cephalosporin, adjusted to local sensitivities.
- **Intravenous albumin, 1.5 g/kg on day 1 and 1 g/kg on day 3.** This is not supportive fluff — it substantially reduces the incidence of hepatorenal syndrome and reduces mortality.
- **Lifelong secondary prophylaxis** with a quinolone after a first episode.

Hepatic encephalopathy

- **Find and treat the precipitant.** This is the treatment; lactulose is the adjunct.
- **Lactulose titrated to two or three soft stools daily** — not to a fixed dose. Rifaximin is added for recurrent episodes.
- Avoid sedatives. Nurse in a well-lit place with orientation cues; assess swallowing before giving oral medication to a drowsy patient.

> **DO NOT RESTRICT THE PROTEIN**
>
> Older teaching restricted dietary protein in encephalopathy. **This is wrong and it is harmful.**
>
> Patients with cirrhosis are catabolic and frequently sarcopenic, and protein restriction worsens both the malnutrition and the outcome. **Give adequate protein**, roughly 1.2–1.5 g/kg daily, with frequent small meals and a **late evening snack** to shorten the overnight fast.

The rest

- **Varices:** a non-selective beta blocker such as propranolol or carvedilol, or endoscopic band ligation, for primary prophylaxis.
- **Hyponatraemia** is usually dilutional — fluid restriction, and reduce or stop diuretics if it is severe. Do not give saline.
- **Hepatorenal syndrome** — a diagnosis of exclusion, made after withdrawing diuretics and nephrotoxins and giving an albumin challenge. Treat with terlipressin and albumin; transplantation is the definitive treatment.
- **Transplant assessment**, alcohol abstinence with support, vaccination, six-monthly cancer surveillance, and an honest conversation about prognosis and preferences.

5. Teaching Points and Viva Questions

- Tap the ascites in every admission. Peritonitis in cirrhosis is usually silent.
- Two hundred and fifty neutrophils makes the diagnosis, with or without a positive culture.
- Albumin with peritonitis and with large-volume paracentesis changes outcomes.
- Feed the patient. Protein restriction is obsolete and harmful.
- Ammonia does not diagnose encephalopathy; the bedside does.
- Anti-inflammatory drugs are contraindicated in cirrhosis, and patients buy them freely.

Questions you should be able to answer:

- Name four possible precipitants in this history and say how you would test for each.
- The ascitic neutrophil count is 340 but the culture is sterile. What is the diagnosis and the treatment?
- Why is albumin given with the antibiotic?
- His serum-ascites albumin gradient is 6 g/L. What does that change?
- A colleague suggests restricting his protein. How do you respond?

Case 38 · Upper Gastrointestinal Bleeding

CLINICAL VIGNETTE

A **61-year-old man** with known cirrhosis is brought in after vomiting a large volume of fresh red blood twice at home. He has passed black tarry stools since yesterday. He feels faint on standing.

On arrival: he is pale and cool peripherally. Heart rate 122/min, blood pressure 88/54 mmHg, respiratory rate 24/min, capillary refill 4 seconds. He is alert but anxious. There are spider naevi and palmar erythema. Rectal examination confirms **melaena**.

Haemoglobin 74 g/L · urea 18 mmol/L with creatinine 92 µmol/L · INR 1.9 · platelets 62 × 10^9/L · albumin 26 g/L · bilirubin 54 µmol/L.

1. Resuscitate First

THE SEQUENCE

The order is resuscitation, then risk assessment, then endoscopy. A patient taken to the endoscopy suite while still shocked is a patient who may arrest there.

Two large-bore cannulae · bloods including **cross-match for 4 units** · balanced crystalloid while blood is prepared · continuous monitoring · senior help, and involvement of endoscopy, anaesthesia and critical care early.

- **A normal or near-normal haemoglobin in the first hours means nothing.** Haemoglobin concentration falls only as haemodilution occurs, so an acutely bleeding patient may have a normal value while losing litres. Judge the severity from the **pulse, blood pressure, perfusion and mental state**.
- **The urea is raised out of proportion to the creatinine** because blood in the gut is digested and absorbed as a protein load. A urea-to-creatinine disproportion in a patient with melaena is a useful confirmatory sign of an upper gastrointestinal source.

RESTRICTIVE TRANSFUSION

Transfuse to a target haemoglobin of 70–80 g/L, not to a normal value — higher thresholds are used in significant cardiovascular disease.

In variceal bleeding especially, **over-transfusion raises portal pressure, provokes rebleeding, and increases mortality.** The instinct to fill the patient up is a strong one and it is wrong.

2. Focused History

- **Distinguish the presentations:** fresh haematemesis suggests brisk bleeding; coffee-ground vomit suggests slower bleeding altered by acid; melaena indicates blood that has been in the gut for hours; and brisk upper bleeding can present as fresh rectal bleeding.
- **Preceding forceful retching before the haematemesis** suggests a Mallory–Weiss tear.
- **Drugs:** anti-inflammatory drugs, aspirin, antiplatelet agents, anticoagulants including direct oral anticoagulants, corticosteroids, and any bleeding disorder.
- Known varices, previous bleeding and banding; dyspepsia and previous ulcer; **weight loss and dysphagia** suggesting malignancy; alcohol history; comorbidity that limits physiological reserve.
- **Previous aortic graft surgery** — aorto-enteric fistula is rare, rapidly fatal, and is only ever diagnosed by the person who thought to ask.

3. Risk Assessment

- **The Glasgow–Blatchford score** is calculated before endoscopy from urea, haemoglobin, blood pressure, pulse, melaena, syncope, and hepatic or cardiac disease. **A score of 0–1 identifies patients who may safely be managed as outpatients** with early endoscopy — a genuinely useful discharge tool.
- **The Rockall score** is completed after endoscopy and predicts rebleeding and mortality.

4. Investigations

- Complete blood count, urea and electrolytes, liver function, **coagulation screen**, cross-match, lactate and venous gas, and an **electrocardiogram** — anaemia and hypotension precipitate demand ischaemia in an older patient.
- **Endoscopy within 24 hours** of presentation for all patients, and **within 12 hours in unstable patients or where variceal bleeding is suspected**, once resuscitation has achieved stability.
- An erect chest radiograph if perforation is a possibility; computed tomography angiography where bleeding continues and endoscopy has not identified or controlled the source.

5. Management

If variceal bleeding is suspected — start before endoscopy

- **Terlipressin**, to reduce portal pressure.
- **Prophylactic antibiotics — a third-generation cephalosporin — for every cirrhotic patient with gastrointestinal bleeding.** This reduces infection, rebleeding and **mortality**, and is one of the most strongly evidence-based interventions in the whole of gastroenterology. It is also one of the most frequently forgotten.
- **Endoscopic band ligation** for oesophageal varices; **cyanoacrylate injection** for gastric varices.
- **If bleeding is uncontrolled:** balloon tamponade as a **bridge only**, with the airway protected, followed by a transjugular intrahepatic portosystemic shunt. Early shunting is also considered in high-risk patients after initial control.
- **Afterwards:** a non-selective beta blocker together with a programme of repeated banding until the varices are eradicated.

If non-variceal bleeding

- **Endoscopic haemostasis using two modalities** — adrenaline injection alone is not adequate, and must be combined with clips or thermal coagulation.
- **High-dose proton pump inhibitor infusion after endoscopic haemostasis** of a high-risk ulcer. Routine treatment before endoscopy is not required.
- **Test for and eradicate *Helicobacter pylori*** in every ulcer bleed, and confirm eradication afterwards. Stop the anti-inflammatory drug.
- Rebleeding: repeat endoscopy, then interventional radiological embolisation, then surgery.

Coagulation and antithrombotic drugs

- Give platelets for a count below 50×10^9/L with active bleeding. Reverse warfarin with prothrombin complex concentrate and vitamin K; use the specific reversal agents for direct oral anticoagulants where available.
- **Do not routinely correct the INR with fresh frozen plasma in cirrhosis.** The INR does not reflect bleeding risk in liver disease, where both procoagulant and anticoagulant factors are reduced together, and plasma transfusion **raises portal pressure and can worsen variceal bleeding**.
- **Restart aspirin early** once haemostasis is secure where it was prescribed for secondary cardiovascular prevention — the risk of stopping it usually exceeds the risk of rebleeding. Discuss anticoagulation with the specialty that prescribed it rather than deciding alone.

6. Teaching Points and Viva Questions

- Resuscitate, then risk-assess, then endoscope. Never the other way round.
- The first haemoglobin does not tell you how much blood has been lost.
- Transfuse to 70–80 g/L. More is worse, particularly with varices.
- Antibiotics for every cirrhotic patient who bleeds — this one saves lives.
- A raised urea with a normal creatinine and melaena is an upper gastrointestinal bleed.
- Do not give plasma to correct the INR in cirrhosis.

Questions you should be able to answer:

- What are your first five actions, in order, for this man?
- Why is his urea 18 with a normal creatinine?
- Which two drugs would you give before he reaches the endoscopy suite, and why each?
- His INR is 1.9. Do you give fresh frozen plasma? Justify your answer.
- He rebleeds 12 hours after banding. What are the options in escalating order?

Case 39 · Inflammatory Bowel Disease

CLINICAL VIGNETTE

A **26-year-old man** describes four months of diarrhoea, now up to eight times a day with **blood and mucus**, with urgency and a constant feeling of incomplete emptying. **He is woken two or three times a night to open his bowels.** He has crampy lower abdominal pain relieved by defaecation and has lost 7 kg.

Over the past two weeks he has deteriorated: **twelve bloody stools a day**, fever and exhaustion.

On examination: temperature 38.2 °C, heart rate 116/min, blood pressure 104/64 mmHg. Pale and thin. The abdomen is distended and diffusely tender **without guarding or rebound**. Two aphthous ulcers in the mouth. Perianal inspection is normal.

Haemoglobin 92 g/L · white cells 15.2 × 10^9/L · platelets 480 · C-reactive protein 88 · albumin 26 g/L · potassium 3.1 mmol/L. Abdominal radiograph: **transverse colon 6.5 cm in diameter** with mucosal oedema and loss of haustration.

RECOGNISE THIS AS ACUTE SEVERE COLITIS — THE TRUELOVE AND WITTS CRITERIA

Six or more bloody stools a day, **plus any one** of: temperature above 37.8 °C · pulse above 90/min · haemoglobin below 105 g/L · erythrocyte sedimentation rate above 30.

This patient meets all of them. Acute severe colitis carries a real mortality, and the deaths come from delay — from treating it as an outpatient flare, from waiting to see whether steroids work, and from regarding colectomy as a failure rather than a treatment.

Admit. Involve a gastroenterologist and a colorectal surgeon on the day of admission, not when things deteriorate.

1. Ulcerative Colitis or Crohn Disease?

	Ulcerative colitis	Crohn disease
Distribution	Continuous from the rectum proximally; colon only	Patchy, with skip lesions, anywhere from mouth to anus — terminal ileum most often
Depth	Mucosal	Transmural
Blood and mucus	Characteristic	Less prominent
Perianal disease, fistula, stricture	Rare	Characteristic — and their presence effectively settles the diagnosis
Histology	Crypt abscesses, no granulomas	Non-caseating granulomas
Smoking	Protective — paradoxically	Harmful — worsens disease and increases recurrence after surgery
Surgery	Colectomy cures the colitis	Not curative; recurrence at the anastomosis is the rule

Note the smoking paradox and get it the right way round — it is a favourite examination question, and telling a patient with Crohn disease that smoking might help would be a serious error.

2. Focused History

- **The stool:** frequency, blood, mucus, urgency, tenesmus, incontinence — and **nocturnal diarrhoea, which is a marker of organic disease** and effectively excludes irritable bowel syndrome.
- Abdominal pain and its site; weight loss quantified; fever; fatigue; growth failure in a younger patient.

System	Extraintestinal manifestation
Joints	Peripheral arthritis; sacroiliitis and axial spondyloarthritis (Case 60)
Eyes	Uveitis, episcleritis — a painful red eye needs same-day ophthalmology
Skin and mouth	Erythema nodosum (Case 70), pyoderma gangrenosum — which must never be debrided, aphthous ulceration
Liver	Primary sclerosing cholangitis — cholestatic liver tests and pruritus, more often with ulcerative colitis, and it raises colorectal and cholangiocarcinoma risk
Blood and bone	Iron, B12 and folate deficiency; a markedly increased venous thromboembolism risk; osteoporosis

WHAT MUST BE EXCLUDED BEFORE YOU IMMUNOSUPPRESS

Send stool for culture, ova and parasites, and *Clostridioides difficile* toxin in every flare and every admission. Infection both mimics a flare and complicates one, and immunosuppressing an infected colon is dangerous.

And in this region, intestinal tuberculosis mimics ileocaecal Crohn disease almost exactly — same site, same imaging appearance, same granulomas on biopsy, same weight loss and night sweats. **Giving an anti-tumour-necrosis-factor agent to a patient with undiagnosed intestinal tuberculosis can produce disseminated disease.**

So before immunosuppression: **tuberculin or interferon-gamma release assay, chest radiograph, and tissue examined specifically for acid-fast bacilli and caseation** — plus hepatitis B and C, human immunodeficiency virus, varicella status, and thiopurine metaboliser genotype.

3. Physical Examination

- Vital signs, hydration and nutritional state; pallor; clubbing.
- **Abdomen: distension, tenderness, a mass, and above all the presence or absence of peritonism** — guarding and rebound in this context mean perforation and a surgeon.
- **Perianal inspection and digital rectal examination in every patient** — fistulae, fissures, abscesses and skin tags point firmly to Crohn disease and are missed if the patient is not examined.
- Mouth, eyes, joints and skin, as in the table above.

4. Investigations

- Complete blood count, C-reactive protein, albumin, urea and electrolytes (**potassium**), liver function, iron studies, B12, folate and vitamin D.
- **Faecal calprotectin** to separate inflammatory from functional disease in the outpatient setting — not needed here, where the diagnosis is not in doubt.
- **Abdominal radiograph in acute severe colitis:** colonic dilatation, mucosal islands, thumbprinting and loss of haustration. **A transverse colon diameter above 5.5 cm with systemic toxicity is toxic megacolon.**
- **Flexible sigmoidoscopy without bowel preparation, with biopsies**, to confirm the diagnosis and to **exclude cytomegalovirus colitis**. **Full colonoscopy is contraindicated in acute severe colitis** because of the perforation risk.

- When stable: **ileocolonoscopy with intubation of the terminal ileum and multiple biopsies**; magnetic resonance enterography or capsule endoscopy for small bowel Crohn disease; **magnetic resonance imaging of the pelvis for perianal disease**.

5. Managing Acute Severe Colitis

- **Intravenous corticosteroid** — hydrocortisone or methylprednisolone.
- Fluid resuscitation, **potassium replacement**, transfusion as needed, and nutritional support.

TWO THINGS THAT ARE ROUTINELY GOT WRONG

Venous thromboembolism prophylaxis, despite the rectal bleeding.

Active inflammatory bowel disease is a strongly prothrombotic state, and these patients die of pulmonary embolism. The bleeding is from an inflamed mucosa, not from a coagulopathy, and it is **not** a contraindication to prophylactic anticoagulation. Omitting it is one of the commonest errors on the ward.

And avoid antidiarrhoeal agents, opioids and anticholinergics entirely — all of them reduce colonic motility and can precipitate toxic megacolon in exactly this patient.

- **Monitor daily:** examination, a stool frequency and blood chart, and an abdominal radiograph while the colon is dilated. **Joint medical and surgical review from day one.**

THE DAY-THREE DECISION

On the third day of intravenous steroid, count the stools and check the C-reactive protein.

More than eight stools a day, or three to eight stools with a C-reactive protein above 45, predicts that steroids will fail in the great majority of patients.

At that point escalate — rescue therapy with infliximab or ciclosporin, or colectomy. Do not give steroids a further week to work. Delay past this point increases the risk of perforation, of emergency rather than elective surgery, and of death.

Colectomy is a treatment, not a defeat, and in ulcerative colitis it cures the colitis. Say so plainly to the patient early, so that the conversation is not being had for the first time in an emergency.

- **Toxic megacolon or perforation: urgent colectomy.**

6. Longer-Term Management

	Approach
Ulcerative colitis	Mesalazine, oral with topical therapy, for induction and maintenance of mild to moderate disease; topical treatment alone for proctitis; corticosteroids for flares only; then thiopurines, anti-tumour-necrosis-factor agents, vedolizumab, ustekinumab or a Janus kinase inhibitor. Colectomy is curative.
Crohn disease	Exclusive enteral nutrition (particularly in children) or corticosteroids for induction; then thiopurines, methotrexate, or biologic therapy. Treat to a target of mucosal healing rather than symptom control alone. Smoking cessation is among the most effective interventions available. Surgery for stricture, fistula or abscess, with combined medical and surgical management of perianal disease.

THE PRESCRIPTION TO STOP REPEATING

Corticosteroids do not maintain remission, and they cause harm.

A patient who has needed two or more courses in a year, or who cannot come off them, is **steroid-dependent** — and that is an indication to escalate to a steroid-sparing agent, not to prescribe another reducing course.

Every patient on repeated steroids needs bone protection and a documented plan for getting off them.

- **Colorectal cancer surveillance colonoscopy from 8 to 10 years after diagnosis** in colitis, at intervals set by extent, inflammation and family history — **and earlier and more frequently in primary sclerosing cholangitis**.
- Iron replacement, vaccination before immunosuppression, bone density assessment, **fertility and pregnancy planning** (most agents are compatible with pregnancy; **methotrexate is teratogenic and must be stopped well beforehand in both sexes**), smoking cessation, nutritional support, and access to psychological support and a specialist nurse.

7. Teaching Points and Viva Questions

- Nocturnal diarrhoea is organic disease. Ask about it.
- Examine the perineum — fistulae and tags settle the diagnosis.
- Send stool for *Clostridioides difficile* in every flare, and exclude tuberculosis before immunosuppressing.
- Give thromboprophylaxis despite the bleeding, and never give an antidiarrhoeal.
- Make the day-three decision on the third day.
- Steroids are not maintenance therapy; steroid dependence means escalate.
- Smoking protects in ulcerative colitis and harms in Crohn disease — know which way round.

Questions you should be able to answer:

- Apply the Truelove and Witts criteria to this patient.
- Why does he need heparin when he is passing twelve bloody stools a day?
- On day three he has nine stools and a C-reactive protein of 60. What are the options and what is the risk of waiting?
- A 24-year-old has terminal ileal thickening, weight loss and granulomas on biopsy. What must be excluded before you start infliximab, and why?
- He asks whether giving up smoking will help his ulcerative colitis. How do you answer?

Case 40 · Hepatocellular Carcinoma

CLINICAL VIGNETTE

A **58-year-old man** with hepatitis B-related cirrhosis, previously stable on antiviral therapy, has had three months of right upper quadrant discomfort and 8 kg of weight loss. **His ascites has become refractory to diuretics** and he has developed mild confusion and reversal of his sleep pattern for the first time.

He was enrolled in a surveillance programme but **did not attend his last two ultrasound appointments**.

On examination: cachectic and jaundiced, with spider naevi. The liver is enlarged, **hard and irregular, with an audible bruit over it**. There is tense ascites and splenomegaly. Asterixis is present.

Alpha-fetoprotein 840 µg/L. Quadruple-phase computed tomography: a **6 cm lesion in the right lobe with arterial phase enhancement and delayed washout**, with **tumour thrombus in the right portal vein**. Child–Pugh class B.

THE PRESENTATION TO RECOGNISE

A previously stable patient with cirrhosis who decompensates has a new problem, and hepatocellular carcinoma is near the top of the list.

New or refractory ascites · new encephalopathy · a first variceal bleed · unexplained weight loss · new abdominal pain — any of these in a compensated cirrhotic patient should prompt imaging and an alpha-fetoprotein, alongside the search for infection and the other precipitants in Case 37.

Portal vein thrombosis is part of the same picture, and it may be bland or tumour thrombus — which the imaging must distinguish, because it changes the stage entirely.

1. Surveillance — Which Is Really the Whole Case

- **Hepatocellular carcinoma arises almost entirely within a known, identifiable, at-risk population.** That makes it one of the very few cancers where early detection is genuinely achievable — and it is usually found late because surveillance was not offered, not done, or not attended.
- **Six-monthly ultrasound, with or without alpha-fetoprotein, in every patient with cirrhosis** — and in selected patients with chronic hepatitis B **without** cirrhosis, on the basis of age, family history, viral load and origin.
- **Chase the non-attenders.** This patient missed two appointments and now has a 6 cm tumour with vascular invasion instead of a 2 cm one that could have been ablated or transplanted. Recall systems, reminders and explaining to the patient *why* the scan matters are part of the clinical work, not administration.

Risk factor	Note
Chronic hepatitis B	Can cause hepatocellular carcinoma without cirrhosis, which is why non-cirrhotic surveillance exists. Antiviral therapy reduces but does not abolish the risk (Case 36).
Chronic hepatitis C	Risk persists after viral cure once cirrhosis is established — so surveillance continues after successful antiviral treatment.
Alcohol-related cirrhosis	Compounded by continued drinking.
Metabolic dysfunction-associated steatotic liver disease	A rapidly rising cause, and one that may produce cancer with relatively little fibrosis.
Haemochromatosis, primary biliary cholangitis, alpha-1 antitrypsin deficiency	Established risk factors.
Aflatoxin exposure	From improperly stored grains and nuts; synergistic with hepatitis B.

2. Focused History and Examination

- The decompensation features above; right upper quadrant or shoulder-tip pain; early satiety; fever; and rarely **paraneoplastic hypoglycaemia, hypercalcaemia, erythrocytosis or watery diarrhoea**.
- Sudden severe abdominal pain with hypotension suggests **tumour rupture with haemoperitoneum** — a surgical and radiological emergency.
- Establish the cause and stage of the liver disease, previous decompensation, alcohol use, antiviral therapy and adherence, and **performance status and comorbidity**, which will constrain every treatment option.
- **Examination:** cachexia, jaundice, and a **hard, irregular, sometimes tender liver with a bruit or friction rub over it**; ascites; encephalopathy; signs of portal hypertension; and a left supraclavicular node.

3. Investigations

THE DIAGNOSTIC RULE THAT IS UNLIKE OTHER CANCERS

In a cirrhotic liver, hepatocellular carcinoma is diagnosed on imaging, not on histology.

A lesion showing **arterial phase hyperenhancement with washout in the portal venous or delayed phase** on quadruple-phase computed tomography or contrast-enhanced magnetic resonance imaging is diagnostic in a patient with cirrhosis.

Biopsy is therefore usually unnecessary, and it carries risks of bleeding and needle-track seeding. This is unusual among cancers and it surprises students, who reasonably expect tissue before a cancer diagnosis. Biopsy is reserved for atypical imaging or a non-cirrhotic liver.

- **Alpha-fetoprotein is neither sensitive nor specific enough to diagnose or to exclude the disease.** It can be normal in a large tumour and raised in active hepatitis or cirrhosis without cancer. Use it as an adjunct and for trend, never as the deciding test.
- **Staging must capture three things at once:** the **tumour** (size, number, vascular invasion, extrahepatic spread), the **liver** (Child–Pugh and MELD), and the **patient** (performance status). The Barcelona Clinic Liver Cancer system integrates all three — **because a small resectable tumour in a decompensated liver is not a surgical problem, and a large tumour in a well-preserved liver may still be treatable.**

- Endoscopy for varices; hepatitis serology and viral load; renal function; and chest and bone imaging where indicated.

4. Management by Stage

Stage	Treatment
Very early and early — single lesion or up to three small lesions, preserved liver function, good performance status	Resection where function is preserved and there is no significant portal hypertension · ablation (radiofrequency or microwave) for small lesions · liver transplantation, which uniquely treats both the tumour and the underlying cirrhosis, in patients meeting the Milan criteria
Intermediate — multinodular, preserved function	Transarterial chemoembolisation, sometimes repeated, with reassessment
Advanced — vascular invasion or extrahepatic spread, preserved function	Systemic therapy: immune checkpoint inhibitor combinations are now first line — atezolizumab with bevacizumab, or durvalumab with tremelimumab — with tyrosine kinase inhibitors such as sorafenib or lenvatinib as alternatives. This patient, with portal vein tumour thrombus, sits here.
Terminal — poor liver function or poor performance status	Best supportive and palliative care, with symptom control and honest discussion

- **Treat the underlying liver disease throughout.** Continuing antiviral therapy for hepatitis B reduces recurrence and improves survival; alcohol abstinence matters; and the complications of cirrhosis are managed as in Case 37 — including large-volume paracentesis with albumin, and antibiotic prophylaxis after spontaneous bacterial peritonitis.
- **Multidisciplinary team management**, with hepatology, oncology, radiology, surgery and transplant input; and **early palliative care involvement**, as in Case 7.
- An honest conversation about prognosis, and advance care planning.

PREVENTION

Of everything in this case, the interventions that save the most lives happen years before the tumour appears: **Hepatitis B vaccination — which prevents a common cancer** · antiviral treatment of chronic hepatitis B and cure of hepatitis C · alcohol reduction · management of obesity, diabetes and metabolic liver disease · and **safe grain and nut storage** to limit aflatoxin exposure.

It is worth saying to students explicitly that the hepatitis B vaccine is an anti-cancer vaccine.

5. Teaching Points and Viva Questions

- A stable cirrhotic who decompensates needs imaging and an alpha-fetoprotein.
- Six-monthly ultrasound in cirrhosis — and chase the patients who do not attend.
- In cirrhosis the diagnosis is radiological; biopsy is usually unnecessary and carries risk.
- Alpha-fetoprotein neither diagnoses nor excludes.
- Treatment depends on the tumour, the liver and the patient together — not on the tumour alone.
- Transplantation treats both diseases at once.

- Surveillance continues after hepatitis C is cured, if cirrhosis is established.

Questions you should be able to answer:

- Which features of his presentation should have prompted imaging weeks earlier?
- Why is a biopsy not required to make this diagnosis?
- His alpha-fetoprotein had been normal six months ago. Does that reassure you in retrospect?
- What does the portal vein tumour thrombus do to his treatment options?
- A patient with hepatitis C cirrhosis achieves a viral cure. Do you stop surveillance?

The Infectious Diseases Block

Brucellosis, malaria, tuberculosis, bacterial meningitis, HIV, pneumonia in the immunocompromised host, encephalitis, and the principles of antimicrobial use.

Cases 41–48 · 10,040 words

This block covers the infectious diseases teaching of both internal medicine courses. The **first course** supplies cases 41 and 44; the **second course** supplies cases 45 and 48.

Case	Lecture it serves
System opener: the febrile patient	Approach common to the whole block; pyrexia of unknown origin seminar
Case 41 — Brucellosis	Brucellosis
Case 42 — Malaria	Malaria
Case 43 — Pulmonary tuberculosis	Tuberculosis
Case 44 — Bacterial meningitis	Meningitis and other central nervous system infections
Case 45 — Human immunodeficiency virus infection	Human immunodeficiency virus infection and AIDS
Case 46 — Pneumonia in the immunocompromised host, and viral pneumonia	Pneumonias: viral, influenza, immunocompromised and others
Case 47 — Encephalitis	Central nervous system infections: meningitis and encephalitis
Case 48 — The principles of antimicrobial use	Use of antibiotics
(Case 1 — Community-acquired pneumonia)	Bacterial pneumonia

More than any other block, these cases depend on where you are practising. The organisms in this section are not exotic here — they are the ones your patients actually have, and the diagnoses that are most often delayed because the exposure question was never asked.

System Opener · The Febrile Patient

In infectious disease the decisive skill is not examination but **exposure history**. The physical findings are often non-specific; the diagnosis usually lies in a question that was or was not asked.

The history

Characterise the fever

- **Duration.** Under a week is acute. **Pyrexia of unknown origin** is conventionally fever above 38.3 °C for more than three weeks that remains undiagnosed after appropriate initial investigation.
- **Pattern.** Less reliable than textbooks suggest, but worth noting: **undulant** fever over weeks in brucellosis; **tertian** periodicity in established malaria, though early malaria is usually irregular; relapsing fevers; and **relative bradycardia** — a pulse lower than expected for the temperature — in typhoid and brucellosis.
- **Rigors** — true shaking chills — indicate bacteraemia, malaria, or abscess, and are worth distinguishing from feeling cold.

THE EXPOSURE HISTORY — THE PART THAT MAKES THE DIAGNOSIS

Ask every one of these, in every febrile patient, before you order a test:

Travel — exactly where, when, for how long, rural or urban; prophylaxis taken and whether it was completed after returning.

Food and drink — **unpasteurised milk, fresh cheese and raw liver**, undercooked meat, street food, shellfish, untreated water.

Animals — **sheep, goats and camels**, assisting at animal births, cats, birds, rodents, tick and insect bites.

Mass gatherings — Hajj and Umrah, and other crowded gatherings, with their attendant respiratory and meningococcal risk.

Occupation — farming, abattoir, veterinary, laboratory, healthcare.

Person to person — household and workplace contacts with similar illness; sexual history; injecting drug use; transfusion, tattoos and unsterile procedures.

Host factors — human immunodeficiency virus, corticosteroids or biologic therapy, chemotherapy, diabetes, transplantation, and **splenectomy or functional asplenia from sickle cell disease**, which permits fulminant infection with encapsulated organisms.

Recent healthcare — lines, prostheses, surgery, and recent antibiotics.

Use the incubation period

- **Short, under 10 days:** most bacterial infections, influenza, dengue, meningococcal disease.
- **Long, over 21 days: tuberculosis, brucellosis**, viral hepatitis, human immunodeficiency virus seroconversion, visceral leishmaniasis, and malaria in a patient who took partial prophylaxis. If the exposure was more than three weeks ago, a great many diagnoses are excluded and a few become likely.

The examination

- **Vital signs and recognition of sepsis** first, using your local early warning score. Note relative bradycardia if present.
- **The whole skin, undressed and in good light** — including the back, the soles, between the toes, the perineum, under dressings, and around every line and device. Examine the conjunctivae and the palate.
- **Describe any rash precisely.** Maculopapular, vesicular, or **non-blanching petechial and purpuric — which with fever is a medical emergency**. Look for an eschar at the site of a tick or mite bite.
- **All lymph node groups**, recording size, tenderness, mobility and matting.

- **Abdomen for hepatosplenomegaly** — one of the most useful discriminating signs in febrile illness.
- Heart for a murmur; chest; joints; **spine and sacroiliac tenderness**; testes; and a full neurological examination including neck stiffness and fundoscopy.

Fever with…	Think of
Hepatosplenomegaly	Brucellosis, malaria, typhoid, visceral leishmaniasis, infective endocarditis, Epstein–Barr virus, lymphoma, tuberculosis
Generalised lymphadenopathy	Epstein–Barr and cytomegalovirus, human immunodeficiency virus seroconversion, toxoplasmosis, tuberculosis, brucellosis, lymphoma
Non-blanching rash	Meningococcal sepsis, other bacterial sepsis with disseminated intravascular coagulation, rickettsial infection, viral haemorrhagic fever
Back pain	Brucella spondylitis, tuberculous spondylitis, pyogenic spondylodiscitis, epidural abscess, endocarditis
Jaundice	Malaria, viral hepatitis, leptospirosis, ascending cholangitis, brucellosis, severe sepsis
Thrombocytopenia	Malaria, dengue, brucellosis, sepsis, rickettsial infection, haematological disease

Case 41 · Brucellosis

CLINICAL VIGNETTE

A **34-year-old man** who keeps goats and sheep in a rural district presents with six weeks of fever that rises each afternoon and settles by morning, with **drenching night sweats** that require him to change his clothes. He has profound fatigue, has lost 7 kg, and describes aching in the large joints and **persistent low back pain** that is worse on movement.

He drinks fresh unboiled goat's milk daily and assisted with several difficult births in the herd two months ago. Two of his brothers have had a similar illness in the past year.

On examination: temperature 38.6 °C with a pulse of 84/min. There is **hepatosplenomegaly**. There is tenderness over the lower lumbar spine and pain on sacroiliac compression. No rash. No murmur.

1. Focused History

- **The exposure is the diagnosis.** Unpasteurised milk, fresh soft cheese, **raw liver**, and above all contact with the products of animal parturition, which carry an enormous organism load. Ask about abattoir, veterinary and laboratory work.
- **Household clustering is common**, because families share the same milk. A similar illness in relatives supports the diagnosis and identifies people who also need testing.
- **The classical constitutional triad:** undulant fever, drenching night sweats, and fatigue that is out of proportion to the physical findings. A characteristic peculiar odour of the sweat is described.
- **Ask specifically about focal complications**, because they change the duration and combination of treatment:
  - **Osteoarticular** — the commonest, in up to a third: sacroiliitis in younger patients, **lumbar spondylitis in older patients**, and large joint arthritis of hip or knee.
  - **Genitourinary** — unilateral epididymo-orchitis.
  - **Neurobrucellosis** — headache, meningism, cranial nerve palsies, radiculopathy, and prominent depression or behavioural change.
  - **Endocarditis** — uncommon but responsible for most of the deaths from this disease.
- **Duration and previous treatment.** Acute is under eight weeks, subacute up to a year, chronic beyond that. Ask whether a previous course was completed — relapse is nearly always a failure of duration or adherence.

2. Physical Examination

- Fever with **relative bradycardia**; hepatosplenomegaly; lymphadenopathy.
- **Examine the spine and sacroiliac joints deliberately** — percussion tenderness over the vertebrae, pain on sacroiliac compression and on the flexion-abduction-external rotation manoeuvre. Localised vertebral tenderness with fever demands imaging.
- Peripheral joints for effusion; testicular examination; a careful cardiac examination for a murmur; and a full neurological examination.

3. Investigations

THE STEP THAT IS UNIQUE TO THIS DIAGNOSIS

Tell the laboratory that you suspect brucellosis.

Two reasons. First, the organism grows slowly and cultures must be **held for prolonged incubation** rather than discarded as sterile at 48 hours. Second, **brucella is among the commonest causes of laboratory-acquired infection**, and technicians handling the plates need to know so that they work under appropriate containment.

Failing to warn the laboratory both loses the diagnosis and puts colleagues at risk.

- **Blood cultures**, ideally before antibiotics. **Bone marrow culture has a higher yield** and is useful where blood cultures are negative but suspicion is high.
- **Serology.** The standard tube agglutination test is the workhorse: **a titre of 1:160 or above in an endemic area**, or a fourfold rise in paired samples, supports the diagnosis. Rose Bengal is a rapid screening test. Enzyme immunoassays distinguish IgM from IgG.
- **Serology remains positive for months or years after cure.** Do not use titres to judge response to treatment, and interpret a single positive titre in an endemic population with care — background seropositivity is common.
- Polymerase chain reaction where available, which is rapid and useful in focal disease.
- **Supporting laboratory findings:** a normal or **low** white cell count with relative lymphocytosis — a leucocytosis argues against the diagnosis; mild transaminase elevation; thrombocytopenia or pancytopenia; and a C-reactive protein that may be only modestly raised.
- **Imaging:** magnetic resonance imaging of the spine where there is back pain, since **plain films are normal early** and the disease characteristically affects the lower lumbar vertebrae; sacroiliac imaging; **echocardiography** if there is any murmur or persistent bacteraemia; and lumbar puncture with brain imaging for suspected neurobrucellosis.

4. Differential Diagnosis

Diagnosis	The feature that discriminates it
Tuberculosis	Also causes fever, sweats, weight loss and spondylitis, and also affects the spine. Distinguished by imaging pattern, sputum and tissue studies. The two coexist in the same populations.
Typhoid fever	Also with relative bradycardia and splenomegaly; more prominent abdominal symptoms, and a different exposure history.
Infective endocarditis	Brucella is itself a cause. Blood cultures, echocardiography and peripheral stigmata.
Lymphoma	Night sweats, weight loss, hepatosplenomegaly and lymphadenopathy — clinically almost identical. Requires tissue.
Visceral leishmaniasis	Massive splenomegaly with pancytopenia, in the appropriate geographical setting.
Connective tissue disease	Rash, serositis, autoantibodies, and no exposure history.

5. Management

THE PRINCIPLE

Never treat brucellosis with a single agent, and never treat it briefly. Monotherapy and short courses are followed by relapse in a high proportion of patients.

The organism is intracellular, which is why combinations and prolonged courses are required, and why relapse reflects inadequate treatment rather than acquired resistance.

Situation	Regimen and duration
Uncomplicated disease	Doxycycline for 6 weeks, combined with either an aminoglycoside (streptomycin or gentamicin) for the first 1–2 weeks, or rifampicin for the full 6 weeks. Aminoglycoside-containing regimens have lower relapse rates.
Spondylitis or sacroiliitis	At least 12 weeks, usually with triple therapy.
Neurobrucellosis	Doxycycline, rifampicin and ceftriaxone for 3–6 months, with corticosteroids in selected cases.
Endocarditis	Prolonged triple therapy, and valve surgery is usually required.
Children under 8 and pregnancy	Doxycycline is contraindicated. Use co-trimoxazole with rifampicin.

- Warn about a **Jarisch–Herxheimer-like reaction** in the first 24 hours of treatment.
- **Follow up for relapse**, which usually occurs within six months and presents in the same way as the original illness. Re-treat with a full course; resistance is not the issue.
- **Public health:** notify; test symptomatic household members; and counsel on **boiling or pasteurising milk**, avoiding fresh soft cheese from unpasteurised milk, animal vaccination programmes, and protective equipment when handling parturient animals or abattoir material.

6. Teaching Points and Viva Questions

- Ask about milk and animals in every febrile patient here. The diagnosis is usually missed at the point of the history, not the laboratory.
- Warn the laboratory — for the culture and for the technician.
- A leucocytosis argues against brucellosis; a normal or low count with lymphocytosis argues for it.
- Serology stays positive after cure, so do not use it to monitor treatment.
- Fever with back pain in this region means brucella or tuberculous spondylitis until imaging says otherwise.
- Consider it in any pyrexia of unknown origin and in any culture-negative endocarditis.

Questions you should be able to answer:

- Which three questions in the history made this diagnosis likely?
- Why must you inform the microbiology laboratory?

- His back pain persists. What imaging, and how does the result change treatment?
- He completed six weeks of doxycycline alone and has relapsed. Explain why.
- His wife is 20 weeks pregnant and now has fever and sweats. How does that change your prescription?

Case 42 · Malaria

CLINICAL VIGNETTE

A **28-year-old man** presents with five days of fever, severe headache, generalised aching and vomiting. He returned twelve days ago from visiting family in a rural area of a malaria-endemic country. He took no prophylaxis, believing that having grown up there he was protected. Today his urine has turned dark and his family say he is muddled.

On examination: temperature 39.4 °C, heart rate 124/min, blood pressure 94/58 mmHg, respiratory rate 30/min and deep. He is **jaundiced**, drowsy but rousable, with a Glasgow Coma Scale of 13. The spleen is palpable 3 cm below the costal margin. There is no rash and no neck stiffness.

Thick and thin films: *Plasmodium falciparum*, parasitaemia 6%. Haemoglobin 82 g/L · platelets 46 × 10^9/L · glucose 3.4 mmol/L · creatinine 168 µmol/L · bilirubin 68 µmol/L · lactate 4.8 mmol/L.

THE RULE

Fever in a returning traveller is malaria until proved otherwise. Falciparum malaria can progress from mild illness to death within 24 hours, and the early symptoms are indistinguishable from influenza.

The commonest reason for a death from malaria in a non-endemic setting is that the travel history was not taken, or was taken and not acted on.

1. Focused History

- **Exactly where, and exactly when.** Countries, rural or urban, and the dates of departure and return, so that the incubation period can be checked.
- **Incubation periods:** falciparum usually presents within 7–30 days of exposure. **Vivax and ovale may present months or even years later**, because they form dormant liver hypnozoites. Partial prophylaxis prolongs incubation and masks the presentation.
- **Prophylaxis** — which drug, whether it was taken correctly, and crucially **whether it was continued for the full period after returning**, which is where adherence usually fails.
- **The dangerous misconception in this patient's history:** immunity acquired in childhood **wanes within a year or two of leaving an endemic area**. People visiting friends and relatives are among the highest-risk groups precisely because they believe themselves protected and take no precautions.
- **Red flag symptoms:** confusion or drowsiness, seizures, reduced urine output, breathlessness, bleeding, jaundice, and inability to keep fluids down.
- Previous malaria, pregnancy, splenectomy, and comorbidity.

2. Physical Examination

- **Conscious level**, formally scored and repeated — cerebral malaria is defined by unrousable coma with parasitaemia and no other cause.
- Temperature, respiratory rate and pattern — **deep acidotic breathing is an ominous sign in a child or adult with malaria**; blood pressure and perfusion.
- Jaundice, pallor, splenomegaly and hepatomegaly, hydration, urine output and **urine colour**.

- Bleeding from puncture sites or gums, and signs of an alternative or coexisting infection. **A rash is not a feature of malaria** and should prompt you to think of dengue, rickettsia or meningococcal disease — while remembering that a patient may have two diseases.

3. Investigations

HOW THE DIAGNOSIS IS MADE

Thick films detect; thin films speciate and quantify.

Three negative sets over 48 hours are required before malaria can be excluded. A single negative film does not exclude it, and the patient should not be discharged on the strength of one.

Rapid antigen tests are a valuable adjunct, particularly out of hours, but they do not quantify parasitaemia, some remain positive for weeks after treatment, and some parasites carry gene deletions that produce false negatives. They do not replace microscopy.

- **Quantify the parasitaemia as a percentage** of infected red cells. It determines severity and is repeated daily to confirm the parasites are clearing.
- **Complete blood count. Thrombocytopenia with fever in a returning traveller is highly suggestive of malaria** and is one of the most useful early clues. Anaemia is common and may be severe.
- **Glucose** — hypoglycaemia is frequent, particularly in children, in pregnancy and with quinine treatment, and it is easily mistaken for deepening coma.
- Urea, electrolytes and creatinine, liver function, **lactate**, coagulation screen, blood gas, blood cultures, and urinalysis for haemoglobinuria.

Severe falciparum malaria — any one is sufficient	
Impaired consciousness or seizures	Acidosis or a raised lactate
Hypoglycaemia	Severe anaemia
Renal impairment	Jaundice with another severity feature
Pulmonary oedema or acute respiratory distress	Shock, or significant bleeding
Parasitaemia above 10% — or above 2% in a non-immune patient	Haemoglobinuria

This patient meets **five** of these criteria. He has severe malaria and requires high-dependency care.

4. Management

- **Severe falciparum malaria: intravenous artesunate.** It is clearly superior to quinine, reducing mortality substantially, and should be given without waiting for transfer or confirmation of every result. Follow with a full oral course of artemisinin-based combination therapy once the patient can swallow.
- **Uncomplicated falciparum malaria:** oral artemisinin-based combination therapy.
- **Vivax and ovale:** chloroquine or an artemisinin combination for the blood stage, **followed by primaquine to eradicate the liver hypnozoites** — without which the patient will relapse weeks or months later.

BEFORE GIVING PRIMAQUINE

Primaquine causes severe haemolysis in glucose-6-phosphate dehydrogenase deficiency. Test before prescribing it — always.

Given how common the deficiency is in this region, this is not a theoretical precaution. Where deficiency is found, primaquine may still be used under specialist supervision with a modified weekly regimen.

- **Supportive care:** cautious fluid resuscitation — **over-hydration precipitates pulmonary oedema and acute respiratory distress**; hourly glucose monitoring; treatment of seizures; transfusion for severe anaemia; renal replacement therapy where needed.
- **Corticosteroids are contraindicated in cerebral malaria** — they worsen outcome.
- **Repeat films daily** until the parasitaemia is negative. Rising parasitaemia after 24 hours of appropriate treatment requires urgent reassessment.
- **Delayed haemolysis occurs one to three weeks after artesunate.** Check the haemoglobin at follow-up and warn the patient — it is easily mistaken for relapse or for a new illness.
- Notify; treat in a monitored setting; and advise properly on prophylaxis, bed nets and repellents for future travel, addressing directly the belief that childhood residence confers lasting protection.

5. Teaching Points and Viva Questions

- Three negative films over 48 hours before you exclude malaria.
- Fever plus thrombocytopenia plus recent travel is malaria until proved otherwise.
- The species determines whether hypnozoites must be eradicated, and therefore whether primaquine and a glucose-6-phosphate dehydrogenase test are needed.
- Artesunate, not quinine, for severe disease.
- Immunity wanes. The traveller visiting family is at high risk, not low.
- Check the haemoglobin again two weeks after artesunate.

Questions you should be able to answer:

- List the severity criteria this patient meets.
- The first film is negative but you remain suspicious. What do you do?
- Why does *Plasmodium vivax* require a second drug, and what must you check first?
- Why is aggressive fluid resuscitation dangerous here?
- He returns three weeks later, pale and tired, with a negative film. What is the likely explanation?

Case 43 · Pulmonary Tuberculosis

CLINICAL VIGNETTE

A **42-year-old man** presents with ten weeks of cough, productive for the last month and streaked with blood on three occasions. He has **drenching night sweats** that soak the bedding, has lost 9 kg, and has no appetite. He feels feverish in the evenings.

He shares accommodation with six other workers. A colleague was treated for tuberculosis last year. He has not been tested for human immunodeficiency virus.

On examination: thin, temperature 37.9 °C. There are coarse crackles and bronchial breathing in the **right upper zone**. There is firm, matted cervical lymphadenopathy on the right.

Chest radiograph: right upper lobe consolidation with a cavity, and volume loss.

1. Focused History

- **The screening question is cough for more than two to three weeks.** Any patient with that, in this setting, is investigated for tuberculosis.
- **The constitutional triad:** drenching night sweats that require changing clothes or bedding, unintentional weight loss, and evening fever. Ask about the *quantity* of weight lost and over what period.
- **Contact history** — a known index case, household crowding, and where the patient sleeps relative to others.
- **Previous tuberculosis and previous treatment**, including whether it was completed. Incomplete prior treatment raises the possibility of drug resistance and changes the entire approach.
- **Risk factors:** human immunodeficiency virus, **diabetes mellitus** — a major and frequently overlooked risk factor in this region — malnutrition, silicosis, chronic kidney disease, anti-tumour-necrosis-factor and other biologic therapy, corticosteroids, smoking, alcohol, incarceration, and migration from a high-burden country.
- **Extrapulmonary symptoms**, because tuberculosis presents in every organ: lymph node swelling, **back pain (spinal tuberculosis)**, abdominal pain or swelling, headache and personality change (meningitis), sterile pyuria, monoarthritis.

2. Physical Examination

- Cachexia and temperature; upper zone signs of consolidation or cavitation; signs of pleural effusion.
- **Lymph nodes** — tuberculous nodes are firm, matted, may become fluctuant and may discharge through the skin.
- **Spine** — localised tenderness or a gibbus deformity; a full neurological examination if spinal disease is suspected.
- Abdomen for ascites and masses; skin for erythema nodosum; eyes; and a search for signs of immunosuppression.

3. Investigations

- **Three sputum specimens, including an early morning sample**, for: **smear microscopy** for acid-fast bacilli; a **nucleic acid amplification test such as Xpert MTB/RIF**, which is rapid and simultaneously detects rifampicin resistance; and **culture on liquid and solid media**, which remains the reference standard and provides full drug sensitivities, but takes weeks.

- If the patient cannot expectorate: induced sputum, bronchoalveolar lavage, or early morning gastric aspirate.

- **Chest radiograph — reading the film:** disease favours the **apical and posterior segments of the upper lobes and the superior segment of the lower lobes**, because the organism is aerophilic. Look for consolidation, **cavitation**, nodules, fibrosis with volume loss and tracheal deviation, a **miliary** pattern of fine uniform nodules, effusion, and hilar lymphadenopathy. Computed tomography where the film is equivocal.

- **Test every patient with tuberculosis for human immunodeficiency virus.** This is not optional; it changes prognosis, treatment and the timing of other therapy.

- **Baseline before starting drugs:** complete blood count, renal function, **liver function**, glucose or glycated haemoglobin to screen for diabetes, weight, and **visual acuity and colour vision before ethambutol**.

- **Tissue for extrapulmonary disease** — node aspirate or biopsy, pleural biopsy, cerebrospinal fluid. Always send tissue for culture as well as histology.

> A DISTINCTION THAT IS REGULARLY CONFUSED
>
> The tuberculin skin test and interferon-gamma release assays detect **infection**, not **disease**. They may be positive in latent infection and negative in overwhelming active disease.
>
> **They neither confirm nor exclude active tuberculosis.** Their role is in diagnosing latent infection in contacts and before immunosuppression — not in the patient in front of you with a cavity on the chest radiograph.

4. Management

Phase	Regimen
Intensive phase — 2 months	Rifampicin, isoniazid, pyrazinamide and ethambutol
Continuation phase — 4 months	Rifampicin and isoniazid
Longer courses	Central nervous system disease for around 12 months; bone and joint disease for 9–12 months; drug-resistant disease under specialist care

- **Pyridoxine with isoniazid** to prevent peripheral neuropathy — particularly in diabetes, malnutrition, alcohol use, renal failure and pregnancy.

- **Treatment support and observed therapy.** Adherence, not the microbiology, determines the outcome and determines whether resistance emerges.

- **Monitoring:** monthly weight and symptom review, sputum smear and culture at 2 months and again at 5 and 6 months, and liver function testing.

Drug	What to warn about and monitor
Rifampicin	Orange discolouration of urine, tears and sweat — warn the patient and warn contact lens wearers. It is a powerful enzyme inducer: the oral contraceptive pill will fail, and warfarin and antiretroviral levels fall. Hepatitis.
Isoniazid	Peripheral neuropathy (prevented by pyridoxine), hepatitis, and drug-induced lupus.
Pyrazinamide	Hepatitis, hyperuricaemia and gout, arthralgia.
Ethambutol	Optic neuritis with loss of visual acuity and red–green colour discrimination. Test before starting, warn the patient to report any visual change immediately, and stop the drug at once if it occurs.

DRUG-INDUCED HEPATITIS

Stop all hepatotoxic drugs if the alanine aminotransferase rises above five times normal, or above three times normal with symptoms, or if bilirubin rises.

Exclude other causes, allow the liver to recover, then **reintroduce the drugs one at a time with monitoring**, in the order recommended locally. Do not restart the whole regimen at once.

- **Infection control:** isolate suspected smear-positive patients, ideally in a negative-pressure room, until they have had adequate treatment; **notify the case**; and arrange **contact tracing**, which is a legal and public health duty and often finds more cases.
- **With human immunodeficiency virus co-infection:** start antiretroviral therapy within 2–8 weeks, watch for **immune reconstitution inflammatory syndrome**, and manage the substantial interactions between rifampicin and antiretroviral drugs.
- **Treat latent infection in contacts** who are identified through tracing, particularly children and the immunosuppressed.

5. Teaching Points and Viva Questions

- Cough for more than three weeks means send sputum, not another antibiotic.
- Test everybody with tuberculosis for human immunodeficiency virus, and screen for diabetes.
- Skin tests and interferon assays diagnose infection, not disease.
- Warn about the orange urine and the failure of the contraceptive pill, or the patient will stop the drug or become pregnant.
- Check colour vision before ethambutol and tell the patient exactly what to report.
- Treatment failure is nearly always adherence, and adherence is the doctor's responsibility as much as the patient's.

Questions you should be able to answer:

- Which three tests do you send the sputum for, and what does each contribute?

- Why does the disease favour the upper zones?
- His alanine aminotransferase is 280 at week three. What do you do, and how do you restart?
- He is taking the oral contraceptive pill. What must you tell her?
- A negative interferon-gamma release assay comes back. Does that change anything?

Case 44 · Bacterial Meningitis

CLINICAL VIGNETTE

A **19-year-old student** is brought to the emergency department with twelve hours of severe headache, fever, vomiting and intolerance of light. Over the last hour he has become drowsy and is answering questions slowly. He returned five days ago from a large religious gathering.

On examination: temperature 39.2 °C, heart rate 128/min, blood pressure 92/50 mmHg, capillary refill 4 seconds. Glasgow Coma Scale 13. There is **neck stiffness** and a positive Kernig sign.

Over the trunk and legs there is a **non-blanching petechial rash** that was not present when the family left home.

BEFORE YOU READ ANY FURTHER

Give the antibiotic now. Not after the lumbar puncture, not after the computed tomogram, not after the senior review. Take blood cultures on the way if it takes seconds, but **nothing delays the first dose of antibiotic by more than a few minutes**. Meningococcal sepsis can kill a previously healthy young adult within hours, and every hour of delay increases mortality.

1. Recognise Which Syndrome You Are Treating

Meningitis	Meningococcal septicaemia
Headache, neck stiffness, photophobia, vomiting	Fever, non-blanching rash, limb pain, cold hands and feet, shock
Conscious level often preserved early	Rapid circulatory collapse
Priority: antibiotics and assessment of intracranial pressure	Priority: antibiotics and aggressive resuscitation; meningism may be absent
Lumbar puncture usually appropriate	Lumbar puncture contraindicated while shocked or with spreading purpura

This patient has **both**. The septicaemic component is what will kill him first.

2. Focused History

- **Speed of onset.** Bacterial meningitis evolves over hours; viral over days; tuberculous and cryptococcal over weeks.
- Headache, fever, photophobia, neck stiffness, vomiting, rash, limb pain, seizures, focal deficits and altered behaviour.
- **Mass gathering attendance, crowded accommodation and close contacts** — the epidemiological context that makes meningococcal disease more likely, and that determines who will need prophylaxis.
- **A portal of entry:** otitis media, sinusitis, head injury, cerebrospinal fluid leak, previous neurosurgery, cochlear implant.
- **Host factors: splenectomy, sickle cell disease with functional asplenia**, complement deficiency, human immunodeficiency virus, corticosteroids, diabetes, and age over 50 or pregnancy — the last two determining whether *Listeria* cover is required.
- **Vaccination history** — meningococcal ACWY, pneumococcal and *Haemophilus influenzae* type b.

3. Physical Examination

- **Conscious level and vital signs first**, and recognition of shock.
- **Examine the entire skin for a non-blanching rash** — trunk, limbs, soles, conjunctivae and palate — using a glass pressed against the lesions. Mark the edge of the rash with a pen and time it; **spreading purpura is a marker of fulminant disease**.
- **Neck stiffness, Kernig and Brudzinski signs** — but note that **these signs are insensitive, and their absence does not exclude meningitis**, particularly in the very young, the elderly and the immunosuppressed.
- Focal neurological signs, cranial nerve palsies, **fundoscopy for papilloedema**, and examination of the ears.

4. Investigations

- **Blood cultures, and blood for meningococcal and pneumococcal polymerase chain reaction.** The PCR remains positive after antibiotics have been given, and is often what secures the diagnosis when cultures are sterile — which is a further reason not to delay treatment for a sample.
- Complete blood count, C-reactive protein, urea and electrolytes, glucose, **coagulation screen** for disseminated intravascular coagulation, lactate, blood gas, throat swab.

Computed tomography before lumbar puncture is required if…	Lumbar puncture is contraindicated if…
Focal neurological deficit	Signs of raised intracranial pressure
New-onset seizure	Shock or cardiorespiratory instability
Reduced or fluctuating conscious level	Coagulopathy or significant thrombocytopenia
Papilloedema	Spreading purpura
Immunocompromise	Local infection at the puncture site

A normal computed tomogram does not exclude raised intracranial pressure — the decision to perform a lumbar puncture remains a clinical one. And in a patient like this, who is shocked with spreading purpura, the puncture is deferred entirely; the diagnosis will be made on blood culture and PCR.

Cerebrospinal fluid interpretation

	Bacterial	Viral	Tuberculous
Appearance	Turbid	Clear	Clear, may form a fibrin web
Predominant cell	Neutrophils	Lymphocytes	Lymphocytes
Protein	High	Normal or mildly raised	Very high
Glucose (ratio to plasma)	Low — below 0.4	Normal	Very low
Other	Gram stain and culture; PCR	PCR for enterovirus, herpes simplex	Acid-fast stain, PCR, raised adenosine deaminase, large-volume culture

Always send a paired plasma glucose, since the cerebrospinal fluid glucose is meaningless without it.

5. Management

- **Antibiotics within one hour of arrival.** Empirically, a high-dose third-generation cephalosporin such as **ceftriaxone or cefotaxime**.
- **Add amoxicillin or ampicillin to cover *Listeria monocytogenes*** in patients over 50, in pregnancy, and in the immunocompromised. Add vancomycin where penicillin-resistant pneumococcus is a local concern.

CORTICOSTEROIDS — TIMING IS EVERYTHING

Give dexamethasone with, or just before, the first dose of antibiotic where pneumococcal meningitis is suspected. Given afterwards, it does not work.

It reduces hearing loss and neurological sequelae in pneumococcal disease. **Stop it if the organism proves to be meningococcal**, and do not give it in septic shock.

- **Add aciclovir** if herpes simplex encephalitis is possible — personality change, seizures, fever and temporal lobe features on imaging.
- **Resuscitate the septicaemic patient:** intravenous fluids, vasopressors, and early critical care involvement. Correct coagulopathy; anticipate limb ischaemia and adrenal haemorrhage.
- Manage raised intracranial pressure, treat seizures, monitor sodium — inappropriate antidiuresis is common.

PUBLIC HEALTH — WITHIN HOURS, NOT DAYS

Notify the case immediately — by telephone, on clinical suspicion, without waiting for laboratory confirmation.

Chemoprophylaxis for close household contacts and anyone with prolonged close contact or exposure to respiratory secretions: a single dose of ciprofloxacin, or rifampicin. Prophylaxis prevents further cases, and the window is short.

Vaccination has a role in outbreak control, and **meningococcal ACWY vaccination is a requirement for pilgrims attending mass gatherings here** — ask whether it was received.

6. Complications and Follow-up

- **Sensorineural hearing loss is the commonest sequela. Every survivor requires formal audiological assessment**, and in children this must be arranged before discharge.
- Seizures and epilepsy, hydrocephalus, subdural empyema, cerebral infarction, cognitive impairment.
- In meningococcal sepsis: disseminated intravascular coagulation, digit and limb loss, and adrenal haemorrhage.
- **Investigate for complement deficiency** after recurrent meningococcal disease or infection with an unusual serogroup, and check for anatomical defects or cerebrospinal fluid leak after recurrent pneumococcal meningitis.

7. Teaching Points and Viva Questions

- Antibiotics first. Imaging and lumbar puncture come afterwards, always.

- Fever with a non-blanching rash is meningococcal sepsis until proved otherwise — treat immediately and resuscitate.
- Absent neck stiffness does not exclude meningitis.
- Dexamethasone with the first antibiotic dose or not at all.
- Blood PCR stays positive after antibiotics, so treating early does not destroy the diagnosis.
- Notify by telephone on suspicion, and arrange contact prophylaxis the same day.
- Every survivor has their hearing tested.

Questions you should be able to answer:

- What are your first four actions for this patient, in order?
- Why will you not perform a lumbar puncture on him now?
- When does a patient need a computed tomogram before lumbar puncture?
- Interpret: 1200 white cells with 95% neutrophils, protein 3.2 g/L, cerebrospinal fluid glucose 0.9 with plasma glucose 6.0.
- His roommates ring the ward asking what they should do. What do you tell them?

Case 45 · Human Immunodeficiency Virus Infection

CLINICAL VIGNETTE

A **34-year-old man** has had three months of soreness in the mouth, 12 kg of weight loss, drenching night sweats and intermittent diarrhoea. For the past three weeks he has had a **dry cough and breathlessness on exertion**, which is now limiting him to about 100 metres.

On examination: cachectic. There is **oral candidiasis and white corrugated plaques on the lateral tongue that do not scrape off**. Generalised small-volume lymphadenopathy and seborrhoeic dermatitis of the scalp and face. **Auscultation of the chest is normal.** Oxygen saturation 96% at rest, **falling to 88% after walking along the corridor**.

Chest radiograph: bilateral perihilar interstitial shadowing. **Fourth-generation HIV test positive · CD4 count 68 cells/µL · high plasma viral load · lactate dehydrogenase raised.**

THE LESSON OF THIS CASE

The single most important change you can make to your practice is to test more people. Late diagnosis is the main determinant of death from human immunodeficiency virus infection, and it happens because the test was not offered.

Test on the clinical picture, not on your assessment of risk. Risk-based testing misses a large proportion of cases, because patients do not disclose, do not perceive risk, or do not fit the doctor's idea of who is at risk. **Never withhold a test because the patient "does not look at risk".**

Indicator conditions that should prompt an HIV test: oral candidiasis · **oral hairy leukoplakia** · seborrhoeic dermatitis · **herpes zoster, especially if young or multidermatomal** · unexplained weight loss, fever or chronic diarrhoea · generalised lymphadenopathy · **tuberculosis at any site** · recurrent bacterial pneumonia · unexplained cytopenias or immune thrombocytopenia · any sexually transmitted infection · cervical dysplasia · Kaposi sarcoma · lymphoma · unexplained dementia or neurological disease · chronic parotitis.

Consent is verbal and straightforward. The elaborate pre-test counselling of the 1990s is obsolete and was itself a barrier.

1. How HIV Presents

- **Acute seroconversion illness** — two to six weeks after exposure: fever, pharyngitis, maculopapular rash, lymphadenopathy, mouth and genital ulcers, myalgia. It resembles glandular fever, is frequently dismissed, and is the period of **highest infectivity**. **The antibody test may still be negative — so send an HIV RNA level if you suspect it.**
- **A long asymptomatic phase**, then symptomatic disease with the indicator conditions above, then AIDS-defining illness.
- **Ask about:** sexual history including partners and their origin, injecting drug use, blood products before screening, occupational exposure, unsterile procedures and tattoos, and vertical exposure — while remembering the point in the box above.
- **Approach confidentiality, disclosure and partner notification carefully and explicitly.** Stigma is a clinical problem here as much as a social one, and it affects whether patients test, attend and take treatment.

2. Examination

- Weight and body mass index with the trend; **mouth — candidiasis, oral hairy leukoplakia, ulcers, Kaposi sarcoma**; skin — seborrhoeic dermatitis, molluscum contagiosum, zoster scarring, Kaposi lesions.
- Lymph nodes; **fundoscopy for cytomegalovirus retinitis**; a full neurological and cognitive assessment; abdomen for organomegaly; and anogenital examination.

- **The chest is often normal on auscultation in Pneumocystis pneumonia** — which is exactly why the exertional oxygen saturation matters.

3. Investigations

- **A fourth-generation antigen–antibody test** detects the p24 antigen and shortens the window to about four weeks; confirm according to the local algorithm. **HIV RNA where acute seroconversion is suspected.**

- **Baseline assessment:** CD4 count and viral load, resistance genotype, complete blood count, renal and liver function, glucose and lipids, **hepatitis A, B and C serology**, syphilis serology, gonorrhoea and chlamydia testing, **latent tuberculosis screening**, toxoplasma and cytomegalovirus serology, cryptococcal antigen if the CD4 count is below 100, urinalysis, cervical cytology, and HLA-B*5701 if abacavir is contemplated.

CD4 count	Infections that become likely
Below 200	Pneumocystis jirovecii pneumonia — and the threshold for starting prophylaxis
Below 100	Toxoplasma encephalitis, cryptococcal meningitis, oesophageal candidiasis
Below 50	Cytomegalovirus retinitis and colitis, disseminated *Mycobacterium avium* complex, primary central nervous system lymphoma, progressive multifocal leukoencephalopathy
Any count	Tuberculosis — which occurs at any CD4 level and is the commonest opportunistic infection worldwide; bacterial pneumonia; Kaposi sarcoma; lymphoma

PNEUMOCYSTIS PNEUMONIA

The clinical signature is a triad: a **subacute dry cough** over weeks, **breathlessness on exertion**, and **desaturation on exercise with a chest that sounds normal**. That mismatch between symptoms and examination is the diagnosis.

Diagnosis: induced sputum or bronchoalveolar lavage for immunofluorescence or polymerase chain reaction. Lactate dehydrogenase is usually raised but is non-specific. High-resolution computed tomography shows ground-glass change.

Treatment: high-dose co-trimoxazole for 21 days.

And add corticosteroids where there is significant hypoxaemia — an arterial oxygen below about 9.3 kPa or a saturation below 92% on air — because steroids reduce mortality in moderate to severe disease. Start them with, or just before, the antibiotic.

Alternatives where co-trimoxazole cannot be used: clindamycin with primaquine (**check glucose-6-phosphate dehydrogenase status first**), atovaquone, or pentamidine. Watch co-trimoxazole for rash, cytopenias, hyperkalaemia, renal impairment and hepatitis. **Secondary prophylaxis continues until the CD4 count is sustained above 200.**

4. Management of the HIV Infection

- **Start antiretroviral therapy in everyone, at any CD4 count, and start it promptly** — usually a single-tablet integrase inhibitor-based regimen. There is no longer a threshold to wait for.

TREATMENT AS PREVENTION

A person on effective treatment with a sustained undetectable viral load does not transmit the virus sexually.

This is one of the most consequential facts in modern medicine and it belongs in the first few consultations — for the patient's relationships, for their willingness to take treatment, and for public health. Say it plainly.

TIMING, AND THE TRAP OF IMMUNE RECONSTITUTION

Treat the opportunistic infection first, then start antiretroviral therapy — usually within about two weeks.

But delay for four to six weeks in tuberculous meningitis and in cryptococcal meningitis, because immune reconstitution inflammatory syndrome within a closed cranium can be catastrophic.

Immune reconstitution inflammatory syndrome is paradoxical clinical worsening as immunity recovers, commonest with mycobacterial and cryptococcal disease. **Continue the antiretrovirals, treat the infection, and add corticosteroids in severe cases** — it is not treatment failure and not a reason to stop therapy.

- **Prophylaxis:** co-trimoxazole when the CD4 count is below 200; treatment of latent tuberculosis; azithromycin for *Mycobacterium avium* complex at very low counts.
- **Drug interactions are a major and continuing hazard** — check every new prescription. Rifampicin lowers antiretroviral levels; ritonavir and cobicistat raise the levels of statins, inhaled and injected corticosteroids, and many other drugs.
- Adherence support; vaccination, **avoiding live vaccines at low CD4 counts**; monitoring of renal, bone, metabolic and cardiovascular risk; cancer screening; mental health; and long-term retention in care.
- **Prevention:** condoms, **pre-exposure prophylaxis**, **post-exposure prophylaxis started within 72 hours**, partner notification, and **antenatal screening with antiretroviral therapy and neonatal prophylaxis, which reduces vertical transmission to near zero.**

5. Teaching Points and Viva Questions

- Test on indicator conditions, not on your impression of risk.
- A negative antibody test does not exclude seroconversion — send RNA.
- Exertional desaturation with a normal chest examination is Pneumocystis.
- Add steroids to co-trimoxazole if hypoxic.
- Delay antiretrovirals in cryptococcal and tuberculous meningitis.
- Undetectable means untransmittable, and the patient should be told.
- Tuberculosis occurs at any CD4 count.

Questions you should be able to answer:

- List six indicator conditions that should prompt an HIV test.
- Why does his oxygen saturation matter more after walking than at rest?
- His arterial oxygen is 8.4 kPa. What do you add to the co-trimoxazole and why?
- He is diagnosed with cryptococcal meningitis. When do you start antiretroviral therapy?
- A patient presents 30 hours after a high-risk sexual exposure. What do you offer?

Case 46 · Pneumonia in the Immunocompromised Host

CLINICAL VIGNETTE

A **58-year-old woman** presents six days after her third cycle of chemotherapy for diffuse large B-cell lymphoma, with fever, a dry cough and breathlessness. She takes co-trimoxazole prophylaxis but admits she has missed most doses.

On examination: temperature 38.6 °C, heart rate 110/min, respiratory rate 24/min, **oxygen saturation 91% on air**. **There are no focal chest signs.** There is mucositis. The tunnelled line site looks clean.

Neutrophils 0.3 × 10^9/L. Chest radiograph: subtle bilateral shadowing. **Computed tomography: bilateral ground-glass change, and a nodule in the right upper lobe with a surrounding halo.**

FIRST, AND WITHOUT DELAY

Fever of 38 °C or more in a neutropenic patient means broad-spectrum antibiotics within one hour — before imaging, before cultures return, before the source is known. Everything below happens alongside that, not before it.

1. Think First — the Deficit Predicts the Organism

There is no single list of "infections in the immunosuppressed". **Establish which arm of the immune system is missing, and the differential follows.**

Deficit	Typical causes	Organisms to expect
Neutropenia	Chemotherapy, acute leukaemia, aplastic anaemia	Gram-negative bacilli including *Pseudomonas*, *Staphylococcus aureus*, streptococci; and with prolonged neutropenia, invasive fungal disease — *Aspergillus* and *Candida*
Impaired cell-mediated immunity	HIV with a low CD4 count, transplantation, prolonged corticosteroids, calcineurin inhibitors, anti-tumour-necrosis-factor agents	Pneumocystis, *Mycobacterium tuberculosis* and non-tuberculous mycobacteria, *Nocardia*, *Cryptococcus*, endemic fungi, cytomegalovirus, *Toxoplasma*, *Listeria*, *Strongyloides*
Humoral deficiency or asplenia	Myeloma, chronic lymphocytic leukaemia, rituximab, splenectomy, sickle cell disease	Encapsulated organisms — pneumococcus, *Haemophilus influenzae*, meningococcus; recurrent sinopulmonary infection
Barrier and device	Central lines, catheters, mucositis, aspiration	Staphylococci and skin flora; aspiration organisms

- **In solid organ and stem cell transplantation the timeline also predicts the organism:** in the first month, nosocomial bacteria and *Candida*; from one to six months, **cytomegalovirus, Pneumocystis, *Aspergillus* and tuberculosis**; beyond six months, community-acquired pathogens — with late opportunistic infection whenever immunosuppression is intensified.

2. Focused History

- **The immunosuppressive regimen in detail, with dates and doses.** Which chemotherapy and when; the expected neutrophil nadir; transplant type and time since; **corticosteroid dose and duration — more than about 20 mg of prednisolone daily for over four weeks confers cell-mediated deficiency**; biologic agents and their mechanism.

- **Which prophylaxis is prescribed, and whether it is actually being taken.** This patient is prescribed co-trimoxazole and is not taking it, which puts Pneumocystis back on the list. **Breakthrough infection on**

prophylaxis changes the differential — it points either to non-adherence or to an organism the prophylaxis does not cover.

- Travel, tuberculosis contact, **animal and camel contact**, sick household contacts, building work or gardening (*Aspergillus*), and vaccination history.

3. Physical Examination

WHY THE EXAMINATION IS MISLEADING

A neutropenic patient cannot form pus, so the classical signs of infection are absent — and fever may be the only finding.

There may be no sputum, no crackles, and **no consolidation on the chest radiograph, because an infiltrate requires neutrophils to create it.** A normal film in a febrile neutropenic patient does not exclude pneumonia; it is an argument for computed tomography.

Examine the mouth, sinuses, skin, perineum, line exit sites and between the toes — and **do not perform a digital rectal examination**. Look specifically for signs of invasive fungal disease: nasal or palatal eschar, orbital swelling, and cutaneous nodules.

4. Investigations

- **Blood cultures from a peripheral vein and from every lumen of any indwelling line**; sputum or induced sputum; urine; and swabs from any suspicious site.
- **Computed tomography of the chest, which is far more sensitive than the plain film — and the pattern is informative:**
  - **Ground-glass change** — Pneumocystis, viral pneumonia, cytomegalovirus, drug reaction.
  - **Nodules with a surrounding halo, or cavitating nodules** — **invasive aspergillosis**, as here.
  - **Cavitation** — tuberculosis, *Nocardia*, *Staphylococcus aureus*, fungal disease.
  - **Lobar consolidation** — conventional bacterial pneumonia.
- **Bronchoalveolar lavage is the key investigation where the diagnosis is not obvious**, and it should be arranged early rather than after several days of empirical escalation. Send for bacterial, fungal and mycobacterial culture, **Pneumocystis** immunofluorescence or polymerase chain reaction, a **respiratory viral multiplex panel**, cytomegalovirus, *Nocardia* and galactomannan.
- **Serum galactomannan and beta-D-glucan** for invasive fungal disease; cryptococcal antigen; cytomegalovirus viral load; nasopharyngeal swab for respiratory viruses; **and an HIV test, which is easy to omit in a patient whose immunosuppression already has a name.**

5. Viral Pneumonia — Including Influenza

- **Influenza:** abrupt onset with fever, myalgia, headache and dry cough. Complications include **primary viral pneumonia**, **secondary bacterial pneumonia — classically pneumococcal or a necrotising staphylococcal pneumonia following influenza**, myocarditis, encephalitis and rhabdomyolysis.

- **Treat high-risk patients with oseltamivir on clinical suspicion, ideally within 48 hours, without waiting for the swab.** High risk: pregnancy, chronic lung, heart, kidney, liver or neurological disease, diabetes, immunosuppression, the very young and very old, and marked obesity. **Vaccinate annually** — including healthcare workers.

- Other respiratory viruses cause equally severe disease in the immunosuppressed: respiratory syncytial virus, parainfluenza, adenovirus, human metapneumovirus, and SARS-CoV-2.

A REGIONAL DIAGNOSIS THAT MUST BE ASKED ABOUT

Consider Middle East respiratory syndrome coronavirus in any patient with severe pneumonia and either contact with camels or camel products, or contact with a confirmed or suspected case, or recent healthcare exposure in an affected facility.

It causes severe pneumonia with a high mortality and has repeatedly caused **healthcare-associated outbreaks**, which is what makes early recognition a matter of protecting the ward as well as the patient.

Isolate with airborne precautions immediately, notify public health without waiting for confirmation, and send the appropriate respiratory samples. Ask the exposure question of every severe pneumonia — it takes ten seconds.

6. Management

- **Empirical broad-spectrum antibacterial therapy within the hour**, with antipseudomonal cover, according to local protocol; add a glycopeptide where line infection or resistant staphylococcal disease is likely.

- **Add empirical antifungal therapy** where fever persists beyond four to seven days in prolonged neutropenia, or where imaging or galactomannan suggests mould — **voriconazole or liposomal amphotericin for suspected aspergillosis**, as in this patient.

- **High-dose co-trimoxazole with corticosteroids** if Pneumocystis is likely and the patient is hypoxic (Case 45). Oseltamivir for influenza; ganciclovir for cytomegalovirus disease.

- **Then de-escalate on the results.** Stewardship applies with equal force here — broad cover started appropriately should be narrowed once an organism is known, and stopped when infection is excluded.

- Growth factor support in selected patients; discuss modification of immunosuppression with the parent specialty; **isolation and infection control**; and involve infectious diseases or microbiology early rather than after three changes of antibiotic.

- **Prevention, which is where most of the benefit lies:** co-trimoxazole prophylaxis for those on high-dose steroids or at-risk regimens, antifungal prophylaxis in high-risk haematology, **screening and treatment of latent tuberculosis and hepatitis B before biologic therapy**, and vaccination **before** immunosuppression begins.

7. Teaching Points and Viva Questions

- Antibiotics within one hour of a neutropenic fever.

- Identify the immune deficit and the differential writes itself.

- A normal chest radiograph in neutropenia proves nothing — get a computed tomogram.

- The computed tomography pattern points to the organism; a halo sign means invasive mould.
- Breakthrough on prophylaxis means non-adherence or an uncovered organism.
- Arrange bronchoalveolar lavage early, not after three antibiotic changes.
- Ask about camel contact in severe pneumonia, and isolate before you confirm.

Questions you should be able to answer:

- Which arm of her immune system has failed, and what does that predict?
- Why are there no crackles and almost nothing on the chest radiograph?
- What does the halo sign suggest, and what would you start?
- She has missed her co-trimoxazole. What does that add to your differential?
- A patient with severe pneumonia keeps camels. What do you do before you examine him further?

Case 47 · Encephalitis

CLINICAL VIGNETTE

A **46-year-old woman** has had four days of fever and headache. Over the last two days her husband reports that she has become **uncharacteristically disinhibited and cannot find the right words**. This morning she had a focal seizure of the right arm that became generalised.

On examination: temperature 38.4 °C, Glasgow Coma Scale 13 and fluctuating. **There is no neck stiffness and no rash.** There is an expressive dysphasia and a right pronator drift.

Computed tomography of the head: normal. Cerebrospinal fluid: 90 white cells, 95% lymphocytes · protein 0.9 g/L · glucose ratio normal · opening pressure normal · Gram stain negative.

BEFORE ANYTHING ELSE

Give intravenous aciclovir now, together with empirical antibiotics for possible bacterial meningitis — **before the polymerase chain reaction result, before the magnetic resonance imaging, and before the senior review.**

Untreated herpes simplex encephalitis kills around 70% of those it affects and leaves most survivors with severe deficits. Treated early, the outcome is transformed. The drug is cheap, safe and available on every ward.

And note two traps: a normal computed tomogram does not exclude it, and the cerebrospinal fluid polymerase chain reaction can be negative in the first 24 to 48 hours. If suspicion persists, continue aciclovir and repeat the lumbar puncture rather than stopping the drug on one negative result.

1. Meningitis, Encephalitis, or Both?

	Meningitis	Encephalitis
Inflamed structure	The meninges	The brain parenchyma
Defining features	Headache, fever, neck stiffness, photophobia	Altered consciousness, personality and behavioural change, confusion, seizures, focal deficit
Cerebral function	Normal	Abnormal — this is the definition
Neck stiffness	Usually present	Often absent — and its absence must not reassure
Covered in	Case 44	This case

The diagnosis of encephalitis rests on altered brain function, not on meningism. A febrile patient who is behaving oddly, or who has a new seizure or focal deficit, has encephalitis until proved otherwise — even with a supple neck.

2. The Causes

Group	Causes
Viral	Herpes simplex virus type 1 — the commonest sporadic cause and the treatable one · varicella zoster · enteroviruses · Epstein–Barr virus · cytomegalovirus and HIV in the immunosuppressed · mumps and measles · rabies · arboviruses including West Nile, dengue and Japanese encephalitis — and, with animal or tick exposure in this region, Alkhurma haemorrhagic fever virus and Rift Valley fever virus
Bacterial and parasitic	Tuberculous meningitis — subacute, basal, with cranial nerve palsies and hydrocephalus, and important here · *Listeria* rhombencephalitis · neurobrucellosis (Case 41) · syphilis · cerebral abscess · cerebral malaria · neurocysticercosis, a leading cause of adult-onset seizures worldwide · toxoplasmosis and cryptococcosis in HIV
Autoimmune	Anti-NMDA receptor encephalitis — typically a young woman with a psychiatric prodrome, seizures, a movement disorder and autonomic instability, sometimes with an ovarian teratoma · LGI1 and other neuronal surface antibody syndromes · paraneoplastic encephalitis. Consider it in any encephalitis without an infective cause, and especially where psychiatric or movement features dominate — because it is treatable.

3. Investigations

- **As for meningitis (Case 44), plus a cerebrospinal fluid viral polymerase chain reaction panel** — herpes simplex 1 and 2, varicella zoster, enterovirus — and, where indicated, tuberculosis polymerase chain reaction and culture, cryptococcal antigen, syphilis and *Brucella* serology, and malaria films.
- **The cerebrospinal fluid in viral encephalitis** shows a lymphocytic pleocytosis with mildly raised protein and a normal glucose ratio — **and it may be entirely normal early in the illness.**
- **Magnetic resonance imaging is much more sensitive than computed tomography**, and in herpes simplex encephalitis shows **asymmetrical change in the temporal and inferior frontal lobes**.
- **Electroencephalography** — temporal lobe discharges support the diagnosis, and it also detects **non-convulsive status epilepticus** in a patient who is not waking up (Seminar 10).
- **Blood: cultures, an HIV test in every case**, viral serology, and **neuronal surface antibodies in both serum and cerebrospinal fluid** where autoimmune encephalitis is possible — with tumour screening if positive.
- The contraindications to lumbar puncture, and the indications for imaging first, are those set out in Case 44.

4. Management

- **High-dose intravenous aciclovir for 14 to 21 days**, with attention to hydration and renal function, since it causes crystal nephropathy.
- **Empirical antibiotics until bacterial meningitis is excluded.** And where tuberculous meningitis is suspected, **start antituberculous therapy with corticosteroids before confirmation** — the diagnosis is slow and the disease is fast.
- Seizure control, management of raised intracranial pressure, sodium monitoring for inappropriate antidiuresis, airway and nursing care, and early critical care involvement if consciousness deteriorates.

- **Autoimmune encephalitis:** corticosteroids, intravenous immunoglobulin or plasma exchange, then second-line immunosuppression — **and a search for an underlying tumour.**
- Notification where required; rabies post-exposure prophylaxis after a relevant animal bite; and vaccination.

WHAT HAPPENS AFTERWARDS

Cognitive impairment, personality change, mood disorder and epilepsy are common after encephalitis, and they are what the patient and family live with.

Plan for them: neuropsychological assessment, epilepsy follow-up with driving advice, rehabilitation, and support for the family — who may find the personality change harder than the illness. **Discharge with a follow-up plan, not with a discharge summary alone.**

5. Teaching Points and Viva Questions

- Encephalitis is defined by altered brain function, not by neck stiffness.
- Aciclovir before the polymerase chain reaction, every time.
- A negative early cerebrospinal fluid polymerase chain reaction does not exclude herpes simplex.
- Magnetic resonance imaging beats computed tomography, and the temporal lobes are the place to look.
- Ask for an electroencephalogram in a patient who is not waking up.
- Think tuberculosis, neurobrucellosis and neurocysticercosis here.
- If no organism is found, consider autoimmune encephalitis — it is treatable.

Questions you should be able to answer:

- She has no neck stiffness. Does that make you less concerned?
- What do you give in the first fifteen minutes, and what do you not wait for?
- The herpes simplex polymerase chain reaction returns negative on day one. What do you do?
- Which imaging do you want and what would you expect it to show?
- A 22-year-old has a psychiatric prodrome, seizures and orofacial dyskinesia with negative viral studies. What is the diagnosis and what must you look for?

Case 48 · The Principles of Antimicrobial Use

A WARD ROUND RATHER THAN A SINGLE PATIENT

Four patients on one ward round:

1. An **82-year-old woman** on day six of intravenous co-amoxiclav for "urosepsis". She is afebrile, eating and mobilising. The urine culture grew mixed flora; the blood cultures were negative. **There is no stop date on the chart.**

2. A **34-year-old man** with cellulitis receiving intravenous vancomycin because the notes record "penicillin allergy — rash as a child".

3. A **60-year-old man** on day twelve of meropenem for a hospital-acquired pneumonia. All cultures are negative. He has developed diarrhoea.

4. A **26-year-old woman** given five days of azithromycin at a walk-in clinic for a sore throat, with a normal examination and no systemic features.

Each of these represents a common, specific and avoidable error. This chapter is about the reasoning that prevents them.

1. Twelve Principles

1. Ask whether an antibiotic is needed at all

- Most sore throats and acute coughs are viral. **Asymptomatic bacteriuria, colonisation of a chronic ulcer or a line, and a positive surface swab are not indications for treatment** (Case 32). Patient four needed no antibiotic.

2. Take cultures before the first dose

- It is the single opportunity to obtain a microbiological diagnosis, and it determines whether therapy can later be narrowed or stopped. **But never delay treatment to obtain them in sepsis, meningitis or neutropenic fever.**

3. Choose empirically by site, severity, host and local resistance

- Not by habit, and not by reaching for the broadest available agent. **Read the previous cultures** — a patient's own microbiological history is the best predictor of their next organism.

THE ANTIMICROBIAL REVIEW — THE MOST IMPORTANT HABIT TO ACQUIRE

Every antibiotic prescription needs, written on the chart at the moment it is started: an indication, a route, and a stop or review date.

Then at 48 to 72 hours, make one of five decisions and document it:

Stop — infection unlikely or excluded · **Switch** from intravenous to oral · **Change** to a narrower agent guided by culture · **Continue** with a defined total duration · **Refer** to microbiology or infectious diseases.

Patient one has had no review for six days. Continuing intravenously by default is the commonest failure in hospital antimicrobial prescribing.

5. Switch intravenous to oral as soon as possible

- Once the patient is improving, afebrile and absorbing enterally. This reduces line infections, thrombophlebitis, length of stay and cost, and it lets patients go home.

6. Shorter is usually better

- **The traditional long courses were largely arbitrary**, and trial evidence has repeatedly shown shorter courses to be equivalent: around **five days for community-acquired pneumonia**, **three days for**

uncomplicated cystitis, and **seven days for most bacteraemias and for hospital-acquired pneumonia**.

- **The genuine exceptions requiring prolonged therapy:** infective endocarditis, osteomyelitis and septic arthritis, brain abscess, **tuberculosis and brucellosis**, prosthetic material infection, and any undrained collection.

SOURCE CONTROL BEATS ESCALATION

No antibiotic will treat an undrained collection.

An abscess, an obstructed and infected kidney, an empyema, an infected line, an infected prosthesis, a septic joint, gangrenous tissue — each needs a drain, a stent, a removal or a knife. Escalating from one antibiotic to a broader one while pus sits undrained is a recurring and sometimes fatal error.

If a patient is not responding, ask what needs draining before you ask what needs adding.

INTERROGATE THE PENICILLIN ALLERGY LABEL

Around nine out of ten patients labelled penicillin-allergic are not allergic to penicillin.

The label is not harmless. It leads to broader, more toxic, less effective and more expensive treatment, with **higher rates of *Clostridioides difficile* infection, resistant organisms, surgical site infection and death.**

Interrogate it in four questions: What exactly happened? How soon after the dose? How long ago? **Have you taken any penicillin since?**

A rash during a childhood viral illness is not anaphylaxis. Nausea and diarrhoea are intolerance, not allergy. Features of genuine immediate hypersensitivity are urticaria, angio-oedema, wheeze and hypotension within an hour. Severe delayed reactions — Stevens–Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms — are absolute contraindications.

Patient two probably does not need vancomycin. Where it matters, refer for formal allergy assessment; correct the record when you have the answer.

9. Dose properly, and know the important adverse effects

- Weight-based and renally adjusted dosing; **therapeutic drug monitoring for vancomycin and aminoglycosides**.

- **Interactions and toxicities worth knowing:** rifampicin as a powerful enzyme inducer, which causes contraceptive failure and lowers antiretroviral and warfarin levels; macrolides and fluoroquinolones prolonging the corrected QT interval; **fluoroquinolone tendinopathy, aortic and neuropsychiatric effects**; nitrofurantoin in renal impairment; **co-trimoxazole raising potassium and creatinine**; aminoglycoside nephrotoxicity and ototoxicity.

10. Understand what getting it wrong costs

- **For the patient:** *Clostridioides difficile* infection — as in patient three, on day twelve of meropenem with negative cultures — candidiasis, drug reactions, acute kidney injury, and a longer stay.

- **Beyond the patient:** selection of resistant organisms, which is a shared and finite resource problem. **In parts of this region, rates of extended-spectrum beta-lactamase-producing and carbapenem-resistant organisms are high, and antibiotics can be obtained without prescription** — which makes stewardship a local duty and not an abstract global one.

11. Special situations

- **Pregnancy and lactation**; renal and hepatic impairment; the frail elderly.

- **Prophylaxis, which is where courses become inappropriately long:** surgical prophylaxis is a **single dose within 60 minutes of incision and is not continued after the operation**; endocarditis prophylaxis is restricted to the highest-risk group (Case 13); lifelong prophylaxis in asplenia; single-dose chemoprophylaxis for meningococcal contacts (Case 44).
- **Outpatient parenteral antimicrobial therapy** for conditions genuinely needing prolonged intravenous treatment.

12. Write it down

- Document the indication, the plan and the intended duration; **record allergies with the actual reaction described, not just the word "allergy"**; and communicate the antimicrobial plan explicitly at discharge, including when it stops.

2. The Ward Round, Resolved

Patient	What should happen
1 — day six intravenous, well, mixed growth	Mixed flora suggests a contaminated sample rather than infection. She is well. Stop the antibiotic, or at most switch to oral with a stop date today. Document the decision.
2 — vancomycin for a childhood rash	Interrogate the label. A childhood rash is very unlikely to be true allergy. Treat with a beta-lactam if the history is reassuring, refer for allergy testing, and correct the record.
3 — day twelve meropenem, cultures negative, diarrhoea	Send stool for *Clostridioides difficile* toxin. Review the original indication, de-escalate or stop, and involve microbiology. Twelve days of a carbapenem with no organism needs justifying.
4 — azithromycin for a sore throat	No antibiotic was indicated. Use a scoring tool for suspected streptococcal pharyngitis, and where treatment is genuinely indicated, penicillin V rather than a macrolide.

3. Teaching Points and Viva Questions

- Indication, route and stop date on the chart when you start; a documented decision at 48 to 72 hours.
- Cultures before the first dose — but never delay treatment in sepsis to get them.
- Shorter courses are usually equivalent. Know the genuine exceptions.
- Drain the pus. No antibiotic treats an undrained collection.
- Nine in ten penicillin allergy labels are wrong, and the label harms the patient.
- Switch to oral as soon as the patient is absorbing and improving.
- Resistance is a local problem here, not only a global one.

Questions you should be able to answer:

- Give the five possible decisions at the 48-hour antimicrobial review.
- What four questions would you ask a patient labelled penicillin-allergic?

- A patient with an intra-abdominal collection is not improving on day four of piperacillin–tazobactam. What is your next step?
- Name four infections that genuinely require prolonged antimicrobial therapy.
- How long should surgical prophylaxis continue after an uncomplicated operation?

The Haematology Block

Microcytic, macrocytic and haemolytic anaemia, sickle cell disease and thalassaemia, the bleeding patient, the acute and chronic leukaemias, lymphoma, myeloma and the myeloproliferative neoplasms.

Cases 49–57 · 10,630 words

This block covers the haematology teaching of both internal medicine courses. The **first course** supplies cases 49 and 52 — the anaemias, the hereditary anaemias and the bleeding disorders. The **second course** supplies cases 53 and 57, which cover the malignant haematology: the acute and chronic leukaemias, lymphoma, myeloma and the myeloproliferative neoplasms.

Case	Lecture it serves
System opener: the haematological history and examination	Approach common to the whole block
Case 49 — Microcytic anaemia and the iron deficiency workup	Anaemias, part 1
Case 50 — Macrocytic and haemolytic anaemia	Anaemias, part 2
Case 51 — Sickle cell disease and thalassaemia	Hereditary anaemias; haemoglobinopathies
Case 52 — The bleeding patient	Bleeding and coagulation disorders
Case 53 — Acute leukaemia	Leukaemias
Case 54 — The chronic leukaemias	Leukaemias
Case 55 — Lymphoma	Lymphomas
Case 56 — Multiple myeloma	Multiple myeloma
Case 57 — The myeloproliferative neoplasms	Myeloproliferative disorders

The approach to the patient with anaemia is taught as a seminar in the second course; it is covered by the reticulocyte-and-mean-cell-volume framework at the start of Case 50 rather than as a separate case.

System Opener · The Haematological History and Examination

The history

Symptoms of anaemia — and why the number does not predict them

- Fatigue, exertional breathlessness, palpitations, dizziness; and in older patients, **angina, worsening claudication or decompensated heart failure** as the first presentation.
- **The rate of fall matters more than the level.** A haemoglobin of 70 g/L reached over a year may be tolerated at work; the same value reached over two days is an emergency. Always ask over what period

the symptoms developed.

Then localise the mechanism

Ask about	What it points to
Menstrual history, quantified — days of bleeding, clots larger than a coin, flooding, sanitary product changes per day, and whether it has always been this heavy	Blood loss — and menorrhagia since menarche suggests an inherited bleeding disorder, not simply heavy periods
Melaena, rectal bleeding, dyspepsia, change in bowel habit, weight loss	Gastrointestinal blood loss — the assumption until disproved in men and postmenopausal women
Pica — craving ice, clay or starch — and restless legs	Iron deficiency. Neither is volunteered; both must be asked about directly
Diet, including strict vegetarian or vegan practice, and tea taken with meals	Iron and vitamin B12 deficiency
Gastrectomy, bariatric surgery, coeliac disease, ileal resection or Crohn disease	Malabsorption of iron, B12 and folate
Jaundice, dark urine, gallstones at a young age, previously known anaemia	Haemolysis
Drenching night sweats, fever, weight loss above 10%	Lymphoma and other haematological malignancy
Long-term metformin or proton pump inhibitors; methotrexate, hydroxycarbamide, phenytoin, trimethoprim	Drug-related deficiency or marrow suppression

The bleeding history — structure it, do not just ask "do you bruise easily?"

- **Establish the pattern first**, because it localises the defect before any test is sent. Then the severity: was transfusion or admission ever needed, and does bleeding occur spontaneously or only after injury.
- **Use past haemostatic challenges as natural tests:** dental extraction, tonsillectomy, circumcision, childbirth, and previous surgery. A patient who has bled excessively after none of these is unlikely to have a severe inherited disorder.
- **Family history and pattern of inheritance**, and **consanguinity** — which substantially raises the likelihood of the rarer autosomal recessive disorders in this population.

> THE QUESTION THAT MUST NOT BE SKIPPED IN THIS POPULATION
>
> **Family history and consanguinity are core haematological history here, not optional extras.** They change the pre-test probability for haemoglobinopathies, red cell enzyme and membrane disorders, and rare recessive coagulation factor deficiencies.
>
> Ask about the couple's relationship, about affected siblings and cousins, and about **premarital screening** — which many patients will have undergone and whose result they may be able to tell you.

The examination

- **Pallor** — assess the conjunctivae, the palmar creases and the nail beds rather than the face.
- **Hands and nails:** koilonychia in iron deficiency; clubbing.

- **Mouth:** angular stomatitis and glossitis (iron, B12, folate); a **beefy red smooth tongue** in B12 deficiency; gum hypertrophy in monocytic leukaemia; **petechiae on the palate and blood blisters in the mouth**, which indicate significant thrombocytopenia.
- **Skin:** petechiae in dependent areas, purpura, ecchymoses, telangiectasia, and **leg ulcers over the malleoli** in sickle cell disease.
- **Eyes:** scleral icterus, and fundoscopy for retinal haemorrhage.
- **All lymph node groups**, with size, consistency, mobility and matting.
- **Abdomen — splenomegaly**, measured in centimetres below the costal margin. Remember it enlarges towards the right iliac fossa, has a notch, you cannot get above it, it moves with respiration and it is dull to percussion.
- **Bones:** sternal and vertebral tenderness in myeloma and leukaemia; **frontal bossing and maxillary overgrowth** from marrow expansion in untreated thalassaemia.
- **Neurological examination** — see the B12 case; and a flow murmur and signs of cardiac failure in severe anaemia.

Massive splenomegaly — crossing the midline or reaching the pelvis	Moderate splenomegaly
Chronic myeloid leukaemia	Portal hypertension
Myelofibrosis	Lymphoma and chronic lymphocytic leukaemia
Visceral leishmaniasis	Haemolytic anaemias, thalassaemia
Chronic malaria and hyper-reactive malarial splenomegaly	Infection — infective endocarditis, brucellosis, Epstein–Barr virus, typhoid
Gaucher disease	Connective tissue disease, amyloidosis, storage disorders

Case 49 · Microcytic Anaemia and the Iron Deficiency Workup

CLINICAL VIGNETTE

A **46-year-old woman** describes six months of increasing fatigue and breathlessness climbing stairs. Her periods have been heavy for several years, lasting seven days with clots and occasional flooding, and she changes protection every two hours on the worst days. She has never thought this abnormal.

On direct questioning she admits to **chewing ice constantly** and to an unpleasant crawling sensation in her legs at night. She eats no red meat and drinks tea with every meal.

On examination: pale conjunctivae, **koilonychia**, angular stomatitis, and a soft ejection systolic flow murmur. No lymphadenopathy or organomegaly.

Haemoglobin 78 g/L · mean cell volume 68 fL · mean cell haemoglobin 22 pg · red cell distribution width raised · platelets 480 × 10^9/L · ferritin 6 µg/L · transferrin saturation 5%.

THE PRINCIPLE OF THIS CASE

Iron deficiency anaemia is a symptom, not a diagnosis. The blood count tells you the iron has gone; it does not tell you where.

Correcting the haemoglobin without finding the cause is the error that allows a colonic carcinoma to present two years later as obstruction. **The investigation is not complete when the ferritin comes back low.**

1. Focused History

- **Quantify the menstrual loss** using the specific questions in the system opener. "Heavy" is not a measurement, and women commonly normalise a lifetime of excessive loss.
- **Ask whether it has been heavy since menarche** — if so, consider von Willebrand disease and other inherited bleeding disorders, which are substantially under-diagnosed in women.
- **Gastrointestinal loss:** melaena, rectal bleeding, dyspepsia, change in bowel habit, abdominal pain, weight loss, and family history of colorectal cancer.
- **Reduced intake and absorption:** diet, tea and coffee with meals (which chelate non-haem iron), coeliac disease, previous gastric or bariatric surgery, *Helicobacter pylori*, and long-term proton pump inhibitor use.
- **Increased demand and other losses:** pregnancies and lactation, regular blood donation, haematuria, epistaxis, and — where relevant — hookworm and schistosomiasis.
- **Drugs:** aspirin, other anti-inflammatory drugs and anticoagulants.

2. Investigations

Confirm the deficiency

- **Blood film:** microcytic hypochromic red cells with anisocytosis, poikilocytosis and **pencil cells**; a reactive thrombocytosis is common and is not itself a cause for concern.
- **Ferritin is the single most useful test** — a low ferritin is diagnostic of iron deficiency and needs no confirmation.

THE LIMITATION THAT CATCHES PEOPLE OUT

Ferritin is an acute phase protein. In inflammation, infection, malignancy, liver disease and chronic kidney disease it rises independently of iron stores, so **a normal or even raised ferritin does not exclude iron deficiency** in a sick patient.

In that setting use the **transferrin saturation**, which falls in deficiency, the soluble transferrin receptor, or a higher ferritin threshold — commonly below 100 µg/L rather than below 15.

Distinguish it from the other causes of microcytosis

The differential is iron deficiency, **thalassaemia trait**, anaemia of chronic disease, sideroblastic anaemia and lead poisoning. In this region the first two account for nearly all of it, and separating them matters — one requires an endoscopy and the other requires genetic counselling.

Feature	Iron deficiency	Thalassaemia trait
Ferritin	Low	Normal
Red cell count	Low or low-normal	Normal or high, despite a very low mean cell volume
Red cell distribution width	Raised	Normal
Mentzer index (mean cell volume ÷ red cell count)	Above 13	Below 13
Blood film	Pencil cells, anisocytosis	Target cells, basophilic stippling, uniform microcytes
Confirmation	Response to iron	Haemoglobin electrophoresis or high-performance liquid chromatography — raised haemoglobin A2 in beta trait

A TRAP WITH REAL CONSEQUENCES HERE

Coexisting iron deficiency lowers the haemoglobin A2 level and can mask beta thalassaemia trait.

If both are suspected, **treat the iron deficiency first and repeat the electrophoresis**. Reporting a patient as trait-negative while they are iron deficient may give a falsely reassuring result to a couple seeking genetic advice — which in this population has consequences well beyond the individual.

Alpha thalassaemia trait has a **normal** haemoglobin A2 and is a diagnosis of exclusion or of genetic testing.

Then find the cause

- **Coeliac serology in every patient** with iron deficiency.
- **Upper and lower gastrointestinal endoscopy in all men, and in all postmenopausal women.** In premenopausal women with clear menorrhagia and no gastrointestinal symptoms, endoscopy is not automatic — but it is indicated if there are symptoms, a family history, weight loss, or failure to respond to iron.
- Urinalysis for haematuria; *Helicobacter pylori* testing; and stool examination for parasites where exposure is likely.

3. Management

- **Treat the cause** — here, referral for management of menorrhagia alongside iron replacement.

HOW TO PRESCRIBE ORAL IRON

Give a single daily dose, or better, alternate-day dosing. Each dose of iron raises hepcidin for around 24 hours, which blocks absorption of the next dose — so **three times daily dosing absorbs less total iron than once daily or alternate-day dosing, and causes far more side effects.**

Take it with vitamin C or orange juice, and **separate it from tea, coffee, milk, calcium, antacids and proton pump inhibitors, and by at least four hours from levothyroxine**.

- **Expected response:** a reticulocytosis within a week, and a **haemoglobin rise of roughly 10–20 g/L every two to three weeks**. Check at two to four weeks.
- **If there is no response, there are only four explanations:** the patient is not taking it; bleeding continues faster than replacement; the diagnosis is wrong; or absorption is impaired. Work through them in that order.
- **Continue for three months after the haemoglobin normalises** to replete stores. Stopping at normalisation guarantees recurrence.
- **Intravenous iron** for intolerance, malabsorption, ongoing losses exceeding oral absorption, chronic kidney disease, inflammatory bowel disease, later pregnancy, or where correction is needed quickly.
- **Transfusion only for haemodynamic compromise or severe symptomatic anaemia** — a restrictive threshold applies. A haemoglobin of 78 in a stable, ambulant patient is treated with iron, not with blood.

4. Teaching Points and Viva Questions

- Low ferritin is the beginning of the investigation, not the end of it.
- Ferritin rises with inflammation — use transferrin saturation in a sick patient.
- A normal or high red cell count with a very low mean cell volume is thalassaemia trait until proved otherwise.
- Correct the iron before interpreting the haemoglobin A2.
- Alternate-day iron absorbs better and is tolerated better than three times daily.
- Ask every woman about pica, restless legs, and whether her periods have always been heavy.

Questions you should be able to answer:

- Her ferritin is 90 but she is clearly microcytic and has rheumatoid arthritis. How do you proceed?
- Distinguish iron deficiency from beta thalassaemia trait on a blood count alone.
- Which patients with iron deficiency need endoscopy, and which do not?
- Her haemoglobin has not moved after six weeks of ferrous sulfate. Give four explanations in order of likelihood.
- Why might her haemoglobin A2 be misleading, and what would you do about it?

Case 50 · Macrocytic and Haemolytic Anaemia

CLINICAL VIGNETTE

A **58-year-old man** presents with four months of fatigue and, more troubling to him, **tingling and numbness in both feet** that has crept up to the ankles. He is unsteady walking to the bathroom at night but manages in daylight. His wife has noticed he is forgetful and irritable.

He has vitiligo and treated hypothyroidism, and has taken a proton pump inhibitor for six years.

On examination: pale with mild scleral icterus. The tongue is **smooth and beefy red**. Vibration sense and joint position sense are lost to the ankles. **Ankle jerks are absent but the plantar responses are extensor.** Romberg test is positive.

Haemoglobin 88 g/L · mean cell volume 118 fL · white cells 3.4 · platelets 118 · reticulocytes low · bilirubin mildly raised · lactate dehydrogenase high. Film: **oval macrocytes and hypersegmented neutrophils.**

1. Classify Before You Investigate

Two numbers on the blood count organise the whole of anaemia. Ask them in this order.

- **First, the reticulocyte count.** A **high** count means the marrow is working and cells are being lost — haemolysis or bleeding. A **low or normal** count in the face of anaemia means the marrow is not responding — a production problem.
- **Second, the mean cell volume**, which subdivides the production problems.

Macrocytic — megaloblastic	Macrocytic — non-megaloblastic
Vitamin B12 deficiency	Alcohol
Folate deficiency	Liver disease
Drugs interfering with DNA synthesis — methotrexate, hydroxycarbamide, azathioprine, trimethoprim, phenytoin, zidovudine	Hypothyroidism
	Myelodysplastic syndrome — consider in any older patient with unexplained macrocytosis and cytopenias
Film: oval macrocytes and hypersegmented neutrophils	Reticulocytosis (young cells are large), pregnancy

2. Vitamin B12 Deficiency

Causes

- **Pernicious anaemia** — autoimmune, associated with vitiligo, thyroid disease and type 1 diabetes, as in this patient. **Anti-intrinsic factor antibody is specific but insensitive; anti-parietal cell antibody is sensitive but not specific.**
- Dietary — strict vegan diet without supplementation.
- Gastric causes — gastrectomy, bariatric surgery, atrophic gastritis; ileal causes — Crohn disease, ileal resection, bacterial overgrowth, fish tapeworm.
- **Drugs — long-term metformin and proton pump inhibitors**, both extremely widely prescribed and both easily overlooked.

THE POINT ON WHICH THIS DIAGNOSIS IS MOST OFTEN MISSED

Subacute combined degeneration of the cord affects the dorsal columns and the corticospinal tracts, producing the combination in this patient: **loss of vibration and joint position sense with absent ankle jerks but extensor plantars**. There may also be peripheral neuropathy, optic atrophy, cognitive impairment and psychiatric disturbance.

Neurological disease can occur with a completely normal haemoglobin and a normal mean cell volume. If you wait for macrocytic anaemia before checking a B12 level in a patient with unexplained neuropathy or cognitive change, you will miss it — and neurological damage present for more than six months may not fully reverse.

Investigation

- Serum B12 and folate, with **red cell folate** where the serum level is borderline.
- **Methylmalonic acid and homocysteine** where the B12 level is equivocal: **both are raised in B12 deficiency, but only homocysteine is raised in folate deficiency** — which is how the two are separated biochemically.
- Anti-intrinsic factor and anti-parietal cell antibodies; thyroid function; coeliac serology.
- Mild haemolysis is expected from ineffective erythropoiesis — hence the raised bilirubin and lactate dehydrogenase here. This is not a second diagnosis.

Treatment

- **Hydroxocobalamin by intramuscular injection** — a loading course followed by maintenance, given **more frequently and for longer where there is neurological involvement**. Lifelong in pernicious anaemia. High-dose oral replacement is adequate in purely dietary deficiency.

TWO ERRORS TO AVOID IN TREATMENT

Never give folate alone to a patient who may be B12 deficient. Folate will correct the anaemia and the macrocytosis while the neurological disease continues to progress, and it may precipitate subacute combined degeneration.

Check both, and if in doubt replace B12 first or give both together.

A second practical point: during the brisk response to treatment, **potassium is consumed by rapid erythropoiesis. Monitor for hypokalaemia** in the first week, particularly in severe deficiency.

- Pernicious anaemia carries an increased risk of gastric carcinoma, and clusters with other autoimmune disease — screen accordingly.

3. Haemolytic Anaemia

Recognise it

- **Anaemia with a raised reticulocyte count, raised unconjugated bilirubin, raised lactate dehydrogenase and a low haptoglobin.** Jaundice without pale stools or dark stools; splenomegaly; and pigment gallstones at a young age.
- **Intravascular haemolysis** — haemoglobinuria, haemosiderinuria, a very low haptoglobin, schistocytes on the film. **Extravascular haemolysis** — splenomegaly, spherocytes.

Inherited	Acquired
Membrane — hereditary spherocytosis, elliptocytosis	Immune — warm autoimmune (IgG, spherocytes), cold agglutinin disease (IgM, following *Mycoplasma* or Epstein–Barr virus, or with lymphoma)
Enzyme — glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency	Alloimmune — transfusion reaction, haemolytic disease of the newborn
Haemoglobin — sickle cell disease, thalassaemia	Microangiopathic — thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, disseminated intravascular coagulation, mechanical heart valve
	Other — malaria, *Clostridium*, toxins, paroxysmal nocturnal haemoglobinuria, hypersplenism

The direct antiglobulin test divides the acquired causes in two. A positive test means immune haemolysis; a negative test sends you towards mechanical, infective, enzymatic and membrane causes. It is the pivotal investigation, and it is cheap.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

X-linked, and common in this population. Haemolysis is triggered by **oxidative stress**: infection — the commonest trigger of all — **fava beans**, and drugs including primaquine, sulphonamides, nitrofurantoin, dapsone, some quinolones, methylene blue and rasburicase. Henna applied to neonates has caused severe haemolysis.

The film during a crisis shows **bite cells and Heinz bodies**.

The enzyme assay may be falsely normal during an acute haemolytic episode, because the surviving and newly produced young red cells have higher enzyme activity. **Repeat the assay about three months after the episode** before concluding the patient is not deficient.

THE ONE THAT CANNOT WAIT UNTIL MORNING

Schistocytes on the film with thrombocytopenia is thrombotic thrombocytopenic purpura until proved otherwise — and it is a haematological emergency.

Look for the pentad, but do not wait for it: microangiopathic haemolysis, thrombocytopenia, fever, neurological signs and renal impairment. **Send ADAMTS13 activity, and arrange urgent plasma exchange** — untreated mortality is very high, and treated it falls dramatically.

Do not transfuse platelets, which may worsen thrombosis.

Principles of treatment

- **Warm autoimmune haemolysis:** corticosteroids first line, then rituximab, then splenectomy. Look for an underlying cause — lymphoproliferative disease, systemic lupus erythematosus, drugs.
- **Cold agglutinin disease:** keep the patient warm, treat the underlying cause; steroids are largely ineffective; rituximab-based therapy for significant disease.
- **Folic acid supplementation in all chronic haemolysis**, because demand is high.
- **Before splenectomy:** vaccinate against encapsulated organisms and arrange lifelong antibiotic prophylaxis and a patient-held card.

4. Teaching Points and Viva Questions

- The reticulocyte count is the first branch of the whole anaemia algorithm.

- B12 neurological disease occurs without anaemia and without macrocytosis.
- Never folate alone; check the potassium during the response.
- Methylmalonic acid separates B12 from folate deficiency.
- The direct antiglobulin test splits acquired haemolysis in two.
- A normal glucose-6-phosphate dehydrogenase level during a crisis proves nothing — repeat it in three months.
- Schistocytes plus a low platelet count means picking up the telephone tonight.

Questions you should be able to answer:

- Explain his absent ankle jerks with extensor plantars in anatomical terms.
- Why are his bilirubin and lactate dehydrogenase raised, and does that mean he has two diagnoses?
- A colleague prescribes folic acid while awaiting the B12 result. What do you say?
- A young man haemolyses after antibiotics for a urinary infection; his enzyme level is normal. What next?
- How does the direct antiglobulin test change your differential?

Case 51 · Sickle Cell Disease and Thalassaemia

CLINICAL VIGNETTE

A **19-year-old man with sickle cell disease** presents with twelve hours of severe pain in both thighs and the lower back, which he says is worse than his usual crises and unrelieved by the analgesia he takes at home. For two days he has had a cough and has felt feverish. He returned yesterday from a trip to a higher-altitude area.

His parents are first cousins. He takes hydroxycarbamide but admits he often forgets it, and penicillin twice daily.

On examination: in obvious distress. Temperature 38.4 °C, heart rate 118/min, respiratory rate 26/min, **oxygen saturation 92% on air**. Crackles at the right base. Diffuse tenderness of both thighs. The spleen is not palpable.

Haemoglobin 72 g/L (his steady state is 84) · reticulocytes 12% · white cells 18 × 10^9/L · chest radiograph: new right basal infiltrate.

READ THE VIGNETTE AGAIN BEFORE CONTINUING

This is not an uncomplicated painful crisis. **A new pulmonary infiltrate with fever and hypoxia in a patient with sickle cell disease is the acute chest syndrome**, which is the leading cause of death in adults with the condition.

It frequently develops **after** admission for a painful crisis, driven by hypoventilation from pain and opioids. That is why the analgesia and the incentive spirometry below are not comfort measures — they are prevention.

1. Focused History

- **Compare with his own usual crisis** — site, severity, and what normally relieves it. A crisis that feels different, or is in an unusual site, deserves more scepticism.
- **What analgesia has already been taken, and when.** Patients arrive having already taken substantial doses at home.
- **Precipitants:** infection, dehydration, cold exposure, hypoxia, **altitude**, physical exertion, stress, alcohol, and menstruation.
- **Crisis frequency, previous admissions, previous acute chest syndrome or stroke, priapism, transfusion history and red cell alloantibodies**, hydroxycarbamide adherence, penicillin prophylaxis and vaccination status.

Red flag	Complication to exclude
Chest pain, breathlessness, hypoxia, new infiltrate	Acute chest syndrome
Any neurological symptom or sign	Stroke — requires urgent imaging and exchange transfusion
Abdominal pain with a rapidly enlarging spleen and falling haemoglobin	Splenic sequestration — mainly in children and in haemoglobin SC disease
Sudden pallor with a low reticulocyte count	Aplastic crisis, characteristically from parvovirus B19
Fever	Infection — these patients are functionally asplenic and at risk of overwhelming encapsulated organism sepsis
Sustained erection beyond 4 hours	Priapism — a urological emergency

2. Physical Examination

- Formal pain score; full vital signs **including oxygen saturation**; respiratory examination.

- **A palpable spleen in an adult with haemoglobin SS disease is abnormal** — most have autosplenectomised by adolescence. Its presence suggests sequestration, or a different genotype such as haemoglobin SC or sickle-beta-thalassaemia.
- Full neurological examination; examination for priapism; joints for avascular necrosis of the hip; **leg ulcers over the malleoli**; scleral icterus; and growth and skeletal changes.

3. Investigations

- **Complete blood count with reticulocyte count, interpreted against the patient's own steady-state values.** This is essential and is the reason every patient should have their baseline recorded — a haemoglobin of 72 means one thing if the baseline is 84 and another if it is 65. **A low reticulocyte count in a falling haemoglobin means aplastic crisis.**
- Urea and electrolytes, liver function, lactate dehydrogenase, C-reactive protein, **blood cultures**, group and save with **extended red cell phenotype** to reduce alloimmunisation.
- **Arterial or capillary blood gas** where saturations are low; chest radiograph; urinalysis and culture.
- Parvovirus B19 serology where the reticulocyte count is low. Transcranial Doppler is used in children for stroke risk stratification.

4. Management of the Acute Crisis

THE FIRST THING YOU DO, AND THE THING MOST OFTEN DONE BADLY

Give effective analgesia within 30 minutes of arrival, and reassess every 30 minutes until controlled.

Under-treatment of sickle cell pain is a well-documented and repeatedly demonstrated failure of care, and it is frequently driven by unfounded assumptions that patients are exaggerating or drug-seeking. **A patient who knows exactly which opioid and what dose works for them is describing years of experience with their own disease, not manipulating you.**

Use strong opioids for severe crisis, ideally patient-controlled, with regular paracetamol and an anti-inflammatory drug where renal function permits — plus laxatives and antiemetics prescribed from the outset.

- **Oxygen** to keep saturations above 95%. **Hydration** — oral where possible, intravenous if not, avoiding both dehydration and overload.
- **Keep the patient warm.** Treat infection with antibiotics; fever in sickle cell disease is treated as sepsis until proved otherwise.
- **Incentive spirometry every two hours while awake** — a simple, cheap intervention that measurably reduces the incidence of acute chest syndrome in patients admitted with pain. Prescribe it as you would a drug.
- **Thromboprophylaxis**, and monitoring for the complications listed above.

ACUTE CHEST SYNDROME

Definition: a new pulmonary infiltrate with fever, chest pain, cough, wheeze or hypoxia.

Treatment: oxygen; **antibiotics covering atypical organisms**; adequate analgesia — enough to permit deep breathing, but avoiding over-sedation; careful fluid balance; incentive spirometry; bronchodilators if there is wheeze.

Urgent simple or exchange transfusion where there is hypoxia or clinical deterioration. **Involve haematology and critical care early** — deterioration can be rapid.

5. Chronic Management

- **Hydroxycarbamide** — raises fetal haemoglobin and reduces crises, acute chest syndrome, transfusion requirement and mortality. Monitor the blood count. **Explore adherence at every visit**, as in this patient.
- **Folic acid**; **lifelong penicillin prophylaxis and full vaccination against encapsulated organisms**, because of functional asplenia.
- Transcranial Doppler screening in children; annual review of renal function, retinopathy, proteinuria and pulmonary hypertension.
- **Transfusion programmes** where indicated, with **iron chelation** to manage the resulting overload.
- **Curative options:** allogeneic haematopoietic stem cell transplantation, and gene therapy where available. Discuss these with families, particularly where a matched sibling exists.
- Pre-pregnancy counselling; genetic counselling for the patient and the extended family.

6. Thalassaemia

	Detail
Beta thalassaemia major	Presents at 6–12 months as fetal haemoglobin declines: severe anaemia, failure to thrive, hepatosplenomegaly, and skeletal changes from marrow expansion — frontal bossing, maxillary overgrowth, and the "hair-on-end" appearance of the skull on radiography.
Management	Regular transfusion to a pre-transfusion haemoglobin around 95–105 g/L, which suppresses ineffective erythropoiesis and prevents the skeletal changes; iron chelation; splenectomy in selected patients; stem cell transplantation is curative.
Monitoring iron	Ferritin, and T2* magnetic resonance imaging of the heart and liver, which measures tissue iron directly. Cardiac iron overload, not anaemia, is the usual cause of death in a transfused patient — which makes chelation adherence the central issue of care.
Beta thalassaemia trait	Microcytosis with a normal or high red cell count, normal ferritin and raised haemoglobin A2. Clinically harmless — and genetically important, which is the whole point of identifying it.
Alpha thalassaemia	Ranges from silent carrier through haemoglobin H disease to haemoglobin Bart hydrops fetalis. Haemoglobin A2 is normal, so diagnosis requires genetic testing.

WHY THIS BLOCK MATTERS MORE HERE THAN IN THE TEXTBOOKS

Both conditions in this case are autosomal recessive, and **consanguineous marriage substantially increases the birth prevalence of both**.

Premarital screening for haemoglobinopathies is a national programme here, and your students will spend a good deal of their careers explaining its results. Learn to counsel a carrier couple clearly and without alarm: explain the one-in-four risk per pregnancy, the difference between carrier and disease, the reproductive options available, and the fact that carrier status itself is not an illness.

7. Teaching Points and Viva Questions

- Know the patient's steady state, or you cannot interpret their blood count.
- Analgesia within thirty minutes, reassessed every thirty. Believe the patient.

- Fever in sickle cell disease is sepsis until proved otherwise — they have no functioning spleen.
- A falling haemoglobin with a low reticulocyte count is parvovirus, not a crisis.
- A palpable spleen in an adult with haemoglobin SS disease means something is wrong.
- Incentive spirometry prevents acute chest syndrome. Prescribe it.
- Transfused thalassaemia patients die of iron, not of anaemia.

Questions you should be able to answer:

- What has this patient developed, and how did you recognise it?
- His reticulocyte count is 0.4% and haemoglobin 52. What is the diagnosis?
- Why does he take penicillin every day at the age of 19?
- Explain what hydroxycarbamide does and why his adherence matters.
- A carrier couple ask what the risk is for their children. Explain it to them.

Case 52 · The Bleeding Patient

CLINICAL VIGNETTE

A **24-year-old woman** presents with three weeks of easy bruising on her legs, bleeding from the gums when she brushes her teeth, two prolonged nosebleeds, and a period that has been far heavier than usual. She had a viral illness a month ago and is otherwise well. She takes no medication.

On examination: widespread **petechiae** over the shins and forearms, scattered ecchymoses, and **blood blisters on the buccal mucosa**. No lymphadenopathy, no hepatosplenomegaly, no bone tenderness. Fundoscopy is normal.

Haemoglobin 118 g/L · white cells normal with a normal differential · platelets 8 × 10^9/L · prothrombin time and activated partial thromboplastin time normal. Film: **reduced platelet numbers with some large forms; no blasts, no schistocytes, no clumping.**

1. The Pattern of Bleeding Localises the Defect

Mucocutaneous pattern — platelets, vessel wall, von Willebrand factor	**Deep tissue pattern — coagulation factors**
Petechiae and purpura	Haemarthrosis
Epistaxis, gum bleeding	Muscle and retroperitoneal haematoma
Menorrhagia	Delayed bleeding after surgery or dental extraction
Immediate bleeding after injury or surgery	Rebleeding after apparent initial haemostasis
Think: immune thrombocytopenia, drugs, von Willebrand disease, platelet function disorders	Think: haemophilia A and B, other factor deficiencies, anticoagulation, liver disease

This patient's pattern is unambiguously mucocutaneous, which directs you to the platelet count before any coagulation test — and the platelet count is 8.

2. Focused History

- **Severity:** spontaneous or provoked; whether transfusion or admission has ever been needed; and any **headache, visual disturbance or neurological symptom**, which raises intracranial haemorrhage.
- **Past haemostatic challenges as natural tests** — dental extraction, tonsillectomy, circumcision, childbirth, surgery — and whether bleeding at menarche was excessive. A normal record through all of these, followed by three weeks of new symptoms, points strongly to an **acquired** disorder.
- **Family history and consanguinity**, as in the system opener.
- **Drugs:** antiplatelets, anticoagulants, anti-inflammatory drugs, quinine, heparin, and herbal preparations.
- **Systemic causes:** liver disease, renal failure with uraemic platelet dysfunction, malabsorption and vitamin K deficiency, malignancy, autoimmune disease, human immunodeficiency virus, recent infection or vaccination, and pregnancy.
- **Constitutional symptoms** — fever, weight loss, night sweats, bone pain — which point away from immune thrombocytopenia and towards marrow disease.

3. Physical Examination

- Distribution of petechiae — dependent areas and pressure sites; purpura and ecchymoses.
- **"Wet purpura" — blood blisters in the mouth — marks a higher risk of serious bleeding** and should raise the urgency of treatment.
- **Fundoscopy** for retinal haemorrhage.
- **Lymphadenopathy, hepatosplenomegaly and bone tenderness — the presence of any of these argues against immune thrombocytopenia** and towards leukaemia, lymphoma or another marrow disorder. Their absence here is a meaningful positive finding.
- Signs of chronic liver disease; joints for haemarthrosis; a full neurological examination.

4. Investigations

THE FIRST INVESTIGATION

Look at the blood film in every patient with an abnormal platelet count — before you treat anything.

It excludes **pseudothrombocytopenia** from platelet clumping in the sample tube, which is not a disease and needs a repeat sample in a different anticoagulant. It also identifies **blasts**, **schistocytes** and dysplastic changes, each of which turns this into an entirely different problem with an entirely different urgency.

Interpreting the coagulation screen

Result	Consider
Prolonged prothrombin time alone	Factor VII deficiency, early warfarin effect, early liver disease, vitamin K deficiency
Prolonged activated partial thromboplastin time alone	Haemophilia A and B, factor XI or XII deficiency, von Willebrand disease, heparin, or a lupus anticoagulant — which paradoxically causes thrombosis rather than bleeding
Both prolonged	Disseminated intravascular coagulation, severe liver disease, vitamin K deficiency, warfarin, massive transfusion and dilution
Both normal with clear bleeding	Platelet count or function disorder, von Willebrand disease, factor XIII deficiency, or a vascular cause

The mixing study is the next step in any unexplained prolongation: mix the patient's plasma with normal plasma. **Correction indicates a factor deficiency; failure to correct indicates an inhibitor.**

- **Immune thrombocytopenia is a diagnosis of exclusion.** Send human immunodeficiency virus and hepatitis C serology, *Helicobacter pylori* testing, antinuclear antibody, immunoglobulins, thyroid function and a pregnancy test.
- **Bone marrow examination is not routinely required** in a typical young patient. It is indicated where there are atypical features: older age, systemic symptoms, other cytopenias, an abnormal film, or failure to respond to first-line treatment.
- **Where von Willebrand disease is suspected** — mucocutaneous bleeding with a normal platelet count, especially with lifelong menorrhagia — send von Willebrand factor antigen, von Willebrand factor activity and factor VIII level.

5. Management of Immune Thrombocytopenia

THE GOVERNING PRINCIPLE

Treat the bleeding, not the number. Many patients with counts above 30 × 10^9/L and no bleeding need observation rather than corticosteroids, and the side effects of prolonged steroid therapy cause more harm than a stable low platelet count. This patient, however, has a count of 8 with **wet purpura and active mucosal bleeding**, and does require treatment.

- **First line:** corticosteroids — prednisolone, or pulsed dexamethasone. Add **intravenous immunoglobulin** where a rapid rise is needed: active significant bleeding, before surgery, or in pregnancy.
- **Life-threatening bleeding:** intravenous immunoglobulin with corticosteroids, **platelet transfusion** (which is otherwise of little value in immune destruction but is appropriate here), and **tranexamic acid** — avoided in haematuria because of the risk of clot retention.
- **Second line:** thrombopoietin receptor agonists such as eltrombopag or romiplostim, rituximab, and splenectomy — **with vaccination beforehand**.
- **Practical advice:** avoid anti-inflammatory drugs and antiplatelet agents; tranexamic acid or hormonal treatment for menorrhagia; avoid contact sport; and **seek immediate assessment after any head injury**, however trivial.

6. The Other Bleeding Disorders in Brief

Disorder	Key features
Von Willebrand disease	The commonest inherited bleeding disorder, autosomal, affecting both sexes. Mucocutaneous bleeding and lifelong menorrhagia. Activated partial thromboplastin time may be normal. Treat with desmopressin in type 1, von Willebrand factor-containing concentrate in others, plus tranexamic acid.
Haemophilia A and B	X-linked, deep bleeding into joints and muscles. Prolonged activated partial thromboplastin time with a normal prothrombin time; confirm with factor VIII or IX assay. Treat with factor concentrate or emicizumab; desmopressin in mild haemophilia A. Avoid intramuscular injections and anti-inflammatory drugs. Watch for inhibitor development.
Disseminated intravascular coagulation	Always secondary — to sepsis, malignancy, obstetric catastrophe or trauma. Both clotting times prolonged, low fibrinogen, high D-dimer, falling platelets, schistocytes. Treat the underlying cause; give blood products guided by bleeding rather than by numbers.
Vitamin K deficiency and liver disease	Both prolong the prothrombin time. Vitamin K deficiency corrects with vitamin K; liver disease does not fully correct, because synthetic function is lost.
Anticoagulant-related bleeding	Know the reversal agent for each: vitamin K and prothrombin complex concentrate for warfarin, protamine for heparin, and the specific agents for direct oral anticoagulants.

7. Teaching Points and Viva Questions

- The pattern of bleeding tells you where the defect is before any test does.
- Always look at the film. Pseudothrombocytopenia is not a disease, and blasts change everything.
- Lymphadenopathy or splenomegaly argues against immune thrombocytopenia.
- Treat bleeding, not the platelet count.

- Wet purpura and retinal haemorrhage mark the patient who needs treating tonight.
- Ask every woman with heavy periods whether they have been heavy since menarche — von Willebrand disease is badly under-diagnosed in women.

Questions you should be able to answer:

- What does her pattern of bleeding tell you before any test is sent?
- Why does the absence of splenomegaly matter?
- The laboratory reports a platelet count of 8 but she has no bruising at all. What must you check?
- The activated partial thromboplastin time is prolonged and does not correct on mixing. What does that mean?
- She now has a severe headache. What are your immediate actions?

Case 53 · Acute Leukaemia

CLINICAL VIGNETTE

A **24-year-old man** describes three weeks of increasing fatigue and breathlessness climbing stairs. He bruises without injury, his gums bleed when he brushes his teeth, and he has had a fever and sore throat for a week that has not responded to two courses of antibiotics.

On examination: pale, with widespread bruising and petechiae over both legs. **The gums are hypertrophied and bleeding.** Temperature 38.7 °C. There is small-volume cervical lymphadenopathy, the spleen is palpable 3 cm below the costal margin, and the sternum is tender.

Haemoglobin 68 g/L · white cells 84 × 10^9/L with 70% blasts · platelets 14 × 10^9/L · INR 1.8 · fibrinogen 0.9 g/L · D-dimer markedly raised. Film: large blasts, some containing **Auer rods**.

READ THE PRESENTATION AS MARROW FAILURE

Everything in this presentation follows from one thing — **the marrow has been replaced**, so all three lineages fail at once: **Anaemia** → fatigue and breathlessness · **neutropenia** → fever and infection that does not respond to antibiotics · **thrombocytopenia** → bruising and mucosal bleeding.

Add **infiltration** — gum hypertrophy, bone tenderness, hepatosplenomegaly, lymphadenopathy — and the clinical picture is complete before any specialist test is sent.

1. Focused History

- **The three failures**, as above, with the duration of each. Weeks rather than months distinguishes acute from chronic disease.
- **Infiltration:** bone and joint pain (common in children), **gum swelling** — characteristic of monocytic subtypes — skin nodules, headache or cranial nerve palsy suggesting central nervous system involvement, **testicular swelling**, and a mediastinal mass with superior vena caval obstruction in T-lineage disease.
- **Predisposing factors:** previous chemotherapy or radiotherapy, benzene and solvent exposure, **preceding myelodysplasia or a myeloproliferative neoplasm**, Down syndrome, inherited marrow failure syndromes, and family history.
- **Practical history taken on day one, not later:** fertility and whether children are wanted; siblings, for tissue typing; and comorbidity that bears on intensive treatment.

2. Physical Examination

- Pallor, purpura and petechiae, **retinal haemorrhage on fundoscopy**, gum hypertrophy and bleeding, mouth ulceration and candidiasis.
- All lymph node groups; liver and spleen; **sternal and vertebral tenderness**; skin infiltration; testes; a full neurological examination.
- **A deliberate search for infection in a neutropenic patient**, including the mouth, perineum, skin folds, cannula sites and between the toes. **Do not perform a digital rectal examination** in profound neutropenia — it risks bacteraemia and a perianal abscess.

3. Investigations

- **Complete blood count and blood film** — the film is what makes the initial diagnosis at the bedside, and it should be looked at rather than merely reported. **Auer rods indicate myeloid lineage.**
- **Coagulation screen with fibrinogen and D-dimer** — this patient has disseminated intravascular coagulation, which in the context of acute leukaemia has a specific meaning (see below).
- **Tumour lysis panel:** potassium, phosphate, calcium, urate, lactate dehydrogenase, creatinine.
- Liver function, group and save, **blood cultures**, chest radiograph, and virology — hepatitis B and C, human immunodeficiency virus, cytomegalovirus — **before** treatment starts.
- **Bone marrow aspirate and trephine with immunophenotyping, cytogenetics and molecular studies.** This is what distinguishes myeloid from lymphoblastic disease, assigns the risk group, and determines the treatment — the morphology alone is no longer sufficient.
- **Lumbar puncture** for central nervous system involvement in lymphoblastic leukaemia; **echocardiography** before anthracyclines; **human leucocyte antigen typing of the patient and siblings**; and dental assessment.

ACUTE PROMYELOCYTIC LEUKAEMIA — RECOGNISE IT BEFORE THE GENETICS

Suspect it when acute leukaemia presents with bleeding out of proportion to the platelet count, with a low fibrinogen and a prolonged prothrombin time. It is defined by t(15;17) and the *PML-RARA* fusion.

It matters because it is the most curable acute leukaemia and because untreated it kills early from haemorrhage — often intracranial, often in the first 48 hours, sometimes before the cytogenetics have returned.

Therefore: start all-trans retinoic acid on clinical suspicion, before genetic confirmation. Support aggressively with platelets and fibrinogen or cryoprecipitate, aiming considerably higher than usual thresholds. Be alert for differentiation syndrome — fever, hypoxia, pulmonary infiltrates, fluid retention — which is treated with dexamethasone.

4. The Four Emergencies

Emergency	Recognition and action
Neutropenic sepsis	Fever of 38 °C or above in a neutropenic patient. Broad-spectrum antibiotics within one hour — before imaging, before cultures return, before a source is found. Do not wait for a chest radiograph. Take cultures on the way.
Tumour lysis syndrome	Hyperkalaemia, hyperphosphataemia, hyperuricaemia, hypocalcaemia and acute kidney injury, from rapid cell turnover. Prevent it: vigorous intravenous hydration plus allopurinol, or rasburicase in high-risk disease. Rasburicase is contraindicated in glucose-6-phosphate dehydrogenase deficiency — which must be checked here before it is given.
Hyperleucocytosis and leucostasis	A white count above about 100×10^9/L with breathlessness, confusion, visual change or priapism. Urgent cytoreduction and consideration of leucapheresis. Avoid red cell transfusion before cytoreduction — it raises viscosity and can precipitate leucostasis.
Coagulopathy of promyelocytic leukaemia	As above — all-trans retinoic acid on suspicion, with aggressive blood product support.

5. Management

- **Supportive care is half the treatment:** red cell and platelet transfusion to protocol thresholds, using irradiated or leucodepleted products where indicated; antibacterial, antifungal and antiviral prophylaxis; mouth care; antiemetics; nutrition; and a central venous catheter with strict line care.
- **Definitive treatment:** intensive induction chemotherapy, then risk-adapted consolidation, with **allogeneic stem cell transplantation** for higher-risk disease.
- **Targeted therapy has transformed several subtypes:** all-trans retinoic acid with arsenic trioxide in promyelocytic leukaemia, now curing the great majority; FLT3 and IDH inhibitors in myeloid disease; a tyrosine kinase inhibitor added in Philadelphia-chromosome-positive lymphoblastic leukaemia; and blinatumomab and chimeric antigen receptor T-cell therapy in relapsed lymphoblastic disease.
- **Central nervous system prophylaxis** in lymphoblastic leukaemia, with intrathecal therapy.
- **Fertility preservation must be discussed and arranged before the first dose of chemotherapy** — sperm banking, or oocyte or ovarian tissue cryopreservation. Once treatment starts the opportunity has usually gone, and this is a 24-year-old.
- Long-term follow-up for relapse, second malignancy, cardiac late effects, endocrine dysfunction and fertility.

6. Teaching Points and Viva Questions

- Fever in a neutropenic patient means antibiotics within the hour, not a work-up.
- Look at the film yourself. Auer rods and blasts change the day's plan.
- Bleeding out of proportion to the platelet count with a low fibrinogen is promyelocytic leukaemia — start all-trans retinoic acid on suspicion.
- Do not transfuse red cells into hyperleucocytosis before cytoreduction.
- Check glucose-6-phosphate dehydrogenase status before rasburicase.
- No rectal examination in profound neutropenia.
- Talk about fertility on day one.

Questions you should be able to answer:

- Explain every abnormality in this blood count in terms of one underlying process.
- Why does his coagulation screen worry you more than his platelet count?
- He spikes a temperature of 38.5 °C at 3 a.m. What do you do, and by when?
- His potassium is 6.1 and creatinine 180 twelve hours after starting treatment. What has happened?
- What must be arranged before the first cycle of chemotherapy?

Case 54 · The Chronic Leukaemias

CLINICAL VIGNETTE

A **46-year-old man** is found on an insurance medical to have a **white cell count of 168 × 10^9/L**. On questioning he admits to some fatigue, feeling full after small meals, drenching sweats at night and 5 kg of weight loss over three months.

On examination: the **spleen is palpable 12 cm below the left costal margin**, firm and smooth. He is mildly pale. There is no lymphadenopathy.

Film: granulocytes at every stage of maturation, with **basophilia** and eosinophilia. Platelets 480. **Molecular testing: *BCR-ABL1* positive; cytogenetics t(9;22).**

1. Chronic Myeloid Leukaemia

- **Massive splenomegaly with a very high white count showing the whole spectrum of granulocyte maturation, plus basophilia, is chronic myeloid leukaemia.** Roughly half of patients are found incidentally on a routine blood count.
- **Three phases:** chronic, accelerated, and **blast crisis** — which behaves like an acute leukaemia and carries a poor prognosis. The purpose of treatment is to keep the patient in chronic phase indefinitely.

History and examination

- Hypermetabolic symptoms — sweats, weight loss, fatigue; **early satiety and left upper quadrant discomfort** from the spleen; gout; priapism; bleeding or bruising; and often nothing at all.
- Examination: splenomegaly, measured and recorded in centimetres so that response can be followed; sternal tenderness; pallor.

Investigations

- Complete blood count and film; **the diagnosis is made by demonstrating *BCR-ABL1* by polymerase chain reaction and t(9;22) on cytogenetics**; bone marrow for phase assessment; urate and lactate dehydrogenase.
- **Before a tyrosine kinase inhibitor:** electrocardiogram for the corrected QT interval, cardiovascular risk assessment, liver function, and hepatitis B status.

THE DRUG THAT REWROTE THE PROGNOSIS

Chronic myeloid leukaemia has been changed from a uniformly fatal disease into a chronic condition with near-normal life expectancy by tyrosine kinase inhibition. Imatinib and its successors are taken orally, usually indefinitely, and some patients in deep sustained remission can attempt treatment-free remission under supervision.

Response is monitored by quantifying the *BCR-ABL1* transcript against defined molecular milestones at 3, 6 and 12 months. Failure to reach a milestone triggers reassessment.

And the commonest reason for failure is not resistance — it is adherence. Patients feel well, the tablets have side effects, and the disease is invisible. Ask about missed doses at every visit, without accusation, before sending a mutation screen.

- Hydroxycarbamide and, rarely, leucapheresis for initial cytoreduction in hyperleucocytosis; allopurinol; hydration.
- Kinase domain mutation testing for genuine resistance, with a switch of agent. **Allogeneic transplantation is now reserved for tyrosine kinase inhibitor failure and for blast crisis.**

- Side effects to counsel on: fluid retention and periorbital oedema, cytopenias, rash, muscle cramps, and agent-specific vascular, pleural and pulmonary effects.

2. Chronic Lymphocytic Leukaemia

A CONTRASTING PRESENTATION

A **71-year-old woman** has a **lymphocyte count of 42 × 10^9/L** found on a blood count taken before a hernia repair. She feels entirely well. There are small mobile nodes in both axillae. Film: mature small lymphocytes with **smudge cells**. Immunophenotype: **CD5, CD19 and CD23 co-expression with weak surface immunoglobulin**.

- **The diagnosis is made on peripheral blood flow cytometry.** The characteristic immunophenotype is diagnostic and **a bone marrow examination is usually unnecessary** — a point worth knowing, because patients are often braced for one.
- **Clinical features:** frequently asymptomatic; symmetrical rubbery lymphadenopathy; splenomegaly; B symptoms; **recurrent infection from hypogammaglobulinaemia**, which is the commonest cause of death; **autoimmune haemolytic anaemia and immune thrombocytopenia**; and **Richter transformation** — rapid nodal enlargement with fever and a rising lactate dehydrogenase, which requires urgent biopsy.
- **Prognostic testing that changes treatment:** deletion 17p and *TP53* mutation, and immunoglobulin heavy chain variable region mutational status. Stage with the Binet or Rai system.

WATCH AND WAIT IS A TREATMENT DECISION, NOT AN ABSENCE OF ONE

In early asymptomatic disease, treatment does not prolong life, and the correct management is observation.

This is genuinely difficult to convey. A patient told they have leukaemia and that nothing will be done hears neglect. **Explain that treatment is held in reserve because starting it early carries harm without benefit, that the disease is being actively monitored, and exactly what would trigger treatment.** Write it down for them.

Treat for: progressive marrow failure with anaemia or thrombocytopenia · bulky or symptomatic lymphadenopathy or splenomegaly · a rapid lymphocyte doubling time · autoimmune cytopenias not responding to corticosteroids · B symptoms.

- **Modern therapy is targeted rather than cytotoxic:** Bruton tyrosine kinase inhibitors and the BCL2 inhibitor venetoclax, with or without an anti-CD20 antibody. **Venetoclax carries a real risk of tumour lysis** and is started with a careful dose ramp and monitoring.
- **Supportive care:** vaccination — **avoiding live vaccines** — a low threshold for treating infection, immunoglobulin replacement where infections are recurrent, corticosteroids for autoimmune cytopenias, and **skin surveillance**, since second malignancies including skin cancer are more frequent.

3. Teaching Points and Viva Questions

- Massive splenomegaly with granulocytes at all stages of maturation and basophilia is chronic myeloid leukaemia.
- *BCR-ABL1* both makes the diagnosis and monitors the treatment.
- Ask about missed tablets before you order a resistance test.
- Chronic lymphocytic leukaemia is diagnosed by flow cytometry on blood — no marrow required.
- Watch and wait needs to be explained, in writing, or it will be heard as abandonment.

- These patients die of infection, because they are hypogammaglobulinaemic.

Questions you should be able to answer:

- Which single test confirms this man's diagnosis, and which monitors his treatment?
- His transcript level has risen after two years of good control. What are the two explanations and which do you check first?
- How would you explain "no treatment" to the woman with lymphocytosis?
- She develops anaemia with a raised reticulocyte count and a positive direct antiglobulin test. What has happened?
- A node enlarges rapidly over three weeks with fever and a high lactate dehydrogenase. What is your concern?

Case 55 · Lymphoma

CLINICAL VIGNETTE

A **27-year-old woman** has noticed a painless lump in the left side of her neck which has slowly enlarged over three months. She has **drenching night sweats that require her to change her nightclothes**, has lost 8 kg, and itches all over. She mentions, when asked, that **the lump aches after she drinks alcohol**.

On examination: firm, rubbery, non-tender, matted nodes in the left cervical and **supraclavicular** regions. No hepatosplenomegaly. **Chest radiograph: widened mediastinum.**

1. Focused History

- **Characterise the node:** painless, progressive, rubbery and non-tender favours lymphoma; hard and fixed favours metastatic carcinoma; tender and fluctuant favours infection. **A supraclavicular node is the most sinister site and always warrants imaging and biopsy.** Lymphomatous nodes may wax and wane, which falsely reassures.

THE B SYMPTOMS

Ask about these three in their exact definitions, because they are **staging criteria** and they alter prognosis and treatment:

Fever above 38 °C without infection · drenching night sweats — enough to require a change of clothes or bedding · unintentional weight loss of more than 10% of body weight over six months.

"Feeling a bit sweaty" is not a B symptom. Quantify it.

- **Features suggestive of Hodgkin lymphoma:** generalised pruritus and **alcohol-induced nodal pain** — uncommon, but close to characteristic.
- **Compression syndromes:** superior vena caval obstruction (facial and arm swelling, distended chest wall veins, breathlessness worse on bending forward), cough or stridor, dysphagia, back pain with cord compression, ureteric obstruction.
- **Extranodal disease:** abdominal mass and bowel symptoms, bone pain, skin lesions, and neurological symptoms.
- **Predisposing factors:** human immunodeficiency virus, Epstein–Barr virus, immunosuppression and transplantation, autoimmune disease, hepatitis C, ***Helicobacter pylori*** for gastric mucosa-associated lymphoid tissue lymphoma, and coeliac disease.

2. The Differential of Lymphadenopathy

Cause	The feature that discriminates it
Tuberculosis	Firm matted nodes that may become fluctuant and discharge; constitutional symptoms indistinguishable from lymphoma. Common here, and it must be excluded on tissue, not on clinical grounds.
Brucellosis	Unpasteurised dairy and animal contact, undulant fever, hepatosplenomegaly, positive serology.
Epstein–Barr virus, cytomegalovirus, toxoplasmosis, human immunodeficiency virus	Younger patient, pharyngitis, atypical lymphocytes, self-limiting course; serology.
Metastatic carcinoma	Hard, fixed, often single-region node; a primary tumour on examination or imaging.
Sarcoidosis	Bilateral hilar lymphadenopathy, erythema nodosum, hypercalcaemia (Case 70).
Drug reaction and connective tissue disease	Temporal relation to a drug; rash, arthralgia, autoantibodies.

3. Investigations

THE SINGLE MOST IMPORTANT INVESTIGATIONAL POINT IN THIS CASE

The diagnosis of lymphoma requires an excision biopsy of a whole node, or a generous core biopsy. Fine-needle aspiration is not adequate.

Aspiration yields cells without architecture, and lymphoma is classified by architecture as much as by cell type. A negative or "reactive" aspirate is a common route to a delayed diagnosis, and subtyping — which determines the entire treatment — cannot be done on it.

A second, related point: avoid giving corticosteroids before the biopsy. They can lyse lymphoma cells and render the histology uninterpretable, which is precisely what happens when a breathless patient with a mediastinal mass is given dexamethasone in the emergency department.

- **Blood and biochemistry:** complete blood count and film, erythrocyte sedimentation rate, **lactate dehydrogenase** (prognostic), urate, calcium, renal and liver function, albumin, beta-2 microglobulin, direct antiglobulin test, immunoglobulins.
- **Virology before treatment: human immunodeficiency virus, hepatitis B and C, Epstein–Barr virus.** Hepatitis B status matters specifically because **rituximab can reactivate it fatally**, including in patients who are core-antibody positive with a negative surface antigen.
- **Staging with fluorodeoxyglucose positron emission tomography and computed tomography**, using the Ann Arbor and Lugano systems; bone marrow examination where indicated; lumbar puncture in high-risk aggressive disease.
- **Before treatment:** echocardiography ahead of anthracyclines, pulmonary function testing ahead of bleomycin, dental review, and **fertility preservation**, which for a 27-year-old is a central part of the first consultation.
- Prognostic scoring — the International Prognostic Score in Hodgkin disease, and the International Prognostic Index in diffuse large B-cell lymphoma.

4. Management — in Outline

Type	Approach
Hodgkin lymphoma	Combination chemotherapy with or without radiotherapy. Highly curable, including in advanced stage. Checkpoint inhibitors and brentuximab vedotin in relapsed disease.
Aggressive non-Hodgkin — diffuse large B-cell	Rituximab with combination chemotherapy, given with curative intent. Central nervous system prophylaxis in selected patients; chimeric antigen receptor T-cell therapy in relapse.
Indolent — follicular	Watch and wait where the burden is low and the patient asymptomatic; rituximab-based therapy when treatment is indicated. Long survival, but not usually curable.
Gastric mucosa-associated lymphoid tissue lymphoma	Eradication of *Helicobacter pylori* alone cures the majority — one of the few malignancies treated with a course of antibiotics.

- **Supportive care:** tumour lysis prevention, growth factor support, antimicrobial prophylaxis, **antiviral prophylaxis where hepatitis B core antibody is positive**, vaccination, and antiemetics.
- **Late effects surveillance**, which matters enormously in a young patient cured of Hodgkin disease: second malignancy, **breast cancer after mediastinal radiotherapy**, cardiac disease, thyroid dysfunction, pulmonary fibrosis and infertility.

5. Teaching Points and Viva Questions

- Excision biopsy, not fine-needle aspiration.
- Do not give steroids before the biopsy.
- Ask the B symptoms in their exact definitions — they are staging criteria.
- A supraclavicular node is always investigated.
- In this region, tuberculosis and brucellosis must be excluded on tissue and serology.
- Check hepatitis B before rituximab, including core antibody.
- Discuss fertility before the first cycle, and plan late-effects follow-up before the last.

Questions you should be able to answer:

- The surgeon offers a fine-needle aspirate this afternoon or an excision biopsy next week. Which do you want and why?
- Which of her symptoms are B symptoms, and what difference do they make?
- Give four alternative diagnoses for these nodes and how you would exclude each.
- She is breathless with facial swelling. What is happening and what must you avoid doing first?
- She asks whether she will be able to have children. How do you answer, and what do you arrange?

Case 56 · Multiple Myeloma

CLINICAL VIGNETTE

A **68-year-old man** has had four months of mid-thoracic back pain, **worse on movement and not relieved by rest**, which now wakes him when he turns over. He has lost 6 kg, feels exhausted, and had a chest infection last month. In the past week he has become constipated and mildly confused.

On examination: pale, with tenderness over the mid-thoracic spine. Neurological examination of the legs is normal. He is dehydrated.

Haemoglobin 84 g/L, normocytic · erythrocyte sedimentation rate 110 · corrected calcium 3.1 mmol/L · creatinine 240 µmol/L · albumin 30 g/L with a raised total protein · film shows rouleaux. Radiograph: **lytic lesion at T7 with partial vertebral collapse.**

THE FOUR FEATURES — CRAB

C — **C**alcium raised · **R** — **R**enal impairment · **A** — **A**naemia · **B** — **B**one lesions

This patient has all four. **Any older patient with unexplained back pain, a normocytic anaemia, a very high erythrocyte sedimentation rate and renal impairment has myeloma until proved otherwise** — and that combination is available from the first set of blood tests.

1. Focused History

- **The bone pain of myeloma is mechanical** — back or rib pain, worse on movement, **not** the night pain relieved by activity that characterises inflammatory disease. Ask about pathological fracture and sudden increases in pain.
- **Cord compression — the emergency to exclude at every visit:** band-like or radicular pain, leg weakness, a sensory level, and any change in bladder or bowel function.
- Fatigue and breathlessness; **recurrent infection** from immune paresis; **hypercalcaemia** — thirst, polyuria, constipation, confusion; renal symptoms; and **hyperviscosity** — headache, visual blurring, mucosal bleeding, confusion.
- **Features of associated amyloidosis:** frothy urine and oedema, cardiac failure, peripheral and autonomic neuropathy, macroglossia, carpal tunnel syndrome, periorbital purpura.

2. Physical Examination

- Pallor, hydration and conscious level; **bone tenderness over the spine, ribs and sternum**.
- **A full neurological examination of the legs including anal tone in any patient with back pain and a paraprotein** — this is the examination that finds cord compression while it is still reversible.
- Signs of infection and of amyloidosis.

3. Investigations

- Complete blood count and film (**rouleaux**), erythrocyte sedimentation rate, renal function, **corrected calcium**, albumin, lactate dehydrogenase, beta-2 microglobulin.
- **Serum protein electrophoresis with immunofixation, serum free light chain assay, and quantification of the paraprotein**; urine electrophoresis for Bence Jones protein.

TWO TRAPS THAT DELAY THIS DIAGNOSIS

The urine dipstick does not detect Bence Jones protein. It reacts with albumin, not with free light chains, so a negative dipstick in a patient with heavy light chain excretion is entirely normal and utterly misleading.

And in light-chain-only myeloma the serum protein electrophoresis may be normal, which is why the **serum free light chain assay** must be requested alongside it rather than instead of it.

Two tests, both cheap, both frequently omitted — and between them the reason myeloma is diagnosed late.

- **Bone marrow aspirate and trephine with cytogenetics and fluorescence in situ hybridisation** for risk stratification.
- **Imaging: whole-body low-dose computed tomography, magnetic resonance imaging or positron emission tomography. The plain skeletal survey is obsolete** — it requires around half the bone to be destroyed before a lesion is visible, and it misses early disease. **Urgent magnetic resonance imaging of the whole spine if cord compression is suspected.**
- **Distinguish from monoclonal gammopathy of undetermined significance** — paraprotein below 30 g/L, marrow plasma cells below 10%, and no end-organ damage. It requires surveillance, not treatment, and it carries a small annual risk of progression. **Smouldering myeloma** sits between the two.

4. Management

The emergencies first

- **Hypercalcaemia:** intravenous fluids then a bisphosphonate, as in Case 23.
- **Acute kidney injury:** vigorous hydration, **stop non-steroidal anti-inflammatory drugs and other nephrotoxins**, treat the hypercalcaemia, start anti-myeloma therapy urgently to reduce the light chain load, and dialyse where necessary. **Be cautious with iodinated contrast.**
- **Cord compression: this is a matter of hours.** Urgent magnetic resonance imaging, high-dose dexamethasone, and immediate discussion with oncology and neurosurgery for radiotherapy or decompression. Neurological function not recovered within hours is often not recovered at all.
- **Hyperviscosity:** plasmapheresis.

Definitive and supportive

- **Induction with a combination** typically including a proteasome inhibitor, an immunomodulatory drug, an anti-CD38 monoclonal antibody and dexamethasone, followed by **autologous stem cell transplantation** in fit patients, then maintenance therapy. The disease is not curable, but survival has improved substantially and continues to.
- **Skeletal protection with a bisphosphonate or denosumab for every patient**, with **dental assessment beforehand** because of the risk of osteonecrosis of the jaw.
- **Analgesia, avoiding non-steroidal anti-inflammatory drugs**; radiotherapy for painful or threatening lesions; vertebroplasty or surgical stabilisation where appropriate.
- **Thromboprophylaxis with immunomodulatory drugs**, which are markedly thrombogenic; vaccination and prompt treatment of infection; immunoglobulin replacement in recurrent infection.

- Monitor response with the paraprotein and free light chain levels.

5. Teaching Points and Viva Questions

- CRAB — and all four can be found in the first blood test.
- The pain is mechanical, not inflammatory. That distinction points you at the right diagnosis.
- The dipstick misses Bence Jones protein; request free light chains alongside electrophoresis.
- The skeletal survey is obsolete. Use cross-sectional imaging.
- Examine the legs and the anal tone. Cord compression is reversible for hours, not days.
- No anti-inflammatory drugs, and think before giving contrast.

Questions you should be able to answer:

- Identify each element of CRAB in this patient's results.
- His urine dipstick shows no protein. Does that exclude light chain excretion?
- Which imaging do you request, and why not a skeletal survey?
- He reports new weakness in both legs overnight. What is your sequence of actions and over what timescale?
- How would you distinguish this from monoclonal gammopathy of undetermined significance?

Case 57 · The Myeloproliferative Neoplasms

CLINICAL VIGNETTE

A **58-year-old man** is referred with a **haemoglobin of 194 g/L and a haematocrit of 0.59** found incidentally. He describes headaches, occasional dizziness, and **intense itching for about half an hour after a hot bath**. He has burning discomfort in both hands. Three months ago he had an unprovoked deep vein thrombosis.

On examination: facial plethora and conjunctival suffusion. Blood pressure 156/94 mmHg. **The spleen is palpable 4 cm below the costal margin.**

Platelets 520 × 10^9/L · white cells 13.4 × 10^9/L · serum erythropoietin low · *JAK2* V617F mutation present · ferritin low.

1. Think First — Not Every High Haemoglobin Is a Neoplasm

Category	Causes
Relative — a plasma problem, not a red cell one	Dehydration, diuretics, plasma loss. Confirm with a repeat sample when euvolaemic.
Secondary and appropriate — driven by hypoxia	Chronic lung disease, right-to-left cardiac shunt, obstructive sleep apnoea, heavy smoking with raised carboxyhaemoglobin, and residence at altitude — which is a routine local consideration rather than a curiosity, and must be established before a marrow is contemplated.
Secondary and inappropriate	Erythropoietin-secreting tumours — renal cell carcinoma, hepatocellular carcinoma, cerebellar haemangioblastoma, uterine fibroid; after renal transplantation; and exogenous testosterone or erythropoietin, which must be asked about directly.
Primary — polycythaemia vera	A low or inappropriately normal erythropoietin with a *JAK2* mutation. This patient.

The three *BCR-ABL1*-negative neoplasms are **polycythaemia vera, essential thrombocythaemia and primary myelofibrosis**, driven by mutations in ***JAK2*, *CALR* or *MPL***. Chronic myeloid leukaemia is the *BCR-ABL1*-positive member of the family and is covered in Case 54.

2. Focused History

- **Hyperviscosity:** headache, dizziness, tinnitus, visual disturbance, poor concentration.
- **Aquagenic pruritus** — itching after a hot bath or shower — which is characteristic of polycythaemia vera and is rarely volunteered because patients do not connect it with a blood disorder.
- **Erythromelalgia** — burning pain and redness of the hands and feet.
- **Thrombosis, and specifically thrombosis in unusual sites.** Arterial and venous events are the main cause of morbidity. **Splanchnic vein thrombosis or Budd–Chiari syndrome in a younger patient should always prompt a *JAK2* test**, even when the blood count looks normal.
- **Paradoxical bleeding** with very high platelet counts, from acquired von Willebrand disease.
- Gout; early satiety and left upper quadrant discomfort; and **constitutional symptoms with weight loss, which point towards myelofibrosis**.
- **Then exclude the secondary causes by history:** smoking, snoring and daytime somnolence, lung disease, altitude of residence, diuretics, and testosterone or performance-enhancing drug use.

3. Investigations

- Complete blood count and **film — tear-drop poikilocytes with a leucoerythroblastic picture indicate marrow infiltration and suggest myelofibrosis**.
- **Serum erythropoietin, then *JAK2* V617F, then *CALR* and *MPL*** where the first is negative.
- Ferritin — often low in polycythaemia vera even before venesection; urate; lactate dehydrogenase; renal and liver function.
- **Oxygen saturation and blood gas with carboxyhaemoglobin**; sleep studies where indicated; **abdominal ultrasound** for spleen size, renal and hepatic lesions and portal vein patency.
- **Bone marrow with assessment of fibrosis** where myelofibrosis is suspected or the diagnosis remains unclear.

4. Management

> THE NUMBER TO REMEMBER
>
> **Venesect to a haematocrit below 0.45.**
>
> This single target reduces cardiovascular death and major thrombosis, and a higher target does not. It is the most important intervention in polycythaemia vera and it is achieved with a needle and a bag.
>
> **Add low-dose aspirin** in all patients without a contraindication, and **control conventional cardiovascular risk factors**, since thrombosis is what harms these patients.

- **Cytoreduction — hydroxycarbamide** — for higher-risk patients: age over 60, previous thrombosis, poor tolerance of venesection, progressive splenomegaly or very high counts. **Interferon** is preferred in younger patients and in pregnancy; **ruxolitinib** in resistant or intolerant disease. Allopurinol for gout.
- **Essential thrombocythaemia:** risk-stratify, give aspirin, and add hydroxycarbamide in high-risk disease. **With extreme platelet counts, look for acquired von Willebrand disease before prescribing aspirin**, which may then cause bleeding.
- **Primary myelofibrosis:** transfusion support, **ruxolitinib for splenomegaly and constitutional symptoms**, and **allogeneic stem cell transplantation as the only curative option** in suitable higher-risk patients, guided by prognostic scoring.
- **All three: monitor for transformation** to myelofibrosis and to acute myeloid leukaemia; avoid dehydration; plan pregnancy with specialist input.

5. Teaching Points and Viva Questions

- Erythropoietin and *JAK2* before anything invasive.
- Exclude hypoxia, smoking, sleep apnoea and altitude first — and ask where the patient lives.
- Itching after a hot bath is a real symptom of a real disease.
- Thrombosis in an unusual site means test for *JAK2*, whatever the blood count shows.
- Haematocrit below 0.45, plus aspirin.

- Tear-drop cells and a leucoerythroblastic film mean the marrow is infiltrated.

Questions you should be able to answer:

- Give four causes of a raised haematocrit other than a myeloproliferative neoplasm.
- Why is his ferritin low before any treatment?
- What is your haematocrit target and what is the evidence for it?
- A 34-year-old presents with Budd–Chiari syndrome and a normal blood count. What do you test for?
- A patient with a platelet count of 1,400 has mucosal bleeding. Explain, and say what you would check before giving aspirin.

The Rheumatology Block

Rheumatoid arthritis, systemic lupus erythematosus, axial spondyloarthritis, vasculitis, crystal arthropathy and antiphospholipid syndrome.

Cases 58–63 · 8,021 words

This block covers the rheumatology teaching of both internal medicine courses. The **first course** supplies cases 58 and 60; the **second course** supplies cases 61 and 63.

Case	Lecture it serves
System opener: the rheumatological history and examination	History taking in rheumatology; physical examination in rheumatology
Case 58 — Rheumatoid arthritis	Rheumatoid arthritis
Case 59 — Systemic lupus erythematosus	Systemic lupus erythematosus
Case 60 — Axial spondyloarthritis	Spondyloarthritis
Case 61 — Vasculitis	Vasculitis syndromes
Case 62 — Gout and calcium pyrophosphate deposition disease	Gout and pseudogout
Case 63 — Antiphospholipid syndrome	Antiphospholipid antibody syndrome

The approach to the patient with polyarthritis, a second-course seminar, is covered as Seminar 6 in Part Two, where the differential can be built from the pattern of joint involvement rather than from a named disease.

System Opener · The Rheumatological History and Examination

Almost every rheumatological diagnosis is reached through three questions asked in order: **is the pain inflammatory or mechanical; what is the pattern of joint involvement; and what is happening outside the joints.** Get those three right and the serology usually confirms what you already suspect.

Question 1 — Inflammatory or mechanical?

	Inflammatory	Mechanical
Morning stiffness	More than 30–60 minutes	Under 30 minutes
Effect of activity	Improves with movement	Worsens with use
Effect of rest	Worsens — stiffness after sitting	Improves
Night pain	Wakes the patient, typically in the second half of the night	Uncommon, and related to position
Swelling	Soft tissue swelling, warmth, effusion	Bony swelling only, or none
Systemic features	Fatigue, fever, weight loss	Absent

Question 2 — What is the pattern?

- **Number:** monoarthritis, oligoarthritis (four or fewer joints), or polyarthritis (five or more).
- **Symmetry:** symmetrical in rheumatoid arthritis and lupus; asymmetrical in the spondyloarthritides and gout.
- **Size and distribution:** small joints of the hands with **metacarpophalangeal and proximal interphalangeal involvement sparing the distal interphalangeal joints** points to rheumatoid arthritis; **distal interphalangeal involvement** points to psoriatic arthritis or osteoarthritis.
- **Axial or peripheral**, and whether the course is additive, migratory or intermittent.
- **Duration:** an inflammatory arthritis of less than six weeks is often viral or reactive and may resolve; beyond six weeks it demands a diagnosis.

Question 3 — What is happening outside the joints?

This is the part of the history that separates rheumatology from orthopaedics, and it is where the diagnosis usually is.

System	Ask about
Skin and hair	Photosensitive or malar rash, psoriasis — and look at the scalp, natal cleft, umbilicus and nails, not only the elbows; nodules; ulcers; purpura; hair loss; Raynaud phenomenon
Eyes	Dry eyes, a painful red eye with photophobia (uveitis), scleritis, and any visual loss
Mouth and genitals	Oral ulcers — painless in lupus, painful and recurrent with genital ulceration in Behçet disease, which is not rare in this region
Chest	Pleuritic pain, breathlessness, dry cough (interstitial lung disease)
Gastrointestinal	Diarrhoea, blood or mucus, weight loss (inflammatory bowel disease); dysphagia
Genitourinary	Urethral discharge or dysuria, and any preceding gastrointestinal or genitourinary infection (reactive arthritis)
Neurological	Temporal headache and jaw claudication in a patient over 50; numbness or weakness suggesting entrapment or mononeuritis multiplex; seizures
Renal	Frothy urine, ankle swelling, hypertension — all of which are silent until asked about

RED FLAGS THAT OVERRIDE THE REST OF THE ASSESSMENT

A single hot, swollen, painful joint is septic arthritis until proved otherwise. Aspirate it, send it, and start antibiotics. A joint can be destroyed within days, and gout and sepsis coexist.

New severe back pain with neurological signs, fever, or a history of malignancy — image urgently.

New headache with jaw claudication or visual symptoms in a patient over 50 — giant cell arteritis; start corticosteroids immediately and arrange same-day assessment. Do not wait for the biopsy.

The examination

- **Screen with gait, arms, legs and spine**, then examine the affected regions in detail using **look, feel, move** followed by an assessment of function.
- **Recognise synovitis:** soft, boggy swelling with warmth and tenderness at the joint line, and an effusion. Distinguish it from the hard bony swelling of osteoarthritis — the treatment implications are entirely different.
- **Squeeze across the metacarpophalangeal and metatarsophalangeal rows.** Pain on the metatarsal squeeze is often the earliest sign of an inflammatory arthritis and is missed because feet are not examined.
- **Assess function, not just findings:** ask the patient to do up a button, hold a pen, lift a cup, and comb their hair. This tells you what the disease is actually costing them.
- **Then examine outside the joints** as the history directs — skin including hidden sites, nails, eyes, chest, abdomen, and the nervous system.

Case 58 · Rheumatoid Arthritis

CLINICAL VIGNETTE

A **42-year-old woman** describes five months of pain and swelling in the small joints of both hands, both wrists and the balls of both feet. She is **stiff for two hours every morning** and improves as the day goes on. She is exhausted, has difficulty with buttons, and can no longer open jars. She has cut back her working hours.

She smokes 10 cigarettes a day. Her mother had "bad arthritis".

On examination: symmetrical soft tissue swelling and tenderness of the metacarpophalangeal and proximal interphalangeal joints and both wrists, with **sparing of the distal interphalangeal joints**. The **metatarsophalangeal squeeze is painful bilaterally**. Grip strength is reduced. There are no nodules and no deformity yet.

Rheumatoid factor positive · anti-cyclic citrullinated peptide antibody strongly positive · C-reactive protein 48 · erythrocyte sedimentation rate 62. Radiographs: periarticular osteopenia with an early erosion at the fifth metatarsophalangeal joint.

THE WINDOW OF OPPORTUNITY

The damage in rheumatoid arthritis happens early, and it is permanent. Erosions appear within the first year, and function lost to established deformity is not recovered by later treatment.

Refer on suspicion, not on confirmation. A patient with persistent symmetrical small joint swelling should reach a rheumatologist within weeks, and disease-modifying therapy should begin within three months of symptom onset. Waiting for radiographic erosions or for a positive rheumatoid factor before referring is the single commonest and most costly error in this disease.

1. Focused History

- **Duration of morning stiffness in minutes**, pattern and symmetry of joint involvement, and which joints are spared.
- **Function** — dressing, grooming, cooking, work, driving. Record what she cannot do, not just what hurts.
- **Systemic features:** fatigue, low-grade fever, weight loss.
- **Extra-articular disease, asked about explicitly:** dry eyes and dry mouth; red painful eye; breathlessness and dry cough (interstitial lung disease); numbness in the hands (carpal tunnel) or asymmetric neuropathy (vasculitis); **neck pain and any arm or leg symptoms**, which raise cervical spine involvement.
- **Smoking** — it increases both the risk and the severity of the disease, reduces treatment response, and is the most important modifiable factor. Say so plainly to the patient.
- **Before immunosuppression:** pregnancy plans and contraception; infection history; **tuberculosis exposure and hepatitis B and C risk**; vaccination status.

2. Physical Examination

- Map the synovitis, counting tender and swollen joints. **Examine the feet** — metatarsophalangeal disease is frequently the earliest change.
- **Deformities of established disease**, which you should be able to name: ulnar deviation at the metacarpophalangeal joints, swan-neck and boutonnière deformities, Z-thumb, and a prominent piano-key ulnar head.

- **Rheumatoid nodules** over the extensor surfaces; carpal tunnel signs.

THE COMPLICATION THAT CATCHES SURGICAL TEAMS OUT

Ask about neck pain and examine the neurology in every patient with longstanding rheumatoid arthritis — particularly before any operation.

Erosion of the transverse ligament and the odontoid peg permits **atlantoaxial subluxation**. Neck extension during intubation can then cause cord compression. Imaging of the cervical spine before general anaesthesia is a standard precaution, and the anaesthetist must be told the diagnosis.

- **Extra-articular examination:** eyes for scleritis, episcleritis and dry eye; chest for fibrotic crackles and pleural effusion; heart for pericarditis; skin for vasculitic lesions and nailfold infarcts; abdomen for splenomegaly, which with neutropenia constitutes **Felty syndrome**.

3. Investigations

- **Rheumatoid factor and anti-cyclic citrullinated peptide antibody.** The latter is considerably more specific and predicts erosive disease. **Between a fifth and a third of patients are seronegative** — a negative result does not exclude the diagnosis in a patient with unmistakable synovitis.
- **C-reactive protein and erythrocyte sedimentation rate** for disease activity, and to follow response.
- Complete blood count — normocytic anaemia of chronic disease and reactive thrombocytosis; renal and liver function as a **baseline before disease-modifying drugs**.
- **Radiographs of hands and feet:** soft tissue swelling, periarticular osteopenia, uniform joint space narrowing, and **marginal erosions**. **Ultrasound or magnetic resonance imaging detects synovitis and erosions far earlier** and is increasingly used to confirm early disease.
- **Before biologic therapy: screen for latent tuberculosis** with an interferon-gamma release assay and chest radiograph, and for **hepatitis B and C** — including hepatitis B core antibody, because of the reactivation risk.

4. Management

Treat to a target

- Set an explicit target of **remission, or at minimum low disease activity**, measure it at each visit with a composite score, and **escalate therapy until the target is met**. Reviewing every one to three months in early disease is part of the treatment, not administrative overhead.

Drugs

Agent	Practical points
Methotrexate — first line	Weekly, never daily. Prescribe folic acid on a different day. Monitor complete blood count, liver and renal function. Contraindicated in pregnancy — effective contraception is required and it must be stopped well before conception. Avoid substantial alcohol. Caution with trimethoprim and co-trimoxazole, which are also antifolates.
Sulfasalazine, hydroxychloroquine, leflunomide	Used alone or in combination where methotrexate is not tolerated. Hydroxychloroquine requires annual retinal screening.
Bridging corticosteroids	Oral or intramuscular, or intra-articular injection, to control symptoms while the disease-modifying drug takes effect over 6–12 weeks. Use the lowest dose for the shortest time, with bone protection.
Biologic and targeted synthetic agents	Tumour necrosis factor inhibitors, rituximab, tocilizumab, abatacept, Janus kinase inhibitors, after inadequate response. Screen for tuberculosis and hepatitis first; vaccinate beforehand; and avoid live vaccines once immunosuppressed.
Anti-inflammatory drugs	For symptoms only — they modify nothing. Use with gastroprotection and with attention to renal and cardiovascular risk.

THE PRESCRIBING ERROR THAT KILLS

Methotrexate is dispensed as a **weekly** dose. Daily administration — through a prescribing error, a transcription error at admission, or a patient misunderstanding — causes fatal pancytopenia and mucositis, and it has happened repeatedly. **Confirm the day of the week with every patient at every visit, and check it on every drug chart you clerk.** Write the day on the prescription.

Beyond the prescription

- **Physiotherapy and occupational therapy** — hand exercises, joint protection, splinting, aids and workplace adaptation. **Smoking cessation.** Regular exercise and weight management.
- **Cardiovascular risk is substantially increased** by the disease itself, independently of traditional risk factors. Assess and treat it actively — this is a major cause of premature death in rheumatoid arthritis and is routinely neglected while attention stays on the joints.
- Osteoporosis assessment and prevention, particularly with corticosteroid exposure. Vaccination. Pregnancy planning with a compatible drug regimen.

5. Teaching Points and Viva Questions

- Refer on suspicion. The joints being destroyed while you wait for confirmation do not grow back.
- Squeeze the metatarsophalangeal joints — the feet declare the disease before the hands deform.
- Seronegative rheumatoid arthritis is common; the antibodies support the diagnosis, they do not make it.
- Methotrexate is weekly. Check it on every drug chart.
- Screen for tuberculosis and hepatitis B before any biologic agent.
- Image the cervical spine before anaesthesia, and tell the anaesthetist.

- Treat the cardiovascular risk as vigorously as the synovitis.

Questions you should be able to answer:

- Which features of this history tell you the arthritis is inflammatory?
- Her rheumatoid factor is negative. Does that change your management?
- She is listed for a hysterectomy. What must happen before she is anaesthetised?
- Name three things you must check before starting a tumour necrosis factor inhibitor.
- Why does she need her lipids and blood pressure checked in a rheumatology clinic?

Case 59 · Systemic Lupus Erythematosus

CLINICAL VIGNETTE

A **26-year-old woman** presents with four months of profound fatigue, aching and swelling of the small joints of both hands and both knees, and a rash across her cheeks that flares after she has been outdoors. She has recurrent **painless ulcers on the roof of her mouth**, and her hair has been coming out. For two weeks she has had sharp chest pain on deep inspiration. Over the past month she has noticed her urine is frothy and her ankles swell by evening.

On examination: an erythematous rash over both cheeks and the bridge of the nose **sparing the nasolabial folds**. Painless palatal ulcers. Synovitis of the metacarpophalangeal joints **without deformity or erosion**. A pleural rub at the left base. **Blood pressure 148/92 mmHg.** Pitting ankle oedema.

Haemoglobin 96 g/L · white cells 3.2 with lymphopenia · platelets 110 · antinuclear antibody 1:1280 · anti-double-stranded DNA strongly positive · C3 and C4 both low · creatinine 108 µmol/L · urine dipstick blood and protein · urine albumin-to-creatinine ratio 320 mg/mmol.

1. Focused History

Lupus is a multisystem disease and the history must be a systematic sweep. A patient who is asked only about their joints will have their nephritis found late.

System	Features to elicit
Constitutional	Fatigue — usually the dominant symptom and the one most often dismissed — fever, weight loss
Skin	Photosensitivity, malar rash sparing the nasolabial folds, discoid lesions that scar, alopecia, Raynaud phenomenon, livedo reticularis
Mucosal	Oral and nasal ulcers, characteristically painless and on the hard palate
Joints	Symmetrical small joint arthritis that is non-erosive; deformity, if present, is reducible
Serosal	Pleuritic chest pain, pericarditic pain relieved by sitting forward, breathlessness
Renal	Frothy urine, ankle swelling, hypertension — and none of these may be present, because lupus nephritis is silent until it is advanced
Neuropsychiatric	Seizures, psychosis, stroke, headache, cognitive impairment, mood disturbance
Haematological	Recurrent infection, bruising, and thrombosis
Obstetric	Recurrent miscarriage, fetal death, pre-eclampsia — which together with thrombosis raise the antiphospholipid syndrome

- **Drug history:** hydralazine, procainamide, isoniazid, minocycline and tumour necrosis factor inhibitors cause **drug-induced lupus**, which is anti-histone positive and characteristically **spares the kidneys and central nervous system** and resolves on withdrawal.
- Family history of autoimmune disease; and a careful infection history, since infection both mimics and complicates lupus.

2. Physical Examination

- **The rash:** the malar rash of lupus **spares the nasolabial folds**, which distinguishes it from rosacea and from dermatomyositis. Discoid lesions scar and cause permanent alopecia.
- Examine the **hard palate** for ulcers — patients do not report them because they do not hurt.

- Joints: synovitis without erosion; deformity, where present, is reducible (Jaccoud arthropathy).
- Chest and heart for rub and effusion; lymph nodes and spleen; a full neurological examination; digits for ischaemia and livedo.

THE TWO-MINUTE RULE

Measure the blood pressure and dipstick the urine at every single lupus consultation, in clinic and on the ward.

Lupus nephritis produces no symptoms until it produces renal failure. It is found by the dipstick or it is found too late. This costs thirty seconds and is the highest-yield thing you will do in the consultation.

3. Investigations

- **Antinuclear antibody is the screening test** — highly sensitive but poorly specific, and positive in many healthy people at low titre. **A negative antinuclear antibody makes lupus very unlikely.**
- **Anti-double-stranded DNA and anti-Smith antibodies are specific.** Anti-double-stranded DNA titre correlates with disease activity, particularly renal activity.
- **Complement C3 and C4 fall during active disease** as complement is consumed. With anti-double-stranded DNA, these are the two markers you follow over time.
- **Anti-Ro and anti-La** — essential before pregnancy, since they cross the placenta and cause **neonatal lupus and congenital complete heart block**. Anti-RNP in overlap syndromes.
- **Antiphospholipid antibodies** — lupus anticoagulant, anticardiolipin and anti-beta-2-glycoprotein I — **repeated at 12 weeks** to confirm persistence.

THE INFLAMMATORY MARKERS BEHAVE DIFFERENTLY HERE

The erythrocyte sedimentation rate rises with lupus activity. The C-reactive protein characteristically does not.

So in a febrile lupus patient, **a high C-reactive protein should make you think infection first**, not a flare — with serositis being the main lupus exception. This single distinction is one of the most useful in the whole disease, because these patients are immunosuppressed and infection is a leading cause of death.

- **Urinalysis with microscopy and a urine protein or albumin-to-creatinine ratio at every visit**; creatinine and estimated filtration rate.
- **Renal biopsy** where there is proteinuria, an active urinary sediment or unexplained renal impairment. It classifies the nephritis, and the class determines the treatment — this patient needs one.
- Complete blood count for the cytopenias; direct antiglobulin test; coagulation screen; imaging as directed.

4. Management

THE ONE DRUG EVERYBODY GETS

Hydroxychloroquine is given to essentially every patient with lupus, and continued indefinitely.

It reduces flares, reduces accrued organ damage, reduces thrombosis, and **improves survival**. It is safe in pregnancy and should be continued through it. Smoking reduces its effectiveness, which is one more reason to address it. Arrange **annual retinal screening**.

It is a cheap, well-tolerated drug that changes the natural history of the disease, and it is under-prescribed.

- **Sun protection and smoking cessation** for every patient.
- **Mild disease:** hydroxychloroquine, with short courses of anti-inflammatory drugs or low-dose corticosteroid for flares.
- **Moderate disease:** add methotrexate or azathioprine as a steroid-sparing agent.
- **Severe organ-threatening disease — nephritis, central nervous system involvement, severe cytopenias:** high-dose corticosteroid with **mycophenolate mofetil or cyclophosphamide** for induction, then maintenance immunosuppression. Biologic agents including belimumab, rituximab and anifrolumab are used as add-on therapy.
- **Minimising corticosteroid exposure is an explicit treatment goal.** A large share of the permanent damage accrued by lupus patients over a lifetime — bone, metabolic, cardiovascular, cataract, infection — comes from the steroids rather than from the disease.
- **Antiphospholipid syndrome:** anticoagulation after thrombosis; **direct oral anticoagulants are avoided in triple-positive and arterial disease**, where warfarin is used. Aspirin with low-molecular-weight heparin in pregnancy.

Pregnancy — plan it, do not react to it

- Conception should be planned during **at least six months of quiescent disease**, particularly after nephritis.
- **Continue hydroxychloroquine.** Azathioprine, tacrolimus and corticosteroids are compatible with pregnancy. **Mycophenolate, cyclophosphamide and methotrexate are teratogenic and must be stopped and substituted well in advance.**
- **Anti-Ro positivity requires fetal cardiac monitoring** for heart block. Aspirin reduces pre-eclampsia risk. Distinguishing pre-eclampsia from a renal flare in the third trimester is difficult and requires joint obstetric and rheumatological care.

Long-term

- Vaccination before immunosuppression; **accelerated atherosclerosis** means active cardiovascular risk management; bone protection; contraceptive advice, with caution over oestrogen in antiphospholipid syndrome; and vigilance for infection, which can look exactly like a flare.

5. Teaching Points and Viva Questions

- Blood pressure and urine dipstick every visit. Nephritis is silent.

- A high C-reactive protein in a febrile lupus patient means infection until proved otherwise.
- A negative antinuclear antibody essentially excludes lupus; a positive one proves very little on its own.
- Follow anti-double-stranded DNA and complement together to track activity.
- Hydroxychloroquine for everyone, forever.
- Much of the long-term damage is caused by steroids — spare them deliberately.
- Plan pregnancy in remission and change the teratogens beforehand.

Questions you should be able to answer:

- Which features of her rash favour lupus over rosacea?
- She is admitted febrile with a C-reactive protein of 180. Flare or infection?
- What does her renal biopsy add that the urine test does not?
- She wants to conceive next year. What are your steps over the next twelve months?
- Why do her complement levels fall when she is unwell?

Case 60 · Axial Spondyloarthritis

CLINICAL VIGNETTE

A **24-year-old man** has had low back and buttock pain for eighteen months. The buttock pain **alternates from side to side**. It wakes him at around four in the morning and he has to get up and move about; he is then **stiff for about ninety minutes**. The pain is better after football and worse after a day at a desk. He has been told he has mechanical back pain and has had two courses of physiotherapy for a disc problem.

He also has persistent right heel pain and a swollen second toe. Three months ago he had a painful red eye that was treated urgently at the eye hospital. His father has psoriasis.

On examination: loss of the normal lumbar lordosis. **Modified Schober test 3.5 cm** (normal is over 5 cm). **Chest expansion 3 cm.** Tenderness over both sacroiliac joints, tenderness at the Achilles insertion, and **dactylitis of the third toe**. Cervical rotation is reduced.

HLA-B27 positive · C-reactive protein 34. Radiographs show bilateral grade 3 sacroiliitis.

WHY THIS DIAGNOSIS IS MISSED FOR YEARS

The average delay between the onset of symptoms and the diagnosis of axial spondyloarthritis remains **several years**, and this patient shows why: a young man with back pain is assumed to have a mechanical problem, and is treated for it repeatedly.

The history distinguishes them completely, and it takes two minutes.

1. Inflammatory Back Pain

Four of the following five features indicate inflammatory back pain:

- **Age at onset below 45 years.**
- **Insidious onset**, present for more than three months.
- **Morning stiffness of more than 30 minutes.**
- **Improvement with exercise but not with rest.**
- **Night pain, particularly in the second half of the night, that improves on getting up.**

Alternating buttock pain is additionally characteristic and is worth asking about specifically. This patient has all of it.

2. Focused History — Beyond the Spine

- **Peripheral joints:** asymmetrical oligoarthritis, predominantly of the lower limbs.
- **Enthesitis** — inflammation where tendon meets bone. Ask about **heel pain**, at the Achilles insertion or the plantar fascia. It is the feature most often not connected to the back pain.
- **Dactylitis** — a uniformly swollen "sausage" digit, which is close to diagnostic of spondyloarthritis.
- **Acute anterior uveitis** — a unilateral, painful, red, photophobic eye with blurred vision. It recurs, and it occurs in up to a third of patients.

- **Psoriasis** — and **look for it yourself**, on the scalp, behind the ears, in the natal cleft, at the umbilicus, and in the nails for pitting and onycholysis. Patients frequently do not know they have it.
- **Inflammatory bowel disease** — diarrhoea, blood or mucus, weight loss.
- **Preceding gastrointestinal or genitourinary infection**, which raises reactive arthritis.
- Family history of spondyloarthritis, psoriasis, inflammatory bowel disease or uveitis. Smoking, which worsens outcome.

3. Physical Examination

- **Posture** — loss of lumbar lordosis, increased thoracic kyphosis, and in advanced disease the fixed "question mark" posture.
- **The measurements that matter, and how to do them:**
  - **Modified Schober test** — mark 10 cm above and 5 cm below the lumbosacral junction; on full forward flexion the distance should increase by more than 5 cm.
  - **Occiput-to-wall distance** — should be zero; any gap indicates fixed cervical flexion.
  - **Chest expansion** at the fourth intercostal space — **less than 5 cm is abnormal** and reflects costovertebral involvement.
  - Lateral lumbar flexion and cervical rotation.
- **Sacroiliac tenderness** and provocation with the flexion–abduction–external rotation manoeuvre.
- **Enthesitis sites**, dactylitis, peripheral joints, skin and nails, eyes.
- **Cardiac auscultation for aortic regurgitation**, and the chest for **apical pulmonary fibrosis** — both recognised extra-articular features.

4. Investigations

- **Radiographs of the sacroiliac joints** — sacroiliitis with erosion, sclerosis and eventual fusion. **They may remain normal for years after symptoms begin**, so a normal film excludes nothing in a young patient.
- **Magnetic resonance imaging of the sacroiliac joints with fat-suppressed sequences shows bone marrow oedema and detects active inflammation years before radiographic change.** This is what allows the diagnosis of **non-radiographic axial spondyloarthritis**, and it has transformed early diagnosis of this disease.
- **HLA-B27 supports the diagnosis but does not make it.** It is common in healthy people, with a prevalence that varies substantially between populations, so a positive result in an unselected patient with back pain means very little. Interpret it alongside the clinical picture.
- **C-reactive protein and erythrocyte sedimentation rate may be entirely normal despite active disease** — unlike rheumatoid arthritis. Normal inflammatory markers do not reassure here.

- Spinal radiographs in established disease: squaring of the vertebral bodies, shiny corners, syndesmophytes, and eventually the fused "bamboo spine".
- Baseline bloods and **tuberculosis and hepatitis screening before biologic therapy**.

5. Management

THE TREATMENT STUDENTS UNDER-RATE

Daily exercise and physiotherapy are the cornerstone of treatment in axial spondyloarthritis, not an adjunct to it.

Spinal extension exercises, postural work, hydrotherapy and maintained aerobic activity preserve mobility and function in a way no drug does. It is the most important intervention in this disease, it is free, and it is the one most often left out of the plan.

Prescribe it specifically — what exercises, how often, and with which physiotherapist — and review adherence as you would for a drug.

- **Non-steroidal anti-inflammatory drugs are the first-line drug therapy** and are strikingly effective; continuous use may slow radiographic progression. Prescribe with gastroprotection and attention to renal and cardiovascular risk.

WHAT DOES NOT WORK — AND IS PRESCRIBED ANYWAY

Methotrexate and sulfasalazine do not work for axial disease. They have a role only in peripheral arthritis.

Prescribing methotrexate for spinal symptoms is a common error carried over from rheumatoid arthritis, and it delays effective treatment while the patient continues to lose spinal mobility.

- **Biologic therapy for persistent active axial disease:** tumour necrosis factor inhibitors or interleukin-17 inhibitors. **Choose according to the extra-articular pattern** — monoclonal tumour necrosis factor inhibitors are preferred where there is uveitis or inflammatory bowel disease, and **interleukin-17 inhibitors are avoided in inflammatory bowel disease** because they may worsen it.
- **Uveitis: same-day ophthalmology assessment.** Give the patient a card and explicit instructions to attend an eye service directly, without a referral, whenever the eye becomes red and painful. Recurrent untreated uveitis causes permanent visual loss.
- Smoking cessation; **osteoporosis assessment**, since bone density is reduced despite the radiographic sclerosis; and surgery for hip disease or severe spinal deformity.

THE EMERGENCY TO REMEMBER

An ankylosed spine is a long rigid bone and it fractures with trivial trauma — typically at the cervicothoracic junction, and typically unstably, with a high risk of spinal cord injury.

Any patient with ankylosing spondylitis and new neck or back pain after even a minor fall requires urgent computed tomography or magnetic resonance imaging, not reassurance and analgesia. Plain films are unreliable in a fused spine.

Warn the patient, and remember it yourself when one arrives in the emergency department after falling from a chair.

6. Teaching Points and Viva Questions

- A young man whose back pain wakes him at four in the morning and improves with exercise does not have mechanical back pain.
- Ask about the heel, the toe and the eye — the diagnosis is often outside the spine.

- Look for psoriasis yourself, in the places patients do not look.
- Normal radiographs and normal inflammatory markers exclude nothing; magnetic resonance imaging makes the early diagnosis.
- HLA-B27 supports, it does not diagnose.
- Exercise is the treatment. Methotrexate is not.
- A fused spine after a minor fall needs cross-sectional imaging.

Questions you should be able to answer:

- List the features of inflammatory back pain and apply them to this patient.
- Describe how you perform the modified Schober test and what a normal result is.
- His radiographs are normal but the history is classical. What do you do next?
- He also has ulcerative colitis. How does that influence your choice of biologic?
- He falls from a standing height and complains of neck pain. What is your concern and your action?

Case 61 · Vasculitis

CLINICAL VIGNETTE

A **62-year-old man** has had three months of malaise, intermittent fever, aching joints and 9 kg of weight loss. For six weeks he has had a **blocked, crusting nose with blood-stained discharge**, treated twice as sinusitis. For two weeks he has coughed up small amounts of blood. Last week his **right foot became painful and numb and he began tripping over it**.

On examination: temperature 37.9 °C. **Nasal crusting with septal ulceration.** The left eye is red and painful. There is a **palpable purpuric rash over both shins** and a **right common peroneal nerve palsy with foot drop**. Blood pressure 148/92 mmHg.

Urine dipstick: blood +++, protein ++; microscopy shows red cell casts. Creatinine 240 µmol/L (normal six months ago) · C-reactive protein 160 · **proteinase-3 ANCA strongly positive**. Chest radiograph: bilateral nodules, one cavitating.

THE PATTERN THAT MAKES THE DIAGNOSIS

A multisystem illness with constitutional symptoms, a high C-reactive protein, an abnormal urine dipstick and no infection found is a vasculitis until proved otherwise.

Look for the combination: **upper airway disease · lung disease · glomerulonephritis · palpable purpura · mononeuritis multiplex · inflammatory eye disease.** No single feature is diagnostic; the pattern is.

Two findings deserve special weight. Mononeuritis multiplex — asymmetrical, painful, stepwise involvement of named nerves — is close to specific for vasculitis (or diabetes). And **"resistant sinusitis" with systemic features is granulomatosis with polyangiitis** far more often than it is stubborn sinusitis: **examine the nose in every suspected vasculitis.**

1. Think First — Classify by Vessel Size

Size	Diseases and their signature
Large vessel	Giant cell arteritis — over 50, temporal headache, scalp tenderness, jaw claudication, visual loss, high inflammatory markers. Takayasu arteritis — younger, absent pulses, limb claudication, bruits, blood pressure differences between arms.
Medium vessel	Polyarteritis nodosa — skin, nerve, gut and renal artery involvement, hypertension, associated with hepatitis B; typically spares the lungs and is ANCA-negative. Kawasaki disease in children.
Small vessel, ANCA-associated	Granulomatosis with polyangiitis — upper airway, lung, kidney; usually PR3-ANCA. Microscopic polyangiitis — kidney and lung without granulomatous upper airway disease; usually MPO-ANCA. Eosinophilic granulomatosis with polyangiitis — late-onset asthma, nasal polyps, marked eosinophilia, neuropathy and cardiac involvement.
Small vessel, immune complex	IgA vasculitis — purpura on buttocks and legs, arthralgia, abdominal pain, nephritis. Cryoglobulinaemic vasculitis — associated with hepatitis C, low complement. Anti-glomerular basement membrane disease — pulmonary haemorrhage with nephritis.
Variable vessel	Behçet disease — recurrent painful oral and genital ulceration, uveitis, pathergy, and a distinctive tendency to venous thrombosis including at unusual sites. Not rare in this region and easily overlooked.
Secondary and mimics	Connective tissue disease; infection — infective endocarditis, hepatitis B and C, HIV, tuberculosis; drugs — hydralazine, propylthiouracil, and cocaine adulterated with levamisole; malignancy.

2. Focused History

- Constitutional: fever, weight loss, night sweats, malaise, arthralgia and myalgia.
- **Upper airway:** nasal crusting and obstruction, epistaxis, hearing loss, hoarseness, and **stridor from subglottic stenosis**.

- **Chest:** haemoptysis, breathlessness, late-onset asthma.
- **Kidney:** frothy or bloody urine, oedema, hypertension — usually silent, hence the dipstick.
- **Skin:** palpable purpura, ulcers, digital ischaemia, livedo, nodules.
- **Nerve:** numbness or weakness in the territory of named nerves, in a stepwise asymmetrical pattern.
- **Eye:** red painful eye, scleritis, visual loss. **Gut:** abdominal pain, which may mean mesenteric ischaemia.
- **Large vessel questions specifically:** temporal headache, scalp tenderness, **jaw claudication**, visual symptoms, limb claudication.
- **Drugs, hepatitis and HIV risk, and intranasal cocaine** — each produces a convincing vasculitis mimic.

3. Physical Examination

- **Blood pressure in both arms, all peripheral pulses, and auscultation for bruits**; temporal artery tenderness, thickening and pulsation.
- **The nose and upper airway** — crusting, septal ulceration or perforation, saddle deformity.
- Eyes; skin including the shins and digits; **a full neurological examination mapping any deficit to named nerves**; chest; and **a urine dipstick performed by you**.

4. Investigations

- **Immediately:** urinalysis with microscopy, creatinine **with its trend**, C-reactive protein and erythrocyte sedimentation rate, complete blood count (**eosinophilia** in eosinophilic granulomatosis with polyangiitis), chest radiograph.
- **Immunology, sent urgently: ANCA — both proteinase-3 and myeloperoxidase** — anti-glomerular basement membrane antibody, antinuclear and anti-double-stranded DNA antibodies, complement, cryoglobulins, immunoglobulins, rheumatoid factor.
- **Infection screen, which is not optional: blood cultures, echocardiography, hepatitis B and C, HIV, and tuberculosis assessment.**
- **Tissue wherever it can be obtained:** renal biopsy, nasal or lung biopsy, skin biopsy, nerve or muscle biopsy; **temporal artery biopsy or ultrasound** in suspected giant cell arteritis.
- **Imaging:** computed tomography of the chest (nodules, cavitation, alveolar haemorrhage) and sinuses; and in large vessel disease, vascular ultrasound, magnetic resonance angiography or positron emission tomography.
- **ANCA supports the diagnosis but does not make it, a negative ANCA does not exclude it, and the titre is an unreliable guide to relapse.** Tissue and the clinical picture remain the arbiters.

THE MIMIC THAT MUST BE EXCLUDED FIRST

Infective endocarditis reproduces vasculitis almost exactly — fever, weight loss, raised inflammatory markers, purpura, splinter haemorrhages, glomerulonephritis, positive rheumatoid factor, low complement, and even a positive ANCA.

Immunosuppressing a patient with endocarditis is catastrophic. So take blood cultures and arrange echocardiography **before** high-dose steroids, in every patient in whom the diagnosis is not already secure. Tuberculosis and HIV deserve the same caution.

This is the single commonest way that a confident vasculitis diagnosis goes badly wrong.

TWO SITUATIONS THAT WILL NOT WAIT

Pulmonary–renal syndrome — haemoptysis with an active urinary sediment — or a **creatinine rising over days**, is an emergency. **Same-day nephrology and rheumatology involvement, urgent ANCA and anti-glomerular basement membrane antibody, urgent biopsy — and where suspicion is high, immunosuppression started before the results**, with plasma exchange for anti-glomerular basement membrane disease and severe alveolar haemorrhage. See Case 33.

Giant cell arteritis with any visual symptom — high-dose corticosteroid immediately and same-day ophthalmology. Do not wait for the biopsy: it remains informative for a week or two after steroids are started, whereas the vision does not come back. See Seminar 5.

5. Management

- **Induction for organ-threatening ANCA-associated vasculitis:** high-dose corticosteroid with **rituximab or cyclophosphamide**; plasma exchange in selected severe renal disease and pulmonary haemorrhage; **avacopan** as a complement-pathway inhibitor allowing substantial steroid sparing.
- **Maintenance for years**, with rituximab, azathioprine, methotrexate or mycophenolate. **Relapse is common**, which is why follow-up is lifelong.

TREATING THE TREATMENT

The treatment causes as much harm as the disease if it is not managed deliberately.

Co-trimoxazole for Pneumocystis prophylaxis · bone protection · gastric protection · glucose monitoring · vaccination **before** immunosuppression where possible · **screening for hepatitis B and latent tuberculosis before rituximab**.

Cyclophosphamide specifically: infertility — offer gamete storage before the first dose — haemorrhagic cystitis, later bladder cancer, and marrow suppression. The fertility conversation must happen at the start, not after four cycles.

- **Giant cell arteritis:** corticosteroid with **tocilizumab** as a steroid-sparing agent, tapering over 12 to 18 months, with bone protection throughout.
- **Takayasu arteritis:** corticosteroid with a steroid-sparing agent, vascular imaging surveillance, and **blood pressure measured in the limb with the best flow**, since a subclavian stenosis will give a falsely low reading.
- **Behçet disease:** colchicine for mucocutaneous disease; immunosuppression or anti-tumour-necrosis-factor therapy for ocular, neurological or vascular involvement; urgent ophthalmology for uveitis.
- **Monitoring: symptoms, C-reactive protein, creatinine and a urine dipstick at every single visit.** The dipstick is the cheapest and earliest detector of renal relapse.

6. Teaching Points and Viva Questions

- Multisystem illness plus a high C-reactive protein plus an abnormal urine is vasculitis until proved otherwise.

- Examine the nose and dipstick the urine — both take seconds and both change the diagnosis.
- Mononeuritis multiplex is nearly specific for vasculitis or diabetes.
- Take blood cultures and an echocardiogram before high-dose steroids.
- ANCA supports, does not prove, and does not reliably track relapse.
- Start steroids in giant cell arteritis before the biopsy.
- Offer gamete storage before cyclophosphamide.

Questions you should be able to answer:

- Which six features of this presentation together make a vasculitis likely?
- What does his foot drop represent, and why is it useful diagnostically?
- What must be excluded before you give him methylprednisolone, and how?
- His ANCA is negative but the picture is unchanged. Does that alter your management?
- He is 62 and wants to know about fertility before cyclophosphamide. What do you offer?

Case 62 · Gout and Calcium Pyrophosphate Deposition Disease

CLINICAL VIGNETTE

A **56-year-old man** presents with his fourth attack in two years. Three days ago he woke at 4 a.m. with pain in the right great toe, which within a few hours became so severe that he could not bear the weight of a bedsheet. Previous attacks affected the same joint and, once, the left knee.

He takes bendroflumethiazide for hypertension, drinks five or six beers most evenings, and has chronic kidney disease with an estimated filtration rate of 48.

On examination: body mass index 33 kg/m^2, blood pressure 152/94 mmHg. The right first metatarsophalangeal joint is red, hot, swollen and exquisitely tender. **There are firm chalky nodules on the helix of the right ear and over both olecranon processes.**

Serum urate 520 µmol/L. Joint aspirate: negatively birefringent needle-shaped crystals; Gram stain and culture negative.

1. Recognising It

- **The attack:** abrupt onset, often waking the patient in the early hours, **maximal within 12 to 24 hours**, with pain out of all proportion to the size of the joint, and self-limiting over seven to ten days even untreated.
- **The joints:** the first metatarsophalangeal joint — podagra — then the instep, ankle and knee. Chronic disease becomes polyarticular and involves the upper limbs, and can closely mimic rheumatoid arthritis.
- **Tophi** — firm chalky deposits on the **helix of the ear, the olecranon, the Achilles tendon, the finger pulps and extensor surfaces**. Look for them; they establish that this is longstanding disease requiring urate-lowering therapy.
- **Provoking factors:** alcohol, especially beer and spirits; purine-rich food; dehydration; **diuretics**; surgery and acute illness; and, paradoxically, **the initiation of urate-lowering therapy**.
- **Drugs that raise urate:** thiazide and loop diuretics, low-dose aspirin, ciclosporin and tacrolimus, pyrazinamide and ethambutol.
- **Comorbidity, which is the reason gout matters beyond the joint:** chronic kidney disease, hypertension, obesity, the metabolic syndrome, ischaemic heart disease and heart failure. **Gout is a marker of cardiovascular risk and should trigger its assessment.**

2. Investigations

- **Joint aspiration with polarised microscopy is definitive** — negatively birefringent needle-shaped crystals — **and it simultaneously excludes septic arthritis, which coexists with gout** (Seminar 6).

THE SERUM URATE, AND WHY THE TIMING MATTERS

A normal urate during an acute attack does not exclude gout, because levels commonly fall during the attack. **And a raised urate does not diagnose it**, because most hyperuricaemic people never develop gout.

So measure the urate four to six weeks after the attack has settled, to establish a baseline and a treatment target — not during it, when the number will mislead in either direction.

- Renal function, glucose, lipids, complete blood count and liver function — for the comorbidity and to guide drug choice.
- **Radiographs in chronic disease:** periarticular erosions with **overhanging edges and preserved joint space**. Ultrasound (the double contour sign) and dual-energy computed tomography where the diagnosis is uncertain and aspiration is not possible.

3. Treating the Attack

- **Any one of an anti-inflammatory drug, colchicine, or a corticosteroid — and the choice is made by comorbidity, not by preference.**
- **In this patient, with chronic kidney disease and hypertension, an anti-inflammatory drug is a poor choice.** Colchicine requires **dose reduction in renal impairment** and interacts dangerously with statins, macrolides, ciclosporin and verapamil. **Oral or intra-articular corticosteroid is often the safest option**, and an intra-articular injection is ideal for a single accessible joint once sepsis is excluded.
- Treat within hours rather than days; rest, ice and elevation help.

THE INSTRUCTION MOST OFTEN GOT WRONG ON THE WARD

Do not start urate-lowering therapy during an acute attack — but if the patient is already taking allopurinol, do not stop it either.

Stopping allopurinol during a flare prolongs the attack and destabilises long-term control, and it is one of the commonest errors made on admission. The drug continues; the flare is treated alongside it.

4. Urate-Lowering Therapy — the Part Done Badly

- **Indications:** two or more attacks a year, **tophi**, chronic gouty arthropathy, radiographic joint damage, urate renal stones, chronic kidney disease, or diuretic therapy that cannot be withdrawn. **This patient qualifies several times over.**

TREAT TO A TARGET, NOT TO A DOSE

Start allopurinol low — 100 mg, or 50 mg in chronic kidney disease — and titrate upwards every two to four weeks against the measured urate.

Treat to target: a serum urate below 360 µmol/L, or below 300 µmol/L where there are tophi or severe disease. Crystals dissolve below the saturation point and tophi shrink; above it, they do not.

"Allopurinol did not work" almost always means allopurinol was left at 100 or 300 mg without anyone measuring the urate. The dose is whatever achieves the target, and in many patients that is 400 to 600 mg or more.

- **Cover the first three to six months of urate-lowering therapy with colchicine or an anti-inflammatory drug**, because mobilising urate provokes flares — **and warn the patient that attacks may initially increase.** Without that warning they will conclude the drug is causing the problem and stop it.
- **Never stop urate-lowering therapy because of a flare.** Explain at the outset that treatment is long term and that gout becomes, in practice, a curable disease once urate is held below target.
- **Febuxostat** where allopurinol is not tolerated, with caution in established cardiovascular disease; uricosuric agents; and pegloticase in refractory tophaceous disease. **Consider HLA-B*5801 testing before allopurinol in populations where it is prevalent**, because of the risk of severe cutaneous reactions.

- **Review the diuretic** — switching to an alternative antihypertensive is often the single most useful change, and **losartan and calcium channel blockers lower urate** while thiazides raise it.
- Weight reduction, reduction of beer, spirits and sugar-sweetened drinks, hydration, and treatment of the cardiovascular and metabolic risk.

CALCIUM PYROPHOSPHATE DEPOSITION DISEASE — "PSEUDOGOUT"

Older patients, and different joints — typically the knee and wrist rather than the great toe.

Aspirate shows positively birefringent rhomboid crystals, and radiographs show **chondrocalcinosis**.

Acute attacks are treated exactly as for gout, but **there is no role for urate-lowering therapy**.

In a young patient, or where the disease is florid, look for an underlying cause: haemochromatosis, hyperparathyroidism, hypomagnesaemia or hypophosphatasia.

5. Teaching Points and Viva Questions

- Aspirate to confirm the crystals and to exclude sepsis — they coexist.
- A normal urate during an attack means nothing; measure it six weeks later.
- Choose the acute drug by the comorbidity, not by habit.
- Never stop allopurinol during a flare.
- Titrate allopurinol to a urate target, and cover the first months with prophylaxis.
- Warn the patient that attacks may increase at first, or they will stop the drug.
- Look for tophi, and review the diuretic.

Questions you should be able to answer:

- Why would you avoid an anti-inflammatory drug in this man, and what would you give instead?
- He is admitted with an attack while taking allopurinol. What do you do with it?
- What is your urate target here, and how will you get there?
- He returns after six weeks of allopurinol saying it has made his gout worse. What has happened and what do you say?
- A 78-year-old has an acute hot knee with rhomboid crystals. What is the diagnosis and does he need allopurinol?

Case 63 · Antiphospholipid Syndrome

CLINICAL VIGNETTE

A **32-year-old woman** is referred after a **second unprovoked deep vein thrombosis**. The first was at the age of 26, while she was taking the combined oral contraceptive pill.

Her obstetric history is of **three first-trimester miscarriages** and a **stillbirth at 24 weeks** with placental insufficiency. She has migraine with aura.

On examination: a mottled, net-like purplish discolouration over both thighs — **livedo reticularis**. No synovitis, no rash elsewhere. Blood pressure 138/86 mmHg.

Platelets 96 × 10^9/L · activated partial thromboplastin time prolonged and does not correct on mixing with normal plasma · lupus anticoagulant positive · anticardiolipin IgG high · anti-beta-2 glycoprotein I high — all confirmed on a repeat sample 12 weeks later. Antinuclear antibody weakly positive, anti-double-stranded DNA negative.

THE DEFINITION, AND WHY THE REPEAT TEST MATTERS

Thrombosis, or defined pregnancy morbidity, plus persistently positive antiphospholipid antibodies on two occasions at least 12 weeks apart.

The 12-week interval is not a formality. Antiphospholipid antibodies appear transiently after infection and in many healthy people, and a single positive result labels a patient with a lifelong diagnosis and lifelong anticoagulation on inadequate evidence. **Never diagnose the syndrome on one sample.**

The three antibodies: lupus anticoagulant, anticardiolipin, and anti-beta-2 glycoprotein I. **"Triple positive" carries the highest risk of recurrence** and the strongest indication for warfarin over other agents.

1. The Clinical Features

Domain	Features
Venous thrombosis	Deep vein thrombosis and pulmonary embolism — and thrombosis at unusual sites: cerebral venous sinus, splanchnic, hepatic, retinal. Unusual-site thrombosis in a young person should always prompt testing.
Arterial thrombosis	Stroke or transient ischaemic attack in a young person without conventional risk factors; myocardial infarction; limb ischaemia.
Obstetric	Three or more consecutive miscarriages before 10 weeks · one or more fetal deaths after 10 weeks · delivery before 34 weeks for pre-eclampsia or placental insufficiency.
Haematological	Thrombocytopenia — and note the paradox that these patients clot despite a low platelet count — and autoimmune haemolytic anaemia.
Skin	Livedo reticularis, skin ulcers, digital ischaemia and gangrene.
Cardiac	Valve thickening and non-infective (Libman–Sacks) vegetations, which may embolise.
Neurological	Migraine, chorea, cognitive impairment, transverse myelitis, seizures.
Renal	Antiphospholipid nephropathy with hypertension and proteinuria.

- **Primary**, or **secondary to systemic lupus erythematosus** and other autoimmune disease — so screen for lupus in every patient (Case 59).

THE LABORATORY PARADOX

A prolonged activated partial thromboplastin time that does not correct on mixing, in a patient who thromboses rather than bleeds.

The lupus anticoagulant is an in-vitro artefact — it interferes with phospholipid-dependent clotting assays — while in vivo it is **prothrombotic**. Students reasonably expect a prolonged clotting time to mean bleeding, and here it means the opposite.

Two practical consequences: anticoagulation and an acute thrombosis both interfere with the assays, so **timing of the test matters**; and the prolonged time should not prompt transfusion of plasma.

2. Catastrophic Antiphospholipid Syndrome

EMERGENCY

Thrombosis in three or more organs within days to a week, with microvascular occlusion and multiorgan failure. Rare, and with a high mortality.

The usual triggers are infection, surgery, pregnancy, and — importantly — withdrawal or interruption of anticoagulation.

Treatment: full anticoagulation, high-dose corticosteroid, and plasma exchange or intravenous immunoglobulin, with treatment of the trigger and critical care support.

Which is the practical reason never to stop anticoagulation abruptly in these patients, and to plan perioperative bridging carefully rather than simply omitting doses.

3. Management

THE ANTICOAGULANT CHOICE

Anticoagulate with a vitamin K antagonist. Direct oral anticoagulants are inferior in antiphospholipid syndrome — particularly in triple-positive patients and in arterial thrombosis — and should be avoided.

This is one of the few remaining firm indications for warfarin in venous thromboembolism, and it is easily missed when a young woman with a deep vein thrombosis is started on a direct oral anticoagulant before anyone has asked why she clotted. **The obstetric history is the clue that should prompt testing** (Seminar 11).

- **Duration: indefinite** after an unprovoked thrombosis in confirmed antiphospholipid syndrome. In arterial events, anticoagulation is used, sometimes with aspirin, and a higher target range is considered after recurrence.
- **Antibody-positive but never thrombosed: do not anticoagulate.** Consider low-dose aspirin in high-risk profiles, and concentrate on modifiable risk — **stop smoking, avoid oestrogen-containing contraception, treat hypertension and lipids, and give thromboprophylaxis around surgery, immobility and pregnancy.**

PREGNANCY

Aspirin plus low-molecular-weight heparin from early pregnancy, continued for six weeks after delivery.

Warfarin is teratogenic and direct oral anticoagulants are contraindicated in pregnancy — so the anticoagulant must be changed **before** conception, not after a positive test.

Joint obstetric and rheumatology care throughout; hydroxychloroquine may improve outcomes; and close surveillance for **pre-eclampsia and fetal growth restriction**.

Plan the pregnancy rather than react to it. For a 32-year-old with three miscarriages and a stillbirth, this conversation is the most valuable thing in the consultation.

- Screen for systemic lupus erythematosus; consider hydroxychloroquine; correct vitamin D; and manage cardiovascular risk actively, since these patients have accelerated arterial disease.

4. Teaching Points and Viva Questions

- Unprovoked thrombosis in a young person, thrombosis at an unusual site, or recurrent pregnancy loss should prompt testing.
- Confirm on a second sample at least 12 weeks later. Never diagnose on one.
- A prolonged activated partial thromboplastin time that does not correct, in a patient who clots.
- Warfarin, not a direct oral anticoagulant.
- Heparin and aspirin in pregnancy, changed over before conception.
- Do not anticoagulate asymptomatic antibody positivity.
- Interrupting anticoagulation can precipitate catastrophic disease.

Questions you should be able to answer:

- Which parts of her history should have prompted testing after the first thrombosis?
- Why was the test repeated at 12 weeks?
- Explain how a patient with a prolonged clotting time thromboses.
- She was started on rivaroxaban in the emergency department. What do you do and why?
- She wants to conceive next year. Set out your plan over the next twelve months.

The Neurology Block

Acute ischaemic stroke, seizures and status epilepticus, acute neuromuscular weakness, peripheral neuropathy, myelopathy and demyelination, and the extrapyramidal disorders.

Cases 64–69 · 8,642 words

This block covers the neurological teaching of both internal medicine courses. The **first course** supplies cases 64 and 66; the **second course** supplies cases 67 and 69.

Case	Lecture it serves
System opener: the neurological history and examination	History taking in neurology; physical examination in neurology; localisation in neurology
Case 64 — Acute ischaemic stroke	Stroke
Case 65 — Seizures and status epilepticus	Seizure disorder and epilepsy; seizure seminar
Case 66 — Acute neuromuscular weakness	Neuromuscular and muscle disorders
Case 67 — Peripheral neuropathy	Peripheral neuropathies
Case 68 — Myelopathy and demyelinating disease	Myelopathies and demyelinating disorders
Case 69 — Parkinson disease and the extrapyramidal disorders	Parkinson and extrapyramidal disorders

The localisation lecture is served by the system opener, which sets out the upper versus lower motor neurone distinction and the site-by-site table. **Coma** is Seminar 10 and **dementia** is a Part Two case; both are second-course seminars.

System Opener · The Neurological History and Examination

THE TWO QUESTIONS, IN THIS ORDER

Where is the lesion? Then, what is the lesion?

The **examination** answers the first question by localising the problem along the neuraxis. The **history — specifically the time course —** answers the second, because pathology has a characteristic tempo.

Students who reverse this order end up with a list of diagnoses and no way to choose between them.

The history — tempo tells you the pathology

Time course	Pathology
Seconds to minutes, maximal at onset	Vascular — ischaemic stroke, haemorrhage; or a seizure
Minutes to an hour, spreading	Migraine aura (spreads and evolves over minutes), seizure with spread, metabolic disturbance
Hours to days	Infection, inflammation, demyelination
Weeks to months, progressive	Tumour, chronic inflammatory disease, degenerative disease
Episodic and stereotyped, with full recovery between	Seizures, migraine, transient ischaemic attack

- **Make the patient describe the symptom rather than name it.** "Dizzy" may mean vertigo, presyncope, unsteadiness or anxiety, and these have entirely different differentials. "Numb" may mean loss of sensation or weakness. Ask what they actually felt and what they could not do.
- **Obtain a witness account** for any episode involving altered consciousness. Without it, blackouts cannot reliably be diagnosed — and the witness is frequently in the corridor and never asked.
- Record **handedness**, functional impact, occupation, and **driving**, which has legal consequences in stroke and epilepsy.

The examination — localise before you diagnose

First: upper or lower motor neurone?

	Upper motor neurone	Lower motor neurone
Tone	Increased, spastic, clasp-knife	Reduced, flaccid
Reflexes	Brisk	Reduced or absent
Plantar response	Extensor	Flexor or absent
Wasting	Absent, or late from disuse	Prominent
Fasciculation	Absent	Present
Weakness pattern	Pyramidal — extensors weak in the arm, flexors weak in the leg	Depends on the nerve, root or segment involved

A caution: in the first hours to days of an acute upper motor neurone lesion — an acute stroke, or spinal shock after cord injury — the limb may be **flaccid with absent reflexes**. The upper motor neurone signs develop later. Do not localise on tone alone in the acute setting.

Then: where along the neuraxis?

Site	The findings that place it there
Cortex	Higher cortical dysfunction — dysphasia, neglect, apraxia; cortical sensory loss; homonymous visual field defect; seizures
Brainstem	Crossed signs — an ipsilateral cranial nerve palsy with contralateral limb signs. Also diplopia, nystagmus, dysarthria, dysphagia, vertigo, and altered consciousness
Spinal cord	A sensory level, sphincter disturbance, bilateral signs below the lesion, and back pain. This is the localisation you cannot afford to miss
Root	Dermatomal sensory loss with myotomal weakness, loss of one reflex, and pain radiating in the root distribution
Peripheral nerve	Distal, often length-dependent; sensory and motor together; areflexia; glove-and-stocking loss in polyneuropathy
Neuromuscular junction	Fatigable weakness with no sensory loss and preserved reflexes; ptosis, diplopia and bulbar involvement
Muscle	Symmetrical proximal weakness, no sensory loss, reflexes preserved until late, raised creatine kinase

The sequence

- **Higher function and speech** — orientation, attention, and whether the problem is **dysphasia** (a language disorder — expressive, receptive or mixed), **dysarthria** (a motor speech disorder with intact language), or **dysphonia**.
- **Cranial nerves**, including **fundoscopy** and visual fields.
- **Motor:** inspection for wasting and fasciculation, tone, power graded on the Medical Research Council scale, reflexes, plantars, coordination.
- **Sensory**, tailored to the hypothesis rather than performed exhaustively — look for a level, a dermatome, or a glove-and-stocking pattern.
- **Gait** — the single most informative part of the neurological examination, and the one most often omitted because the patient is already on the bed.

Case 64 · Acute Ischaemic Stroke

CLINICAL VIGNETTE

A **68-year-old man** collapsed into a chair at **08:15** while eating breakfast. His wife, who was with him, says he suddenly could not speak and his right arm fell to his side. He arrives in the emergency department at **09:40**.

He has hypertension and takes amlodipine. He is not on any anticoagulant. No previous stroke, surgery or bleeding.

On examination: alert but **globally aphasic**. Gaze is deviated to the left. There is a dense right hemiplegia with a right homonymous hemianopia and right facial weakness. **Capillary glucose 7.2 mmol/L.** Blood pressure 178/98 mmHg. **The pulse is irregularly irregular.**

Non-contrast computed tomography of the head: no haemorrhage; a hyperdense left middle cerebral artery. Computed tomographic angiography shows an **occlusion of the left middle cerebral artery**.

TIME IS BRAIN

Roughly **1.9 million neurons are lost every minute** that a large vessel occlusion goes untreated. Every step below is organised around time.

Target door-to-needle time for thrombolysis is under 60 minutes, and shorter is better. The history, examination, imaging and consent all happen in parallel, not in sequence.

1. Focused History — Four Things, Fast

- **The time of onset, or the time the patient was last known to be well.** This is the single most important fact in the entire encounter. If he woke with the deficit, the clock starts when he was last seen normal — although advanced imaging now allows selected patients outside the conventional window to be treated.
- **Contraindications to thrombolysis:** recent surgery or major trauma, active bleeding, previous intracranial haemorrhage, known aneurysm or vascular malformation, recent stroke, **anticoagulant use and the time of the last dose**, and any bleeding disorder.
- **Was there a seizure at onset, or a preceding headache and vomiting?** The first raises a postictal deficit; the second raises haemorrhage.
- **Premorbid function**, which shapes decisions about aggressive intervention — obtained from the family in a few sentences.

Stroke mimic	What gives it away
Hypoglycaemia	The reason you check the glucose before anything else. It can produce a dense hemiplegia and aphasia that resolve completely with glucose.
Postictal (Todd) paresis	Witnessed seizure, gradual recovery, previous epilepsy
Migraine with aura	Younger patient, positive symptoms spreading over minutes, headache
Sepsis or metabolic upset unmasking an old deficit	Fever, delirium, a previous stroke in the same territory
Subdural haematoma or tumour	Longer history, fluctuation, headache, imaging
Functional neurological disorder	Inconsistent findings, give-way weakness, positive Hoover sign

2. Physical Examination

- **Airway, breathing, circulation, conscious level, and capillary glucose** — in that order, and glucose within the first minute.
- **A formal stroke severity score**, which guides thrombectomy decisions and allows objective comparison later.
- Blood pressure in both arms, cardiac rhythm and murmurs, carotid bruits, peripheral pulses, temperature, and a search for a source of embolism including signs of endocarditis.

BEFORE ANYTHING IS GIVEN BY MOUTH

Nothing by mouth until a swallow screen has been performed — no water, no food, and **no oral medication, including the aspirin**.

Aspiration pneumonia is a leading cause of death after stroke and is largely preventable. A bedside swallow screen takes minutes and can be done by trained nursing staff. Prescribing oral aspirin to a dysphagic patient with a dense hemiplegia is a common and consequential error.

3. Localising the Stroke

Syndrome	Features
Total anterior circulation	All three of: higher cortical dysfunction, homonymous hemianopia, and hemiparesis or hemisensory loss. This patient.
Partial anterior circulation	Two of the three, or isolated higher cortical dysfunction
Lacunar	Pure motor, pure sensory, sensorimotor, ataxic hemiparesis, or dysarthria with a clumsy hand — and no cortical signs and no visual field defect
Posterior circulation	Cranial nerve palsy with contralateral deficit, bilateral signs, cerebellar signs, conjugate gaze disturbance, or isolated homonymous hemianopia

THE STROKES THAT GET MISSED

Posterior circulation strokes present with **vertigo, vomiting, unsteadiness and nystagmus** — and are repeatedly misdiagnosed as labyrinthitis and sent home.

Warning features: inability to stand or walk unaided, new headache or neck pain, any other brainstem sign, and vascular risk factors. In acute vestibular syndrome, a structured bedside oculomotor examination distinguishes peripheral from central causes better than early imaging does — **computed tomography is insensitive in the posterior fossa.**

4. Investigations

- **Immediate non-contrast computed tomography of the head** — its first purpose is to exclude haemorrhage. Early ischaemic signs include loss of grey–white differentiation, loss of the insular ribbon, sulcal effacement, and the **hyperdense artery sign** of thrombus within the vessel.
- **Computed tomographic angiography** to identify a large vessel occlusion, which determines eligibility for thrombectomy. **Perfusion imaging** selects patients for treatment in the extended time window.
- Glucose, complete blood count, coagulation screen, urea and electrolytes, and an **electrocardiogram**, which here shows atrial fibrillation and identifies the mechanism.

- **Later, to determine aetiology and secondary prevention:** prolonged cardiac monitoring for paroxysmal atrial fibrillation, carotid imaging, echocardiography, lipids and glycated haemoglobin. **Magnetic resonance imaging with diffusion-weighted sequences** where the diagnosis is uncertain or the stroke is posterior.

- **In a young patient**, extend the workup: arterial dissection, patent foramen ovale, thrombophilia, vasculitis, and infective endocarditis.

5. Management

Reperfusion

- **Intravenous thrombolysis within 4.5 hours** of onset in the absence of contraindications. **Blood pressure must be below 185/110 mmHg before treatment** and controlled afterwards.

- **Mechanical thrombectomy for large vessel occlusion**, conventionally within 6 hours and extending to 24 hours in patients selected by perfusion imaging. This patient has a middle cerebral artery occlusion and should be referred for thrombectomy **at the same time** as thrombolysis is being given.

- **Do not delay transfer to a thrombectomy centre in order to complete a thrombolysis infusion.** The two run in parallel.

PERMISSIVE HYPERTENSION

Do not lower the blood pressure in acute ischaemic stroke unless it exceeds approximately 220/120 mmHg, thrombolysis is planned, or there is another indication such as aortic dissection or heart failure.

The ischaemic penumbra has lost autoregulation and depends on systemic pressure for perfusion. Lowering the pressure converts salvageable tissue into infarct. The instinct to treat a reading of 190/100 is strong, and it is wrong here.

Note that the opposite applies in **intracerebral haemorrhage**, where early blood pressure lowering is appropriate.

The first 48 hours

- **Stroke unit care** — the intervention that benefits the largest number of patients, more than any drug.

- **Aspirin 300 mg** — immediately if not thrombolysed, or after 24 hours and a repeat scan if thrombolysed. Given rectally or by nasogastric tube if swallowing is unsafe.

- Maintain normoglycaemia and normothermia; oxygen only if hypoxic; **intermittent pneumatic compression** rather than routine early heparin for venous thromboembolism prophylaxis; early mobilisation and pressure care.

- **Malignant middle cerebral artery syndrome** — deteriorating consciousness with massive infarction in the first 48 hours. **Decompressive hemicraniectomy** improves survival in selected younger patients and must be discussed early, before the patient deteriorates beyond eligibility.

Secondary prevention and rehabilitation

- **Anticoagulation for atrial fibrillation**, with timing determined by infarct size — larger infarcts are anticoagulated later because of haemorrhagic transformation risk.

- Antiplatelet therapy where the mechanism is not cardioembolic; **high-intensity statin**; blood pressure control started after the acute phase; diabetes and smoking.

- **Carotid endarterectomy within two weeks** for symptomatic severe stenosis — the benefit falls sharply with delay.
- **Multidisciplinary rehabilitation** — physiotherapy, occupational therapy, speech and language therapy; nutrition; screening for post-stroke depression; driving advice; and, for an aphasic patient, deliberate attention to how consent and communication are managed.

6. Teaching Points and Viva Questions

- Check the glucose before anything else. Hypoglycaemia mimics everything.
- Time last known well, recorded to the minute, drives every subsequent decision.
- Do not treat the blood pressure in ischaemic stroke — the penumbra depends on it.
- Swallow screen before the first tablet or sip.
- Vertigo with ataxia and vascular risk factors is a posterior circulation stroke until proved otherwise, and the computed tomogram will not reassure you.
- Thrombolysis and thrombectomy referral happen together, not one after the other.

Questions you should be able to answer:

- Classify this stroke syndrome and name the vessel.
- His blood pressure is 196/104. What do you do, and why?
- He was found on the floor at 07:00 having gone to bed at 23:00. What time do you use, and what are his options?
- The nurse asks whether she can give his morning tablets. What is your answer?
- When would you start anticoagulation for his atrial fibrillation?

Case 65 · Seizures and Status Epilepticus

CLINICAL VIGNETTE

A **23-year-old woman** with known epilepsy is brought in after a witnessed generalised convulsion at work lasting about two minutes. She had a second convulsion in the ambulance without regaining awareness. **As she is transferred to the trolley a third seizure begins, and it is still continuing six minutes later.**

Her colleague reports that she stopped her levetiracetam about two weeks ago. She had been sleeping badly and had a feverish illness last week.

On arrival: convulsing, cyanosed around the lips, oxygen saturation 88%. Temperature 37.8 °C. **Capillary glucose 6.4 mmol/L.**

THE DEFINITION THAT DETERMINES YOUR ACTION

A seizure lasting 5 minutes or more, or repeated seizures without recovery of consciousness in between, is status epilepticus and must be treated as such.

The older 30-minute definition is obsolete. Five minutes is the operational trigger, because most self-limiting seizures have stopped by two minutes and the longer a seizure runs the harder it becomes to terminate.

This patient is in status epilepticus. Treatment starts now.

1. Managing Status Epilepticus

Time	Action
0–5 minutes	Airway, high-flow oxygen, recovery position, suction. Capillary glucose. Intravenous access and bloods. Cardiac and oxygen saturation monitoring. Note the time the seizure began.
5–20 minutes — first line	A benzodiazepine: intravenous lorazepam, or intramuscular or buccal midazolam where there is no access. May be repeated once after 5–10 minutes. In alcohol dependence or malnutrition, give thiamine before or with any glucose.
20–40 minutes — second line	An intravenous antiseizure drug: levetiracetam, sodium valproate — avoided in girls and women of childbearing potential — or phenytoin, which requires cardiac monitoring, a controlled infusion rate, and must not be given in a dextrose-containing line.
40–60 minutes — refractory status	General anaesthesia with intubation and ventilation: midazolam, propofol or thiopental infusion, with continuous electroencephalographic monitoring in intensive care.
Throughout	Find and treat the cause. Consider eclampsia (magnesium sulfate), isoniazid toxicity (pyridoxine), meningitis, and correct sodium, calcium and magnesium.

THE COMMONEST ERROR

The commonest reason status epilepticus fails to respond to first-line treatment is that the benzodiazepine was under-dosed, or given only once.

Give the full weight-appropriate dose, and give the second dose if the first does not work. Reluctance — usually a fear of respiratory depression — leads to prolonged seizing, which causes far more harm than the drug.

- **Complications to anticipate:** hypoxia and aspiration, **rhabdomyolysis with acute kidney injury**, hyperthermia, arrhythmia, lactic acidosis, fractures and dislocations, and neuronal injury from prolonged seizure activity.

2. Once She Has Stopped — the History

Get the witness account. A seizure diagnosis made without one is unreliable, and the witness is usually available in the department for only a short time.

- **Before:** what she was doing, any warning or aura, posture, and triggers such as sleep deprivation, alcohol, missed medication or flashing lights.
- **During:** focal onset or generalised from the start, head or eye deviation, duration, colour change, **lateral tongue biting** — which is relatively specific — incontinence, and injury.
- **After:** duration of confusion, **focal weakness (Todd paresis)**, headache, muscle pain.
- **In a known epileptic, find the precipitant:** missed or stopped medication, a new interacting drug, infection, sleep deprivation, alcohol, or menstruation.

	Seizure	Syncope	Psychogenic non-epileptic attack
Onset	Sudden, may have aura	Lightheadedness, nausea, greying vision, sweating	Often gradual, situational
Duration	Usually 1–3 minutes	Seconds	Often prolonged, waxing and waning
Eyes	Open, may deviate	Open or closed	Closed and actively resisting opening
Movements	Rhythmic, synchronous, decreasing frequency	Brief irregular jerks may occur	Asynchronous, side-to-side head movement, pelvic thrusting
Recovery	Postictal confusion, often prolonged	Rapid and complete	Rapid; may weep; awareness often retained

3. Investigations

- **Glucose, sodium, calcium, magnesium**, complete blood count, liver and renal function, **creatine kinase**, and drug levels where relevant. Toxicology and a **pregnancy test**. Blood cultures if febrile.
- **A raised lactate is expected immediately after a generalised convulsion** and clears within an hour or two. It is a useful confirmatory finding and is regularly misread as evidence of sepsis or shock.
- **Computed tomography of the head** for a first seizure with a focal deficit, persistent alteration of consciousness, head injury, fever, anticoagulation, immunosuppression or known malignancy.
- **Lumbar puncture** where meningitis or encephalitis is suspected, with imaging first where indicated.
- **Electroencephalography** supports the diagnosis and classifies the epilepsy syndrome, but **a normal recording does not exclude epilepsy** — most patients are normal between seizures. **Magnetic resonance imaging** is the structural investigation of choice in focal epilepsy.

4. Longer-Term Management

- **Match the drug to the seizure type.** Focal epilepsy: lamotrigine, levetiracetam, carbamazepine. Generalised epilepsy: valproate, lamotrigine, levetiracetam. **Carbamazepine can worsen generalised epilepsies** — classification matters.

VALPROATE AND WOMEN OF CHILDBEARING POTENTIAL

Sodium valproate must not be used in girls or in women of childbearing potential unless no alternative exists and stringent pregnancy prevention conditions are met.

It carries a high risk of major congenital malformation and of neurodevelopmental disorders in exposed children. This is one of the clearest prescribing rules in modern neurology, and it applies from childhood onwards — not from the moment a woman announces she is planning pregnancy.

- **After a first unprovoked seizure, treatment is not automatic.** It depends on the risk of recurrence — an abnormal electroencephalogram, a structural lesion, a focal or nocturnal seizure — and on the patient's own priorities, including driving and occupation.

THE MOST IMPORTANT QUESTION OF THE ADMISSION

This patient stopped her medication two weeks ago. **Find out why, without judgement** — cost, side effects, feeling well, forgetting, stigma, or not understanding that treatment is long term. Each has a different remedy, and none is addressed by simply restarting the same prescription.

Non-adherence is the commonest precipitant of status epilepticus in a known epileptic. The consultation that explores it is more valuable than the one that adds a second drug.

- **Driving.** The patient must be advised not to drive and to inform the licensing authority. **Have the conversation and document it** — it is a legal obligation as well as a clinical one.
- **Safety advice:** showers rather than baths, never swim alone, caution with heights, unguarded machinery and cooking, and a rescue medication plan taught to the family.
- **Women:** folic acid; interactions between enzyme-inducing drugs and hormonal contraception in both directions; and preconception counselling well before pregnancy.
- **Discuss sudden unexpected death in epilepsy** honestly. The risk is reduced by good seizure control and by adherence, which is itself a reason to have the conversation.

5. Teaching Points and Viva Questions

- Five minutes defines status epilepticus. Start treating at five, not at thirty.
- Under-dosing the benzodiazepine is the commonest reason status persists.
- Thiamine before glucose in anyone malnourished or alcohol-dependent.
- A raised lactate after a convulsion is expected, not alarming.
- A normal electroencephalogram does not exclude epilepsy.
- Ask why she stopped the tablets, and document the driving conversation.

Questions you should be able to answer:

- At what point did this become status epilepticus, and what is your first drug?
- She is still fitting after two doses of lorazepam. What next, and in what order?
- Her creatine kinase is 8400. What is the complication and how do you manage it?

- How would you distinguish this from a psychogenic non-epileptic attack?
- She asks when she can drive again, and whether she can take valproate. Answer both.

Case 66 · Acute Neuromuscular Weakness

CLINICAL VIGNETTE

A **38-year-old man** describes five days of progressive weakness. It began as difficulty climbing stairs, then spread to his thighs, and today he cannot lift a cup. He has tingling in both feet and severe aching pain in his back and thighs. He had a diarrhoeal illness three weeks ago.

On examination: symmetrical flaccid weakness — 3/5 in the legs, 4/5 in the arms. **All deep tendon reflexes are absent.** There is mild distal sensory loss to pinprick. There is bilateral facial weakness. **There is no sensory level and no sphincter disturbance.** Pupils are normal.

Forced vital capacity 1.6 litres (predicted approximately 4.5). He can count only to 14 on a single breath. Blood pressure has fluctuated between 90/60 and 175/95 mmHg over two hours.

1. Localise First

Site	Pattern	Key discriminator
Spinal cord	Paraparesis or quadriparesis	Sensory level and sphincter disturbance. Must be excluded urgently — cord compression is treatable and time-critical
Anterior horn cell	Asymmetric, pure motor	Wasting and fasciculation, no sensory loss
Root or plexus	Dermatomal and myotomal	Radiating pain, single reflex lost
Peripheral nerve	Distal, ascending, symmetrical	Areflexia with sensory involvement — this patient
Neuromuscular junction	Ocular, bulbar, proximal	Fatigability, no sensory loss, reflexes preserved
Muscle	Symmetrical proximal	No sensory loss, reflexes preserved, raised creatine kinase

The absence of a sensory level and of sphincter disturbance, with global areflexia and a preceding diarrhoeal illness, places this in the peripheral nerves — Guillain–Barré syndrome. But if there had been any suspicion of a cord lesion, **magnetic resonance imaging of the spine comes before anything else**.

2. Focused History

- **Antecedent illness** — *Campylobacter* gastroenteritis is the classic trigger, along with cytomegalovirus, Epstein–Barr virus, *Mycoplasma*, and recent surgery or vaccination.
- **Tempo** — Guillain–Barré syndrome progresses over days to a maximum at up to four weeks. Weakness progressing over months is a different disease.
- **Pain** — severe back and limb pain is present in most patients, is often the first symptom, and is regularly under-treated because it is not expected.
- **Bulbar and respiratory symptoms:** difficulty swallowing, nasal speech, weak cough, breathlessness on lying flat.
- **Autonomic symptoms:** palpitations, fainting, constipation, urinary retention, sweating changes.

- **If the pattern suggests myasthenia instead:** fatigability worse towards the end of the day, ptosis, diplopia, and precipitating drugs — **aminoglycosides, macrolides, quinolones, beta blockers and magnesium**.

3. Physical Examination

- Pattern and grading of weakness; **reflexes and plantars**; a careful search for a **sensory level**; assessment of fatigability by sustained upgaze and repeated arm abduction where myasthenia is possible.
- **Bulbar function** — speech, swallow, cough strength — and **neck flexion strength**, which parallels diaphragmatic strength.

THE SINGLE MOST IMPORTANT POINT IN THIS CASE

Measure the forced vital capacity at the bedside, and repeat it every four hours. This is the observation on which the patient's life depends.

Do not rely on oxygen saturation or arterial blood gases. In neuromuscular respiratory failure they remain normal until the patient is close to arrest — hypoxaemia and hypercapnia are **late, pre-terminal** findings.

Indications for intensive care review and probable intubation: vital capacity below about 20 mL/kg (or under 1 litre in an adult), a fall of more than 30% from baseline, **paradoxical abdominal movement**, inability to count above about 15 in one breath, weak cough, or bulbar weakness with a risk of aspiration.

The decision to intubate is made **electively on the trend**, in daylight, with a senior anaesthetist — not as an emergency at three in the morning.

4. Investigations

- **Serial forced vital capacity**, as above, charted like an observation.
- **Lumbar puncture: albuminocytological dissociation** — a raised protein with a normal cell count. **It is frequently normal in the first week**, so an early normal result does not exclude the diagnosis. A raised cell count should prompt consideration of infection, including human immunodeficiency virus, and of malignant infiltration.
- **Nerve conduction studies and electromyography** — demyelinating features in Guillain–Barré syndrome; a **decremental response on repetitive nerve stimulation** in myasthenia gravis.
- **Anti-ganglioside antibodies**, including anti-GQ1b in the Miller Fisher variant of ophthalmoplegia, ataxia and areflexia; stool culture and serology for *Campylobacter*.
- **If myasthenia is suspected:** acetylcholine receptor and muscle-specific kinase antibodies, thyroid function, and **computed tomography of the chest for thymoma**.
- **Exclude the mimics:** potassium, magnesium, calcium and phosphate; creatine kinase; vitamin B12; human immunodeficiency virus; and consider botulism, tick paralysis, porphyria, vasculitic neuropathy, and heavy metal poisoning.
- **Magnetic resonance imaging of the spine wherever a cord lesion is conceivable.** Cord compression is the diagnosis you cannot afford to miss, and it is the one that most closely mimics an ascending paralysis.

5. Management

- **Admit to a monitored bed with four-hourly vital capacity and continuous cardiac monitoring.** Involve intensive care early, before deterioration.
- **Immunotherapy: intravenous immunoglobulin or plasma exchange.** They are of equivalent efficacy, and **they are not combined.** Intravenous immunoglobulin is more widely available and easier to give.

> WHAT NOT TO GIVE
>
> **Corticosteroids do not work in Guillain–Barré syndrome and are not used.**
>
> This is a genuine and examinable contrast with **chronic inflammatory demyelinating polyradiculoneuropathy**, which is steroid-responsive. The instinct to reach for prednisolone in an inflammatory neuropathy is understandable and, in the acute syndrome, wrong.

- **Autonomic instability is a leading cause of death.** Monitor the rhythm, avoid drugs that swing the blood pressure, be alert for bradyarrhythmias, ileus and urinary retention, and treat labile hypertension cautiously.
- **Treat the pain properly** — neuropathic agents together with simple analgesia. Patients are fully conscious throughout.
- **Venous thromboembolism prophylaxis** in every immobile patient; pressure area care; nutrition and swallow assessment; early physiotherapy.
- **Psychological support.** A patient who is progressively paralysed but entirely alert and aware is frightened, and communication becomes harder exactly as the fear increases. Explain what is happening and what will happen next, repeatedly.
- **Myasthenic crisis:** intravenous immunoglobulin or plasma exchange, treatment of the precipitant, withdrawal of the offending drug, and cautious corticosteroid introduction — **steroids can transiently worsen weakness at the start of treatment**.
- **Prognosis:** most patients with Guillain–Barré syndrome recover substantially, but recovery takes months, a significant minority require ventilation, and mortality is not negligible. Say this honestly to the family.

6. Teaching Points and Viva Questions

- Localise before you diagnose — and exclude cord compression first.
- The vital capacity is the observation. Saturations and gases reassure you right up until they do not.
- Areflexia with ascending symmetrical weakness after a diarrhoeal illness is Guillain–Barré syndrome until proved otherwise.
- A normal lumbar puncture in the first week excludes nothing.
- Steroids are ineffective in the acute syndrome, and immunoglobulin and plasma exchange are not combined.
- Autonomic instability, not weakness, is what kills these patients.

- Treat the pain, and keep talking to a patient who cannot answer.

Questions you should be able to answer:

- Which findings place the lesion in the peripheral nerves rather than the cord?
- His saturations are 98% on air. Does that reassure you? Justify your answer.
- The lumbar puncture on day 4 shows normal protein. What do you conclude?
- A colleague suggests high-dose methylprednisolone. How do you respond?
- His heart rate drops to 38 during suctioning. What is happening?

Case 67 · Peripheral Neuropathy

CLINICAL VIGNETTE

A **63-year-old man** describes two years of numbness that began in the toes and has crept up to mid-calf, with **burning pain worst at night**. He is unsteady walking to the bathroom in the dark but manages in daylight. He has developed two painless ulcers under the forefoot, and last month **burned the sole of his foot on a hot floor without feeling it**.

He has had type 2 diabetes for twelve years with a glycated haemoglobin of 9.1%, and drinks around 40 units of alcohol a week.

On examination: symmetrical loss of pinprick and temperature to mid-calf in a glove-and-stocking distribution, **absent ankle jerks**, reduced vibration and joint position sense to the knees, mild weakness of toe extension, and **high-arched feet with clawed toes, thick callus and a clean neuropathic ulcer** under the right first metatarsal head. Romberg test positive. No proximal weakness, no fasciculation.

Vitamin B12 low-normal with a raised methylmalonic acid.

1. Four Questions That Classify Any Neuropathy

Neuropathy has an intimidating list of causes and a very manageable structure. Answer these four questions and the list becomes short.

Question	What the answer means
1. Which fibres?	Large fibre — vibration, joint position, reflexes, and unsteadiness in the dark. Small fibre — burning pain, temperature loss and autonomic symptoms, with preserved reflexes and normal nerve conduction studies. Motor, sensory, autonomic, or mixed.
2. What distribution?	Symmetrical and distal — length-dependent polyneuropathy. Asymmetrical, multiple named nerves — mononeuritis multiplex, which means vasculitis or diabetes (Case 61). A single nerve — entrapment or compression. Proximal and distal with early loss of reflexes — a demyelinating polyradiculoneuropathy.
3. What tempo?	Days to weeks — Guillain–Barré syndrome, vasculitis, porphyria, toxins, critical illness. Months to years — diabetes, alcohol, hereditary disease, paraproteinaemia.
4. Axonal or demyelinating?	The nerve conduction studies answer this and it splits the causes. Axonal — diabetes, alcohol, B12 deficiency, uraemia, drugs, hereditary sensorimotor neuropathy, amyloid. Demyelinating — Guillain–Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, paraprotein-associated neuropathy, Charcot–Marie–Tooth type 1, leprosy, diphtheria.

2. The Causes

Group	Causes
Metabolic and nutritional	Diabetes — the commonest cause; alcohol; B12 deficiency; thiamine and vitamin E deficiency; vitamin B6 in excess as well as in deficiency; hypothyroidism; chronic kidney disease; liver disease
Drugs and toxins	Isoniazid, metronidazole, nitrofurantoin, amiodarone, phenytoin; chemotherapy — vincristine, platinum agents, taxanes, thalidomide, bortezomib; lead, arsenic, organophosphates
Infective	Leprosy — a leading infectious cause worldwide, with thickened palpable nerves and skin lesions; human immunodeficiency virus; hepatitis B and C; Lyme disease; diphtheria; brucellosis
Immune and inflammatory	Guillain–Barré syndrome (Case 66); chronic inflammatory demyelinating polyradiculoneuropathy — which is treatable; vasculitis; connective tissue disease; sarcoidosis; coeliac disease
Paraproteinaemic and neoplastic	Myeloma and monoclonal gammopathy; amyloidosis; POEMS syndrome; paraneoplastic neuropathy
Hereditary	Charcot–Marie–Tooth disease — look for pes cavus, hammer toes, distal wasting giving an inverted-champagne-bottle appearance, and affected relatives. Patients often have marked signs with surprisingly few symptoms, because the disease has been present all their life

Around a quarter remain idiopathic after full investigation, and it is legitimate to say so once the treatable causes have been excluded — but only then.

3. Focused History

- Onset, progression and distribution; which fibre types are involved; the character of any pain.
- **Function, which is what the patient actually cares about:** falls, unnoticed injuries and **burns**, difficulty with buttons and keys, tripping, and unsteadiness in the dark.
- **Autonomic symptoms:** postural dizziness, early satiety and vomiting, altered bowel habit, bladder and sexual dysfunction, sweating changes.
- **Alcohol quantified**; diet, vegan practice and **bariatric surgery**; every drug including chemotherapy and over-the-counter vitamins; occupational and toxin exposure.
- **Family history — and examine the parents' and siblings' feet if you can**, because hereditary neuropathy is often undiagnosed in the family.
- **Red flags demanding urgent investigation:** rapid progression, prominent or asymmetrical **motor** involvement, autonomic failure, weight loss, or systemic features.

4. Examination

- **Establish the pattern first**, then map the sensory level and test vibration, joint position, pinprick and temperature separately.
- Reflexes; power tested with attention to a **distal-to-proximal gradient**; gait and Romberg test; **pes cavus and clawing**.
- **Palpate for thickened nerves** — the ulnar nerve at the elbow, the greater auricular in the neck, the common peroneal at the fibular neck. **Thickened nerves mean leprosy or hereditary neuropathy**, and

take fifteen seconds to check.

- **Inspect the feet and the footwear**, as in Case 25 — this man has already ulcerated and burned himself.
- Postural blood pressure; and a search for the systemic causes above.

5. Investigations

THE FIRST-LINE SCREEN — CHEAP, AND IT FINDS MOST OF THE TREATABLE CAUSES

Glucose and glycated haemoglobin — and an oral glucose tolerance test if these are normal, because impaired glucose tolerance alone causes neuropathy · **vitamin B12, with methylmalonic acid or homocysteine if borderline** · folate · thyroid function · renal and liver function · complete blood count and erythrocyte sedimentation rate · **serum protein electrophoresis with immunofixation and serum free light chains** · human immunodeficiency virus and hepatitis serology.

A paraprotein is found in roughly one in ten otherwise idiopathic neuropathies, and it is the test most often left off the request form. It costs little and it changes the diagnosis from "idiopathic" to something with a name and, sometimes, a treatment.

- **Second line, guided by suspicion:** antinuclear and antineutrophil cytoplasmic antibodies, rheumatoid factor, coeliac serology, angiotensin-converting enzyme, copper and caeruloplasmin, vitamin E, heavy metals, anti-ganglioside antibodies, and genetic testing.
- **Nerve conduction studies and electromyography** to confirm, localise, and classify as axonal or demyelinating.
- **Normal nerve conduction studies in a patient with burning feet do not exclude neuropathy — they suggest small fibre disease**, which is confirmed by skin biopsy or quantitative sensory testing where available.
- **Nerve biopsy** occasionally — for suspected vasculitis, amyloidosis or leprosy. Imaging of the spine where a myelopathy or radiculopathy is possible.

6. Management

- **Treat the cause.** Glycaemic control slows progression; alcohol abstinence with thiamine replacement; B12 and thyroid replacement; withdrawal of the offending drug; treatment of the vasculitis, paraprotein or leprosy.

TREATING NEUROPATHIC PAIN HONESTLY

Set the expectation before you write the prescription: a 30 to 50 per cent reduction in pain is a good result, and abolition is not achievable.

Promising more guarantees that the patient will judge the treatment a failure and stop it.

Duloxetine, amitriptyline, gabapentin or pregabalin, started low and titrated, with topical capsaicin or lidocaine for localised pain. **Avoid opioids for chronic neuropathic pain** — they work poorly and cause harm.

THE MOST IMPORTANT PART OF THE PLAN

In a patient who has lost protective sensation, foot care is the intervention that prevents amputation — and it matters more than the analgesia.

Daily inspection including with a mirror; never barefoot; test bath water with the hand or a thermometer; professional nail and callus care; properly fitted footwear; and **same-week referral to a multidisciplinary foot service for any ulcer** (Case 25).

- Falls prevention, physiotherapy and occupational therapy, an ankle-foot orthosis for foot drop, and driving assessment.
- **Autonomic management:** compression stockings and fludrocortisone or midodrine for postural hypotension; prokinetics for gastroparesis.
- **Do not accept a chronic progressive demyelinating neuropathy as untreatable. Chronic inflammatory demyelinating polyradiculoneuropathy responds to corticosteroids, immunoglobulin or plasma exchange** — in contrast to Guillain–Barré syndrome, where steroids do not work (Case 66). It deserves referral rather than resignation.
- Genetic counselling in hereditary disease.

7. Teaching Points and Viva Questions

- Classify by fibres, distribution, tempo, and axonal versus demyelinating.
- The cheap first-line screen finds most of the treatable causes — and includes a paraprotein screen.
- Normal nerve conduction studies with burning feet means small fibre neuropathy, not a normal patient.
- Palpate for thickened nerves.
- Mononeuritis multiplex means vasculitis or diabetes.
- Promise 30 to 50 per cent pain relief, not abolition.
- Foot protection prevents amputation; chronic demyelinating neuropathy is treatable.

Questions you should be able to answer:

- Which four questions would you ask of any neuropathy, and what are the answers in this man?
- He has diabetes and drinks heavily. Why still send the full screen?
- A patient with burning feet has entirely normal nerve conduction studies. What do you conclude?
- What will you tell him about how much his pain will improve?
- A 45-year-old has a two-year progressive weakness with globally absent reflexes and demyelinating conduction studies. Why does this matter?

Case 68 · Myelopathy and Demyelinating Disease

CLINICAL VIGNETTE

A **34-year-old woman** describes five days of numbness that began in both feet and has ascended to the level of her umbilicus, with heaviness of both legs and **difficulty starting micturition with a feeling of incomplete emptying**.

Two years ago she had **painful loss of vision in the right eye** which recovered over several weeks. Last year she had a week of vertigo and double vision.

On examination: a **spastic paraparesis** with increased tone, pyramidal-pattern weakness, brisk reflexes and **extensor plantar responses**. There is a **sensory level at T10**. Abdominal reflexes are absent. There is a **right relative afferent pupillary defect with temporal pallor of the optic disc**. Vibration sense is reduced to the knees.

Magnetic resonance imaging: multiple T2 lesions in the periventricular white matter, corpus callosum and cervical cord, two of which enhance. **Cerebrospinal fluid: oligoclonal bands present, normal cell count.**

THE RULE BEFORE ANY DIAGNOSIS IS MADE

A sensory level, bilateral motor signs and sphincter disturbance define a myelopathy — and every myelopathy is cord compression until imaging says otherwise.

Image the WHOLE spine, urgently, not just the level you think is affected — compressive lesions are frequently multiple, and a scan of the wrong segment is worse than no scan because it falsely reassures.

Remember from the system opener that in the acute phase the legs may be flaccid and areflexic — spinal shock — so normal tone and absent reflexes do not exclude a cord lesion.

1. Compressive Myelopathy — the Emergency

- **Causes: metastatic malignancy — breast, lung, prostate, myeloma and lymphoma — which is the commonest cause in an adult**; **epidural abscess** (fever, back pain, immunosuppression, diabetes, intravenous drug use, recent spinal instrumentation); epidural haematoma (anticoagulation or a recent procedure); disc prolapse and vertebral fracture; and **tuberculous or brucellar spondylitis, which are important here and may present with a gibbus** (Cases 41 and 43).

- **Red flags:** progressive leg weakness, a sensory level, **urinary retention or new incontinence**, saddle anaesthesia, band-like pain around the trunk, back pain worse at night or on straining, fever, or a known malignancy.

WHAT HAPPENS IN THE NEXT HOUR

Urgent magnetic resonance imaging of the whole spine · high-dose dexamethasone if malignant compression is suspected · same-hour discussion with neurosurgery and oncology · then radiotherapy or surgical decompression.

Neurological function that is not recovered within hours is often not recovered at all. The difference between a patient who walks and one who does not is usually the speed of the first scan.

For an epidural abscess: blood cultures, antibiotics and urgent surgical drainage.

2. Non-Compressive Myelopathy

Group	Causes
Inflammatory and demyelinating	Multiple sclerosis · neuromyelitis optica spectrum disorder — aquaporin-4 antibody, with longitudinally extensive cord lesions and severe optic neuritis · MOG antibody disease · acute disseminated encephalomyelitis · sarcoidosis · lupus
Metabolic	Vitamin B12 deficiency — subacute combined degeneration (Case 50) · copper deficiency · nitrous oxide misuse
Infective	Human immunodeficiency virus · HTLV-1 · varicella zoster · syphilis · schistosomiasis · tuberculosis
Vascular	Spinal cord infarction — sudden onset, anterior spinal artery territory with dorsal column sparing · dural arteriovenous fistula
Degenerative and structural	Cervical spondylotic myelopathy — the commonest myelopathy in older adults: insidious, with clumsy hands, gait disturbance and brisk legs with a normal or reduced arm reflex at the level
Other	Intrinsic cord tumour · syringomyelia · radiation myelopathy

THE MIMIC THAT MUST BE EXCLUDED

Distinguishing neuromyelitis optica spectrum disorder from multiple sclerosis matters, because the treatments differ and several multiple sclerosis drugs make neuromyelitis optica worse.

Suspect it with: severe or bilateral optic neuritis with poor recovery · a **longitudinally extensive cord lesion spanning three or more vertebral segments** · intractable hiccups or vomiting from an area postrema lesion · relapses that leave severe deficits.

Send aquaporin-4 and MOG antibodies in every first presentation of demyelinating myelitis or optic neuritis.

3. Multiple Sclerosis

- **The diagnosis requires dissemination in space and in time** — lesions in more than one site, occurring on more than one occasion. This patient has optic neuritis, a brainstem episode and now a myelitis, with characteristic imaging and oligoclonal bands.
- **Phenotypes:** relapsing–remitting, secondary progressive, primary progressive; and the clinically isolated syndrome.
- **Typical presentations: optic neuritis** — painful monocular visual loss with a relative afferent pupillary defect, recovering over weeks and leaving optic atrophy; **transverse myelitis**; brainstem syndromes with **internuclear ophthalmoplegia**, vertigo or diplopia; sensory disturbance; **Lhermitte sign** — an electric sensation down the spine on neck flexion; **Uhthoff phenomenon** — symptoms worse in heat; and the features patients rate as most disabling: **fatigue, bladder dysfunction, spasticity and cognitive change**.

Investigations

- **Magnetic resonance imaging of the brain and the whole spine with contrast** — periventricular, juxtacortical, infratentorial and cord lesions, with enhancement indicating active inflammation.
- **Cerebrospinal fluid oligoclonal bands** with a normal or mildly raised cell count; visual evoked potentials.
- **Aquaporin-4 and MOG antibodies**, and **exclusion of the mimics: B12, human immunodeficiency virus, syphilis, antinuclear antibody, angiotensin-converting enzyme, thyroid function and the vasculitides.**

Management

- **Acute relapse: high-dose corticosteroid shortens the relapse but does not change the long-term course**, and is used only where the relapse is disabling. **Exclude infection first — urinary infection both mimics and precipitates relapse, and should be treated before any steroid is given.**
- **Disease-modifying therapy in relapsing disease, started early**, because disability accrues early and is not recovered later. Agents range from interferons and glatiramer through dimethyl fumarate and teriflunomide to natalizumab, fingolimod, ocrelizumab, alemtuzumab and cladribine, selected by disease activity and risk. **Screen before starting: JC virus serology, hepatitis B, tuberculosis, varicella status, and pregnancy planning.**

SYMPTOM MANAGEMENT IS WHERE QUALITY OF LIFE LIES

Ask about, and treat, the things the patient actually complains of — which are rarely the things on the imaging.

Fatigue · bladder dysfunction — measure a post-void residual before prescribing an anticholinergic, and teach intermittent self-catheterisation where retention is the problem · spasticity (baclofen, tizanidine, physiotherapy, botulinum toxin) · bowel care · neuropathic pain · **depression, which is common and under-treated** · sexual dysfunction · cognitive difficulty.

And two things with evidence behind them: exercise, and smoking cessation — smoking accelerates progression. Vitamin D replacement.

- **Pregnancy:** the relapse rate falls during pregnancy and rises in the puerperium; plan drug changes in advance rather than reacting to a positive test.
- Multidisciplinary care with a specialist nurse, physiotherapy, occupational therapy and continence services; and an honest conversation about prognosis, which is far more variable than patients expect.

4. Teaching Points and Viva Questions

- A sensory level plus sphincter disturbance means imaging the whole spine today.
- Flaccid areflexic legs early do not exclude a cord lesion.
- The commonest compressive cause in an adult is metastatic malignancy — and here, think tuberculous and brucellar spondylitis too.
- Send aquaporin-4 antibodies: neuromyelitis optica is treated differently and some multiple sclerosis drugs worsen it.
- Steroids shorten a relapse but do not change the course — and treat the urinary infection first.
- Start disease-modifying therapy early; disability accrues early.
- Measure the post-void residual before treating the bladder.

Questions you should be able to answer:

- What does the sensory level at T10 tell you, and what is your first investigation?
- Her legs are flaccid with absent reflexes on day one. Does that exclude a cord lesion?
- Which two antibodies must you send, and why does the answer matter?

- She has a relapse and is dysuric. What do you do before prescribing methylprednisolone?
- Give four symptoms you would ask about that will not appear on her scan.

Case 69 · Parkinson Disease and the Extrapyramidal Disorders

CLINICAL VIGNETTE

A **68-year-old man** is brought by his wife, who has noticed over eighteen months that he walks more slowly, his handwriting has become small, his voice is quieter and his face less expressive. He has a **tremor of the right hand when it is resting in his lap, which disappears when he reaches for a cup**. He struggles to turn over in bed. He is constipated.

On direct questioning: he **lost his sense of smell several years ago**, and for at least a decade he has **shouted and thrashed in his sleep as though acting out dreams**.

On examination: reduced facial expression and blink rate, quiet monotonous speech. **Asymmetrical resting tremor of the right hand at about 5 Hz**, cogwheel rigidity of the right arm, and **bradykinesia on finger tapping with progressive decrement in amplitude**. Reduced right arm swing, stooped posture, short shuffling steps and slow turning. **Eye movements are full, there have been no falls, and there is no postural drop in blood pressure.**

FIRST NAME THE SYNDROME, THEN FIND THE CAUSE

Parkinsonism = bradykinesia, plus at least one of resting tremor, rigidity, or postural instability.

That establishes the **syndrome**. The work then is to establish the **cause** — and there are four groups: idiopathic Parkinson disease, **drug-induced parkinsonism**, the atypical degenerative syndromes, and the structural and metabolic mimics.

1. The Causes

Cause	What identifies it
Idiopathic Parkinson disease	Asymmetrical onset, resting tremor, a good and sustained levodopa response, slow progression — and the prodromal non-motor features: loss of smell, rapid eye movement sleep behaviour disorder, constipation and depression, often present for years or decades beforehand, as in this man
Drug-induced parkinsonism	The commonest reversible cause, and it must be asked about first. Antipsychotics, and above all metoclopramide and prochlorperazine, plus sodium valproate, lithium and tetrabenazine. Typically symmetrical, and may take months to resolve after the drug is stopped
Progressive supranuclear palsy	Early falls, characteristically backwards, a vertical supranuclear gaze palsy, axial rigidity, and pseudobulbar features
Multiple system atrophy	Early and severe autonomic failure — postural hypotension, urinary retention or incontinence, erectile dysfunction — with parkinsonian or cerebellar features, and inspiratory stridor
Corticobasal degeneration	Marked asymmetry with apraxia, alien limb phenomenon, cortical sensory loss and dystonia
Dementia with Lewy bodies	Fluctuating cognition, visual hallucinations, dream enactment, and severe — sometimes fatal — neuroleptic sensitivity, with dementia appearing within a year of the motor features
Vascular parkinsonism	Lower-body predominant, vascular risk factors, stepwise course, poor levodopa response
Wilson disease	In anyone under 50 — with Kayser–Fleischer rings, liver disease and psychiatric features. Check caeruloplasmin and copper
Normal pressure hydrocephalus	Gait apraxia, urinary incontinence and cognitive decline, with ventriculomegaly

RED FLAGS AGAINST PARKINSON DISEASE

Symmetrical onset · falls within the first year · early autonomic failure · early dementia or visual hallucinations · vertical gaze palsy · pyramidal or cerebellar signs · inspiratory stridor · rapid progression · and a poor or absent response to levodopa.

Any of these should make you doubt idiopathic Parkinson disease and think of an atypical syndrome — which matters for prognosis, for the drugs that will and will not help, and for what the family is told.

2. The Tremor Differential

Tremor	Features
Parkinsonian	4–6 Hz, present at rest, asymmetrical, reduced by voluntary movement, re-emerges on sustained posture; accompanied by bradykinesia and rigidity
Essential	6–12 Hz, postural and kinetic rather than at rest, symmetrical, often involves the head and voice, family history, improved by alcohol, and no bradykinesia
Cerebellar (intention)	Worsens as the finger approaches the target, with other cerebellar signs
Enhanced physiological	Fine and postural — anxiety, thyrotoxicosis, caffeine, beta agonists, alcohol withdrawal
Dystonic and functional	Task- or position-specific; variable, distractible and entrainable in functional tremor

3. Focused History

- **Motor:** slowness, micrographia, quiet voice, loss of dexterity, difficulty turning in bed, freezing in doorways, falls.
- **The full drug history, and specifically the antiemetics** — a course of metoclopramide or prochlorperazine is the commonest thing to find, and it is reversible.

THE QUESTIONS THAT ARE NOT ASKED

The non-motor features are at least as disabling as the motor ones, and they are almost never volunteered.

Ask about: constipation · urinary urgency and nocturia · postural dizziness · drooling and dysphagia · **loss of smell** · **acting out dreams** · depression, anxiety and apathy · pain · fatigue · sleep disturbance · hallucinations · and cognitive change.

Two of these — anosmia and dream enactment — precede the motor features by years and are strong supporting evidence for the diagnosis.

- Family history; occupational and toxin exposure; and the impact on function, work, driving and — importantly — on the carer.

4. Examination

- **Observe before you touch:** facial expression, blink rate, posture, and tremor at rest with the hands in the lap.
- **Demonstrate bradykinesia properly** — finger tapping, hand opening and closing, and foot tapping, watching for **decrement in amplitude and speed**, which is what distinguishes bradykinesia from simple weakness or slowness.

- Rigidity, with and without contralateral activation to bring out cogwheeling.
- **Gait: initiation, stride length, arm swing, turning, festination and freezing** — plus the pull test for postural instability.
- **Eye movements, especially vertical saccades and pursuit**; **postural blood pressure**; cognitive screen; speech and swallowing; and **Kayser–Fleischer rings in a younger patient**.

5. Investigations

- **The diagnosis is clinical. No test confirms Parkinson disease**, and students expect one.
- **Structural imaging** where the picture is atypical, to exclude vascular disease, hydrocephalus or a structural lesion.
- **Dopamine transporter imaging distinguishes degenerative parkinsonism from essential tremor and from drug-induced parkinsonism — but it does not distinguish Parkinson disease from the atypical degenerative syndromes**, which is the distinction that usually matters clinically.
- **Caeruloplasmin, copper and liver function in anyone under 50**; thyroid function; vitamin B12.
- **The levodopa response is itself diagnostic information** — a clear and sustained response supports Parkinson disease, and a poor one argues for an atypical syndrome.

6. Management

- **Refer to a specialist before starting treatment where possible, and do not start antiparkinsonian drugs simply to see what happens in an unclear case.**

WHEN TO START LEVODOPA

Levodopa with a decarboxylase inhibitor is the most effective drug, and it is started when symptoms are troublesome — at the lowest effective dose.

There is no benefit in withholding it to "save it for later". That was an older practice based on a misunderstanding, and it cost patients years of unnecessary disability.

Discuss the long-term motor complications honestly: **wearing-off, dyskinesia and unpredictable on–off fluctuations**, managed by fractionating the dose, adding a COMT or MAO-B inhibitor or a dopamine agonist, and later apomorphine, intestinal levodopa gel or **deep brain stimulation** in selected patients.

THE SIDE EFFECT THAT MUST BE ASKED ABOUT BY NAME

Dopamine agonists cause impulse control disorders — pathological gambling, hypersexuality, compulsive shopping and binge eating — in a substantial minority.

Patients conceal them, and families discover them after serious financial or relationship damage. Warn the patient and, with consent, the family at the time of prescribing, and **ask about them directly at every review** rather than waiting to be told.

THREE HOSPITAL RULES THAT PREVENT REAL HARM

Never stop levodopa abruptly — it risks an akinetic crisis and a neuroleptic malignant-like syndrome.

Give the doses on time. Parkinson medication is exquisitely time-critical, and standard hospital drug rounds do not match a patient's regimen. Missed and late doses cause avoidable immobility, aspiration and falls. **If the patient is nil by mouth, use a nasogastric tube or a rotigotine patch — do not simply omit the drug.**

And avoid dopamine-blocking drugs: use **domperidone or ondansetron** rather than metoclopramide or prochlorperazine for nausea, and **quetiapine or clozapine** if an antipsychotic is unavoidable. **In dementia with Lewy bodies, neuroleptic sensitivity can be fatal.**

- **Non-motor management, which is where most of the quality of life is:** constipation, orthostatic hypotension, bladder symptoms, drooling, sleep disorder, **depression — common and under-treated**, pain, and cognitive impairment, for which **rivastigmine is used in Parkinson disease dementia**.
- **Multidisciplinary care: a Parkinson specialist nurse, physiotherapy for gait and falls, occupational therapy, speech and language therapy for voice and swallow**, and dietetics. **Exercise has genuine evidence for slowing functional decline.** Driving advice, carer support and advance care planning.
- **Atypical syndromes** are managed supportively, with particular attention to falls, swallowing and autonomic failure, and earlier involvement of palliative care.

7. Teaching Points and Viva Questions

- Parkinsonism is bradykinesia plus one. Then find the cause.
- Ask about every drug, and especially the antiemetics.
- Anosmia and dream enactment precede the tremor by years.
- Know the red flags that argue against Parkinson disease.
- The diagnosis is clinical, and dopamine transporter imaging does not separate the degenerative syndromes.
- Do not delay levodopa, and ask about impulse control at every visit.
- Never stop levodopa, never give metoclopramide, and give the doses on time.

Questions you should be able to answer:

- Which features here support idiopathic Parkinson disease rather than an atypical syndrome?
- What is the significance of his anosmia and his sleep behaviour?
- Give five red flags that would make you doubt the diagnosis.
- He is admitted with pneumonia and is nil by mouth. What must happen to his medication?
- His wife telephones to say he has gambled away their savings. What has happened?

Dermatology and Envenomation

Skin signs of systemic disease, eczema, snake, scorpion and spider envenomation, cutaneous infections and infestations, psoriasis, the blistering and drug emergencies, skin tumours, and sexually transmitted infections.

Cases 70–79 · 10,054 words

This block covers the dermatology teaching of both internal medicine courses. The **first course** supplies cases 70 and 72; the **second course** contributes ten dermatology lectures, covered here by cases 73 and 79. Dermatology is the block where the second course adds most, and it is taught largely by pattern recognition — so these cases lean more on comparison tables than the rest of the book.

Case	Lecture it serves
System opener: describing the skin	Introduction and terminology in dermatology
Case 70 — Cutaneous manifestations of systemic disease	Cutaneous manifestations of systemic disease
Case 71 — Eczema	Eczema and papulosquamous disease
Case 72 — Snake, scorpion and spider envenomation	Snake and spider envenomation
Case 73 — Bacterial and viral infections of the skin	Viral and bacterial infections of the skin
Case 74 — Fungal infections and infestations	Fungal infections and infestations of the skin
Case 75 — Psoriasis and the papulosquamous diseases	Eczema and papulosquamous disease
Case 76 — Blistering disease and the cutaneous drug emergencies	Vesiculobullous disease; drug eruptions and cutaneous emergencies
Case 77 — Skin tumours and the pigmented lesion	Benign and malignant skin tumours
Case 78 — Acne, rosacea, and disorders of pigmentation, hair and nails	Acne, rosacea and adnexal disorders; pigmentation, hair and nail disorders
Case 79 — Sexually transmitted infections	Sexually transmitted diseases

Purpura, the erythemas and urticarial disorders are distributed across the book rather than gathered into one case: purpura in Case 52 and Case 61, erythema nodosum in Case 70, erythema multiforme and urticaria in Case 76.

System Opener · Describing the Skin

Dermatology is learned as a vocabulary before it is learned as a set of diseases. A student who can describe a rash accurately can be helped by a dermatologist over the telephone; a student who says "a red rash on the leg" cannot.

The history

- **Time course:** when it started, where it started, how it spread, and whether it is continuous or episodic.
- **Symptoms:** itch — and **how much it disturbs sleep**, which is the best measure of severity — pain, burning, or nothing at all.
- **Provoking factors:** sunlight, heat and sweat, water, friction, occupation, cosmetics, contacts, and foods.
- **Drugs.** Ask about everything started in the preceding two months, including over-the-counter and traditional preparations. **A morbilliform drug eruption typically appears 7–14 days after a new drug**, and sooner on re-exposure — so the culprit is often not the most recently started medicine.
- **Previous treatment — and specifically how much and for how long.** "I tried a steroid cream" usually means a small tube used for two days, which is not a treatment failure.
- **Personal and family history** of atopy, psoriasis and autoimmune disease; systemic symptoms; and **impact on sleep, work, school and mood**, which is substantial and routinely unasked.

The examination

- **Examine the whole skin in good light** — including the scalp, behind the ears, the nails, the mouth, the genitals, the palms and soles, and between the toes. Rashes are diagnosed by their distribution, and the diagnostic part is frequently the part left covered.
- **Then describe in a fixed order:** site and distribution → configuration → number → **primary lesion morphology** → secondary change → colour → size → surface → margin.
- **Palpate** — temperature, tenderness, texture, depth — and press with a glass slide to test whether the lesion **blanches**.

The primary lesions

Term	Definition
Macule	Flat area of altered colour, under 1 cm
Patch	Flat area of altered colour, over 1 cm
Papule	Raised solid lesion, under 1 cm
Plaque	Raised flat-topped lesion, over 1 cm
Nodule	Raised solid lesion over 1 cm, extending deeper into dermis or subcutis
Vesicle / bulla	Fluid-filled lesion — vesicle small, bulla over 1 cm
Pustule	Pus-filled lesion — which does not necessarily mean infection
Wheal	Transient oedematous papule or plaque, resolving within 24 hours
Purpura	Non-blanching extravasated blood. Petechiae are pinpoint; ecchymoses are larger
Telangiectasia	Visible permanently dilated small vessel

Secondary change and configuration

- **Secondary change:** scale, crust, excoriation, **lichenification** (thickened skin with exaggerated markings from chronic rubbing), fissure, **erosion** (loss of epidermis only, heals without scarring), **ulcer** (extends into dermis, heals with a scar), atrophy, scar, sclerosis.
- **Configuration:** annular, linear, grouped or herpetiform, target, reticulate, serpiginous.
- **Distribution:** flexural, extensor, photodistributed, dermatomal, acral, symmetrical — each of which narrows the differential sharply.

THE DERMATOLOGICAL EMERGENCIES

Erythroderma — erythema over more than 90% of the body surface, with fluid loss, heat loss and high-output cardiac failure.

Stevens–Johnson syndrome and toxic epidermal necrolysis — painful skin, **mucosal involvement at two or more sites**, and a positive Nikolsky sign, days to weeks after a new drug. Stop the drug and transfer.

Meningococcal purpura — non-blanching rash with fever. Antibiotics immediately.

Necrotising fasciitis — **pain out of proportion to the visible signs**, rapid progression, systemic toxicity, crepitus. A surgical emergency.

Eczema herpeticum — monomorphic punched-out erosions in a patient with eczema, who is unwell. Aciclovir urgently.

Drug reaction with eosinophilia and systemic symptoms — rash, fever, facial oedema, eosinophilia and organ involvement, typically 2–8 weeks after the drug.

Angioedema involving the airway.

Case 70 · Cutaneous Manifestations of Systemic Disease

CLINICAL VIGNETTE

A **34-year-old woman** is referred with three weeks of **tender red raised lesions on both shins**. They are painful to touch, have not ulcerated, and the older ones are fading through the colours of a bruise. Over the same period she has had a dry cough, mild breathlessness on exertion, intermittent fever and painful swollen ankles.

On examination: multiple tender erythematous **nodules** over both shins, poorly demarcated, warm, none ulcerated. Both ankles are swollen and tender. Temperature 37.8 °C. Chest is clear.

Chest radiograph: bilateral hilar lymphadenopathy.

READING THE SKIN AS A SYSTEMIC SIGN

The skin lesions are **erythema nodosum** — a septal panniculitis that is a **reaction pattern, not a diagnosis**. The task is always to find what provoked it.

Here, erythema nodosum with **bilateral hilar lymphadenopathy, ankle arthritis and fever** constitutes **Löfgren syndrome**, an acute presentation of sarcoidosis with an excellent prognosis.

1. Erythema Nodosum — Find the Cause

Cause	How to pursue it
Sarcoidosis	Chest radiograph, serum calcium, angiotensin-converting enzyme, ophthalmology review
Streptococcal infection	Throat swab and antistreptolysin O titre — the commonest identifiable cause in younger patients
Tuberculosis	Chest radiograph, interferon-gamma release assay or tuberculin test, sputum — and it must be excluded before corticosteroids
Brucellosis	Serology and blood cultures — a realistic cause in this region, and easily missed
Inflammatory bowel disease	Bowel symptoms, faecal calprotectin, endoscopy
Drugs	Sulfonamides, penicillins, the combined oral contraceptive
Pregnancy, Behçet disease, fungal infection, malignancy	Pregnancy test; oral and genital ulceration; exposure history
Idiopathic	Up to half of all cases, after the above have been excluded

2. Reading the Skin in Systemic Disease

The rest of this case is a reference table. Learn to recognise these, because in each of them **the skin sign appears before the diagnosis is made**.

Endocrine and metabolic

Sign	Disease
Necrobiosis lipoidica — shiny yellow-brown atrophic plaques with telangiectasia on the shins	Diabetes mellitus
Acanthosis nigricans — velvety hyperpigmented thickening of the neck, axillae and groin	Insulin resistance and type 2 diabetes. Sudden, extensive or mucosal involvement suggests underlying malignancy, classically gastric adenocarcinoma
Granuloma annulare, eruptive xanthomas, diabetic dermopathy, recurrent candidiasis	Diabetes mellitus
Pretibial myxoedema and thyroid acropachy	Graves disease
Dry coarse skin, hair loss, carotenaemia	Hypothyroidism
Pigmentation of buccal mucosa, palmar creases and scars	Adrenal insufficiency
Thin skin, easy bruising, purple striae, proximal myopathy	Cushing syndrome
Xanthelasma and tendon xanthomata	Hyperlipidaemia — particularly familial hypercholesterolaemia

Gastrointestinal, hepatic and renal

Sign	Disease
Spider naevi, palmar erythema, jaundice, scratch marks, leuconychia	Chronic liver disease
Pyoderma gangrenosum — a rapidly enlarging painful ulcer with a violaceous undermined border	Inflammatory bowel disease, rheumatoid arthritis, haematological malignancy. Do not debride it — surgery worsens it through pathergy. It is treated with immunosuppression, not with a scalpel
Erythema nodosum, aphthous ulceration	Inflammatory bowel disease
Generalised pruritus, half-and-half nails, calciphylaxis	Chronic kidney disease

Connective tissue disease and malignancy

Sign	Disease
Malar rash sparing the nasolabial folds; discoid lesions that scar	Systemic lupus erythematosus
Heliotrope rash of the eyelids and Gottron papules over the knuckles	Dermatomyositis — and in an adult this mandates a search for underlying malignancy
Sclerodactyly, calcinosis, Raynaud phenomenon, telangiectasia	Systemic sclerosis
Palpable purpura on dependent areas	Small vessel vasculitis — check urine and renal function
Acquired ichthyosis, generalised pruritus, erythema gyratum repens, sudden eruption of seborrhoeic keratoses	Underlying malignancy — the paraneoplastic dermatoses

Infection

Sign	Disease
Non-blanching purpura with fever	Meningococcal sepsis — antibiotics now
Splinter haemorrhages, Osler nodes, Janeway lesions	Infective endocarditis
Rash involving the palms and soles	Secondary syphilis, rickettsial infection, hand-foot-and-mouth disease
A chronic painless ulcer with a raised indurated border on an exposed site	Cutaneous leishmaniasis — endemic in parts of this region and frequently treated as a bacterial ulcer for months before the diagnosis is considered

3. Investigation and Management of This Patient

- **Chest radiograph** — done, and diagnostic of the syndrome in this context. Serum **calcium** (hypercalcaemia occurs in sarcoidosis), angiotensin-converting enzyme, inflammatory markers, complete blood count, liver and renal function, **urinalysis**.
- **Exclude the alternative causes:** throat swab and antistreptolysin O titre, **tuberculosis screening**, and **brucella serology**.
- **Ophthalmology review for uveitis** and an electrocardiogram for cardiac involvement — both silent and both important in sarcoidosis.
- **Biopsy of the nodules is not usually necessary** where the clinical picture is characteristic, and biopsy of erythema nodosum shows only a septal panniculitis without identifying the cause.
- **Löfgren syndrome resolves spontaneously in most patients over weeks to months.** Treat with rest, leg elevation, compression and anti-inflammatory drugs.
- **Corticosteroids are reserved for organ-threatening disease** — ocular, cardiac or neurological involvement, hypercalcaemia, or progressive pulmonary disease. **Exclude tuberculosis before starting them.**

4. Teaching Points and Viva Questions

- Erythema nodosum is a reaction pattern. The diagnosis is whatever caused it.
- In this region, tuberculosis and brucellosis belong at the top of that list, not the bottom.
- Never debride pyoderma gangrenosum.
- Adult dermatomyositis requires a malignancy screen.
- Sudden extensive acanthosis nigricans is a warning sign, not a metabolic curiosity.
- A chronic ulcer with a raised border on an exposed site here is leishmaniasis until proved otherwise.

Questions you should be able to answer:

- Name six causes of erythema nodosum and the test you would use for each.

- Why must tuberculosis be excluded before you prescribe prednisolone here?
- A surgical colleague proposes debriding a rapidly enlarging leg ulcer with a purple undermined edge. What do you say?
- A 62-year-old man has a heliotrope rash and proximal weakness. What is your next step?
- What is the prognosis of this syndrome, and what will you tell her?

Case 71 · Eczema

CLINICAL VIGNETTE

A **22-year-old woman** has had an itchy rash since infancy, currently at its worst for years. She scratches through the night, sleeps about four hours, and has taken three days off work. She has asthma and allergic rhinitis.

She was given "a steroid cream" but stopped it after two days because she had read that it thins the skin. She washes with soap and takes hot showers, which relieve the itch briefly.

On examination: thickened, **lichenified**, excoriated plaques in both antecubital and popliteal fossae, on the neck and on the backs of the hands, with generalised dry scaly skin. Over the left forearm there is **golden-yellow crusting**. There are infra-orbital folds beneath both eyes.

1. Focused History

- **Age of onset and how the distribution has changed** — facial and extensor in infancy, flexural in older children and adults, and often predominantly on the hands in adults.
- **Itch severity measured by sleep loss and time off work or school**, which is the most honest measure of how bad the disease is.
- **Triggers:** heat and sweat, soaps and detergents, wool, house dust mite, stress, infection, and — in a minority of young children only — foods.
- **Occupation and hobbies**, particularly wet work and contact with irritants, which drive adult hand eczema.
- **Current treatment, quantified.** How large a tube, how often, over how many days, and to which areas. Then ask directly what worries her about using it.

2. Differential Diagnosis

Diagnosis	The feature that discriminates it
Scabies	Intense nocturnal itch, burrows in finger web spaces and wrists, involvement of genitals and axillae, and other members of the household itching. Commonly missed and treated as eczema for months.
Tinea	Annular with a raised scaly advancing edge and central clearing, often asymmetrical. Topical steroid makes it spread while reducing the inflammation — tinea incognito. Scrape it before you treat it.
Psoriasis	Well-demarcated plaques with silvery scale on extensor surfaces, scalp and natal cleft, with nail pitting and onycholysis.
Contact dermatitis	Distribution follows the exposure — under a watch strap, at the hairline, on the hands. Patch testing distinguishes allergic from irritant.
Seborrhoeic dermatitis	Greasy scale in the scalp, eyebrows, nasolabial folds and behind the ears.
Cutaneous T-cell lymphoma	An older patient with persistent, atypical, fixed patches that do not respond to adequate treatment. Biopsy.

3. Investigations

- **The diagnosis is clinical.** Investigations are directed at complications and at the mimics.

- Bacterial swab where there is crusting or weeping, as here; **viral swab and polymerase chain reaction if eczema herpeticum is suspected**; **skin scrapings for fungal microscopy and culture** where the rash is asymmetrical or atypical.
- **Patch testing** where allergic contact dermatitis is suspected. Total and specific immunoglobulin E rarely change management in adults.

4. Management

THE CENTRAL PROBLEM IN ECZEMA CARE

Eczema is under-treated far more often than it is over-treated.

The usual pattern is a small tube of a weak steroid, used for two days, applied to a fraction of the affected skin, stopped early through fear — and then recorded as treatment failure. **Almost all of what follows is about giving enough, of the right strength, for long enough.**

Emollients — prescribe by the kilogram

- **Apply liberally several times daily, and continue when the skin is clear.** For widespread disease an adult needs something of the order of 500 g per month; a prescription for a 50 g tube is not treatment.
- **Use a soap substitute and stop soap and shower gel entirely.** Warm rather than hot water — hot water relieves itch for minutes and worsens it for hours.
- Apply emollient in the direction of hair growth to avoid folliculitis, and leave a gap of around 20–30 minutes between emollient and topical steroid.

Topical corticosteroids — match potency to site and severity

- **Mild or moderate potency for the face, flexures and genitals; potent preparations for the body and limbs; very potent short courses for thickened lichenified areas** such as this patient's.
- **Teach the fingertip unit** — the amount squeezed from the tip of an adult index finger to the first crease treats an area equal to two adult palms. Give her a written quantity, not "apply sparingly", which is the phrase that causes most under-treatment.
- **Proactive maintenance:** once controlled, applying topical steroid or a calcineurin inhibitor twice weekly to sites that habitually flare substantially reduces relapse.
- **Topical calcineurin inhibitors** — tacrolimus and pimecrolimus — for the face, eyelids and flexures, and as a steroid-sparing agent in areas needing long-term treatment.

STEROID PHOBIA

She stopped an appropriate treatment because of a fear she had read about. **Address it directly rather than repeating the prescription.**

Explain the distinction that matters: **short courses of appropriately matched potency, supervised, are safe** — whereas long-term unsupervised use of potent steroid on the face and flexures does cause atrophy. Then explain the harms of under-treatment: sleeplessness, infection, lichenification, time off work, and the mood consequences of years of itch.

A patient who understands why she is using it will use enough of it.

The rest

- **Treat the infection.** Golden crusting is impetiginised eczema — oral flucloxacillin, and consider antiseptic or dilute bleach baths where infection recurs.
- **Sedating antihistamines may help sleep during a bad flare.** Non-sedating antihistamines do little for the itch of eczema, although they help coexisting urticaria and rhinitis.
- Bandaging and wet wraps for severe lichenified disease; treat coexisting asthma and rhinitis.
- **Refractory disease:** phototherapy, ciclosporin, methotrexate, azathioprine, and the newer targeted agents — **dupilumab and Janus kinase inhibitors** — which have changed outcomes in severe atopic dermatitis.
- **Give a written treatment plan** setting out what to use where, how much, and what to do in a flare. Arrange follow-up rather than a single consultation.

ECZEMA HERPETICUM — THE COMPLICATION TO RECOGNISE

Rapidly worsening, painful eczema with clusters of monomorphic punched-out erosions and vesicles, often with fever and malaise, in a patient with atopic dermatitis. It is disseminated herpes simplex infection of eczematous skin.

Start aciclovir urgently. If it involves the skin around the eye, arrange same-day ophthalmology review. It can be fatal, and it is regularly mistaken for bacterial infection and treated with antibiotics alone while it spreads.

5. Teaching Points and Viva Questions

- Prescribe emollient by the kilogram and steroid by the fingertip unit. Never write "apply sparingly".
- Ask what worries the patient about steroids, then answer it.
- Scabies and tinea are the two mimics that get worse when you treat them as eczema.
- Golden crust means bacterial infection; punched-out erosions mean herpes and an urgent antiviral.
- Measure severity by sleep loss and days lost, not by the appearance alone.

Questions you should be able to answer:

- How much emollient should she be using in a month, and how would you write the prescription?
- Which potency would you choose for her face, and which for her lichenified forearms? Why the difference?
- She asks whether steroids will thin her skin. Answer her.
- Her rash is asymmetrical, annular and spreading despite treatment. What has happened?
- She returns febrile with painful clustered erosions. What is your diagnosis and immediate action?

Case 72 · Snake, Scorpion and Spider Envenomation

CLINICAL VIGNETTE

A **28-year-old man** was bitten on the back of the right hand two hours ago while moving rocks on farmland. He saw a snake but cannot describe it. A companion tied a cord tightly around his forearm and made two small cuts over the bite.

The hand and forearm are now painfully swollen to just below the elbow. He has noticed **bleeding from his gums** and oozing from the cuts.

On examination: heart rate 108/min, blood pressure 108/70 mmHg, alert. Tense swelling of the hand and forearm with bruising around two fang marks. **Bleeding from the gums and from the venepuncture site.** No ptosis, normal eye movements, normal single-breath count.

Twenty-minute whole blood clotting test: the blood has not clotted. Platelets 78 × 10^9/L · INR unrecordable · fibrinogen low · creatinine rising.

FIRST AID — AND THE FIRST AID THAT CAUSES HARM

The companion applied a **tight tourniquet** and **incised the wound**. Both are harmful and both are still widely practised.

Do not: apply a tourniquet or tight band · cut or incise · suck the wound · apply ice, heat, electric shock or chemicals · use traditional or herbal applications · attempt to capture or kill the snake.

Do: reassure the patient, **immobilise the limb in a neutral position with a splint**, remove rings, watches and anything constrictive, keep the patient still, and transport urgently to hospital.

Releasing a long-standing tight tourniquet can release a bolus of venom, so do so **with resuscitation facilities to hand**.

1. Focused History

- **Time of the bite** and the interval since; the site; and what the patient was doing.
- **Any description of the snake** — but **do not delay treatment to identify it, and never ask anyone to bring in the animal.** Treatment is guided by the clinical syndrome.
- **First aid already applied**, including traditional remedies.
- **Symptoms of systemic envenoming:**
  - **Haemotoxic** — bleeding from gums, nose, wounds or venepuncture sites, haematuria, bruising. Characteristic of viper envenoming, which predominates in this region.
  - **Neurotoxic** — **ptosis first**, then diplopia, difficulty swallowing and speaking, then limb and respiratory muscle weakness. Characteristic of cobra and related elapid envenoming.
  - **Myotoxic** — severe muscle pain and dark urine.
  - **Systemic** — vomiting, abdominal pain, collapse, shock.
- **Comorbidity, anticoagulant use, previous antivenom exposure** — which increases reaction risk — and tetanus immunisation status.

2. Physical Examination

THE SIMPLEST USEFUL THING YOU WILL DO

Draw a line at the leading edge of the swelling and write the time beside it. Repeat hourly.

Progression of swelling is the most useful bedside measure of ongoing envenoming, and it is entirely lost if nobody marks the starting point. Measure and record the limb circumference at a fixed landmark at the same time.

- **Bleeding:** inspect gums, nose, the bite site, venepuncture sites and the urine.
- **Neurological: ptosis is the earliest sign of neurotoxicity** — look for it deliberately and repeatedly. Then eye movements, bulbar function, neck flexion strength, **single-breath count and forced vital capacity**.
- Vital signs, perfusion, tender regional lymphadenopathy, local blistering and necrosis, and assessment for compartment syndrome.

3. Investigations

THE 20-MINUTE WHOLE BLOOD CLOTTING TEST

Place **2 mL of fresh venous blood in a clean, dry glass tube**, leave it completely undisturbed for **20 minutes**, then tip it gently.

If the blood has not clotted, there is a coagulopathy indicating systemic envenoming by a viper, and antivenom is indicated.

It requires no laboratory, no reagents and no electricity, and it remains one of the most useful bedside tests in medicine wherever snakebite is common. The tube must be glass and must not be shaken.

- Complete blood count, coagulation screen with **fibrinogen** and D-dimer, urea, electrolytes and creatinine, **creatine kinase**, urinalysis for blood and myoglobin, electrocardiogram, group and save, blood gas and lactate.
- **Repeat the clotting test and the bloods every 6 hours, and 6 hours after each dose of antivenom**, since coagulopathy can recur as venom continues to be absorbed from the bite site.

4. Management

- Airway, breathing, circulation. **Intravenous access in an unaffected limb.** Continuous monitoring.

Antivenom — the only specific treatment

	Detail
Indications	Systemic envenoming — coagulopathy or spontaneous bleeding, neurotoxicity, cardiovascular instability, acute kidney injury, rhabdomyolysis — or severe local envenoming with rapidly progressive swelling involving more than half the bitten limb.
Not indicated	A bite with no evidence of envenoming. Dry bites are common. Observe for at least 24 hours with serial clotting tests rather than treating pre-emptively.
Administration	Intravenously, according to the product instructions. Draw up adrenaline before you start and have resuscitation equipment at the bedside — anaphylaxis is a real and immediate risk.
Repeat dosing	If coagulopathy persists on repeat testing after 6 hours, or if neurotoxicity progresses. The dose is the same for children as for adults — the amount of venom is the same.

Supportive care

- **Analgesia with paracetamol or opioids. Avoid non-steroidal anti-inflammatory drugs and aspirin**, which worsen bleeding.
- **Avoid intramuscular injections** entirely while coagulopathy persists. Tetanus prophylaxis once clotting has been restored.
- **Antibiotics are not routine** — give them only where there is evidence of infection. Clean and dress the wound; elevate the limb once antivenom has been given.
- **Blood products only for active bleeding, and only after antivenom** — giving clotting factors while venom is still circulating simply consumes them.
- **Neurotoxic envenoming:** monitor the vital capacity as in the neurology block, prepare for intubation, and consider a trial of an anticholinesterase in cobra envenoming.
- **Compartment syndrome is over-diagnosed** in swollen envenomed limbs. Measure the pressure rather than assuming. **Fasciotomy in an uncorrected coagulopathy causes catastrophic bleeding**, and antivenom rather than surgery is the treatment for the swelling itself.
- Support renal function; watch for **serum sickness 5–10 days after antivenom**; and give prevention advice — footwear, lighting, care when moving rocks and firewood.

SCORPION ENVENOMATION

Scorpion sting is far commoner than snakebite in this region, and children are at greatest risk.

The picture: severe local pain with strikingly little to see, followed in significant envenoming by an **autonomic storm** — sweating, salivation, vomiting, agitation, hypertension then shock, pulmonary oedema and myocarditis.

Management: analgesia including local anaesthetic infiltration; close cardiorespiratory monitoring in children; treatment of the autonomic and cardiac effects with critical care support; and scorpion antivenom according to local protocol. **A child with a scorpion sting and systemic features needs monitoring, not reassurance and discharge.**

Spider bites

- **Widow spiders** (*Latrodectus*) — severe generalised muscle cramps and **abdominal rigidity that mimics peritonitis**, with sweating and hypertension. Treat with analgesia, benzodiazepines and antivenom where available.
- **Recluse spiders** (*Loxosceles*) — a progressive necrotic ulcer, occasionally with systemic haemolysis. Management is supportive wound care; **early surgical excision is not helpful** and should be deferred until the lesion has demarcated.
- Most reported "spider bites" are not spider bites. **A necrotic skin lesion attributed to a spider is more often a staphylococcal abscess**, and should be managed as one unless the spider was actually seen.

5. Teaching Points and Viva Questions

- No tourniquets, no incisions, no suction. Immobilise, splint and transport.
- Mark the swelling edge and the time. Repeat hourly.
- The 20-minute whole blood clotting test needs a glass tube and nothing else.

- Antivenom treats systemic envenoming, not the bite. Dry bites are observed, not treated.
- Adrenaline drawn up before the antivenom runs.
- Ptosis is the first sign of neurotoxicity, and the vital capacity is the observation that follows it.
- No anti-inflammatory drugs, no intramuscular injections, and no fasciotomy in an uncorrected coagulopathy.

Questions you should be able to answer:

- The tourniquet has been on for two hours. How do you remove it and why the caution?
- Describe how you would perform the 20-minute whole blood clotting test.
- He has swelling to the elbow but a normal clotting test and no systemic features. Do you give antivenom?
- The limb is tense and painful. A colleague suggests fasciotomy. What is your response?
- A 6-year-old is brought in an hour after a scorpion sting, sweating and vomiting. What is your plan?

Case 73 · Bacterial and Viral Infections of the Skin

CLINICAL VIGNETTE

A **58-year-old man** with type 2 diabetes has had three days of a hot, red, painful, swollen left lower leg which is spreading upwards. There is a small fissure between the fourth and fifth toes.

But: the pain is **far worse than the appearance suggests**, the skin over the shin has become **dusky purple with two haemorrhagic blisters**, there is **crepitus** on palpation, and the induration extends well beyond the visible erythema.

On examination: temperature 38.4 °C, heart rate 124/min, blood pressure 94/56 mmHg, confused. **Lactate 4.2 mmol/L.**

NECROTISING FASCIITIS — RECOGNISE IT IN THE FIRST MINUTE

This is **not** cellulitis. The features that give it away are the ones the examination was designed to find:

Pain out of proportion to the appearance · rapid progression over hours · systemic toxicity out of proportion to the skin · dusky or purple discolouration · **haemorrhagic bullae · crepitus ·** anaesthesia of the overlying skin · woody induration extending beyond the erythema.

The diagnosis is clinical and surgical. Do not wait for imaging and do not use a score to rule it out — the LRINEC score supports the diagnosis but does not exclude it.

Immediate surgical exploration and debridement · broad-spectrum antibiotics with clindamycin added for toxin suppression · aggressive resuscitation · critical care. Survival is measured against the time to the first operation.

1. Cellulitis and Its Mimics

- **Cellulitis** is unilateral, warm, tender, spreading, with an ill-defined edge. **Erysipelas** is sharply demarcated, raised and bright red, often on the face, and usually streptococcal.

TWO THINGS ROUTINELY GOT WRONG

Bilateral "cellulitis" is almost never cellulitis. Consider venous eczema, stasis dermatitis, lymphoedema, and acute lipodermatosclerosis — none of which need antibiotics.

And always look for the portal of entry: interdigital fissures and tinea pedis, an ulcer, eczema, lymphoedema, an insect bite, or trauma.

Treating the tinea pedis is what prevents the next episode, and it is the step most often omitted in a patient with recurrent cellulitis.

- Other mimics: deep vein thrombosis, acute gout, contact dermatitis, erythema nodosum (Case 70).
- **Practical management:** mark the edge of the erythema with the date and time and review it; elevate the limb; treat the portal of entry; choose the antibiotic by severity and local resistance, **considering resistant staphylococcal cover where prevalent**; look for an abscess, because **an abscess is drained and antibiotics are the adjunct**; and consider osteomyelitis in a diabetic foot (Case 25).

2. The Other Bacterial Infections

- **Impetigo** — golden crust, staphylococcal or streptococcal; topical antiseptic or antibiotic for limited disease, oral therapy if extensive. **Bullous impetigo** in children.
- **Folliculitis, furuncle and carbuncle**; **abscess — incision and drainage**; and **hidradenitis suppurativa** (Case 78), which is repeatedly misdiagnosed as recurrent boils.
- **Staphylococcal scalded skin syndrome** and **toxic shock syndrome** — toxin-mediated, with fever, rash, desquamation and shock; supportive care with antitoxin-suppressing antibiotics.

3. The Viral Infections

Infection	Points that matter
Herpes simplex	Primary gingivostomatitis; recurrent cold sores; herpetic whitlow; eczema herpeticum (Case 71); a common trigger of erythema multiforme. Aciclovir, with suppression for frequent recurrence.
Varicella	More severe in adults — varicella pneumonia, hepatitis, encephalitis. Dangerous in pregnancy, the immunosuppressed and neonates. Treat adults and at-risk patients with aciclovir; consider immunoglobulin for exposed at-risk contacts.
Herpes zoster	Dermatomal, with pain often preceding the rash by days. Treat within 72 hours to reduce post-herpetic neuralgia. Ophthalmic zoster with a lesion on the nose — Hutchinson sign — needs same-day ophthalmology. Ramsay Hunt syndrome with facial palsy and ear vesicles. Multidermatomal or disseminated zoster means immunosuppression — test for HIV (Case 45). Vaccination in older adults.
Warts and molluscum contagiosum	Self-limiting; destructive or topical therapy. Extensive molluscum in an adult should prompt an HIV test.
Hand-foot-and-mouth disease; measles	Measles — prodrome, Koplik spots, cephalocaudal rash, with pneumonia, otitis and encephalitis as complications. Notify, and give vitamin A where indicated.

4. Teaching Points and Viva Questions

- Pain out of proportion to the appearance means the operating theatre, not a scan.
- Bilateral leg redness is almost never cellulitis.
- Find and treat the portal of entry, or the cellulitis will recur.
- Drain the abscess.
- Treat zoster within 72 hours, and refer ophthalmic zoster the same day.
- Disseminated zoster or florid molluscum in an adult means test for HIV.

Questions you should be able to answer:

- Which six features told you this was not simple cellulitis?
- A patient has red, scaly, itchy skin on both lower legs and no fever. What is the diagnosis and what would you not prescribe?
- He has had four episodes of cellulitis in the same leg this year. What have you missed?
- A 40-year-old has zoster in three separate dermatomes. What do you test for?
- Why does the timing of aciclovir matter in shingles?

Case 74 • Fungal Infections and Infestations

CLINICAL VIGNETTE

A **30-year-old woman** has had an itchy rash on the trunk for three months. It began as a small scaly ring with a raised edge, and a pharmacist supplied a potent steroid cream. **The itch improved for a few days, and then the rash spread widely** and lost its scaly border. She now has extensive, poorly demarcated erythema across the trunk and both flanks.

Her six-year-old son has a scaly patch on the scalp with hair loss.

Skin scrapings: fungal hyphae seen on microscopy.

TINEA INCOGNITO

A topical corticosteroid suppresses the inflammation while the fungus spreads. The itch settles briefly, the diagnostic scaly advancing edge disappears, the rash becomes widespread and poorly demarcated — and it now looks like eczema, so more steroid is applied.

Scrape before you steroid. Any rash that is **annular, asymmetrical or unilateral**, or that **worsens or spreads on a topical steroid**, is tinea until scrapings prove otherwise.

And scalp tinea in a child needs oral therapy — topical treatment will not cure it.

1. The Dermatophyte Infections

- **The classical appearance:** an annular scaly plaque with a **raised advancing edge and central clearing**, usually asymmetrical or unilateral.
- By site: **corporis, cruris, pedis, manuum, faciei, capitis** (children, needs oral therapy) and **unguium**.
- **Diagnosis: skin scrapings, nail clippings or plucked hairs for microscopy and culture.** It is cheap, and it prevents months of the wrong treatment. Confirm before committing a patient to a long oral course.
- **Treatment:** topical azole or terbinafine for limited disease; **oral terbinafine or itraconazole for scalp, nail, extensive or steroid-modified disease** — nails require three to six months, with liver function monitoring and attention to drug interactions.

2. Yeasts

- **Candidiasis** — intertrigo in skin folds, oral, and genital. **Recurrent or extensive candidiasis is a reason to check the glucose and consider immunodeficiency, including HIV** (Case 45). Ask about antibiotic and inhaled steroid use and denture hygiene.
- **Pityriasis versicolor** — finely scaly hypo- or hyperpigmented macules on the trunk, common in hot humid climates; microscopy shows the "spaghetti and meatballs" appearance. Treated with topical ketoconazole. **Warn the patient that the pigment change takes months to normalise after the fungus has gone**, or the treatment will be judged a failure.
- Deep and systemic mycoses in the immunosuppressed (Case 46); and **mycetoma**, which is endemic in parts of this region and presents as a chronic swelling with discharging sinuses and grains.

3. Infestations

SCABIES

Suspect it from: itch that is worse at night, burrows in the finger web spaces, wrists, axillae and genitals — and other members of the household itching.

Treatment: topical permethrin 5% or oral ivermectin — and treat every household and close contact simultaneously, whether or not they itch. Wash bedding and clothing at high temperature. Treating the patient alone guarantees reinfestation.

Then warn that the itch persists for two to four weeks after successful treatment — it is an immune response to dead mites, not treatment failure. Without that warning the patient will re-treat repeatedly and develop an irritant dermatitis.

Crusted (Norwegian) scabies in the elderly and immunosuppressed — hyperkeratotic, sometimes barely itchy, **enormously contagious**, and regularly misdiagnosed as eczema or psoriasis for months while it spreads through a ward or care home.

- **Head and body lice**; **cutaneous larva migrans** — a serpiginous migrating track after beach or soil exposure, treated with ivermectin or albendazole; and **cutaneous leishmaniasis**, covered in Case 70.

4. Teaching Points and Viva Questions

- Scrape before you steroid. Annular, asymmetrical or steroid-worsened means tinea.
- Scalp and nail disease need oral treatment.
- Recurrent candidiasis means check the glucose and think about immunodeficiency.
- Treat all the household contacts for scabies at the same time.
- Warn that scabies itch lasts weeks after cure, and that versicolor pigment takes months.
- Crusted scabies masquerades as eczema and infects whole wards.

Questions you should be able to answer:

- Explain what the steroid cream did to her rash and to your ability to diagnose it.
- Her son has scalp involvement. Why will a cream not work?
- A whole family itches at night. What do you prescribe, and for whom?
- A treated patient returns at three weeks still itching. Has the treatment failed?
- An elderly nursing home resident has thick scaly plaques thought to be psoriasis, and three staff members are now itching. What is the diagnosis?

Case 75 · Psoriasis and the Papulosquamous Diseases

CLINICAL VIGNETTE

A **32-year-old man** has had scaly plaques on his elbows, knees and scalp for six years, worse in winter. Two weeks ago his skin became far more extensive and inflamed **shortly after finishing a course of oral prednisolone** given for back pain. He has also developed pain and swelling of the right index finger and pitting of several nails.

On examination: well-demarcated salmon-pink plaques with **silvery scale** over both elbows, knees, the scalp margin, the natal cleft and the umbilicus. **Nail pitting and onycholysis.** The right index finger is uniformly swollen — **dactylitis**. Removing scale from a plaque produces pinpoint bleeding.

THE ERROR IN THIS VIGNETTE

Do not treat psoriasis with systemic corticosteroids.

They work briefly, and **withdrawal can precipitate generalised pustular or erythrodermic psoriasis**, which is a medical emergency. This patient's flare was caused by his treatment.

Other triggers to ask about: streptococcal throat infection (guttate psoriasis), stress, skin trauma (the **Koebner phenomenon**), alcohol, smoking, and **drugs — beta blockers, lithium, antimalarials and non-steroidal anti-inflammatory drugs.**

1. Recognising Psoriasis

- **Signs:** well-demarcated plaques with silvery scale on **extensor** surfaces; **Auspitz sign** (pinpoint bleeding after scale removal); **Koebner phenomenon** (lesions at sites of trauma); and involvement of the **scalp margin, natal cleft, umbilicus and nails** — the places to look when the diagnosis is uncertain.
- **Nail changes:** pitting, onycholysis, subungual hyperkeratosis, and the oil-drop sign.
- **Types:** chronic plaque; **guttate**, following streptococcal infection in a young person; flexural or inverse; **generalised pustular psoriasis and erythrodermic psoriasis, both emergencies with fever and systemic upset**; scalp; and nail disease alone.

WHAT TO SCREEN FOR AT EVERY REVIEW

Psoriatic arthritis affects up to a third of patients and is often missed — ask about inflammatory joint pain, dactylitis, heel pain and back pain at every review, and examine the joints (Case 60).

And psoriasis is a cardiovascular and metabolic risk state — metabolic syndrome, fatty liver, cardiovascular disease, depression and alcohol misuse are all more common. Check blood pressure, lipids, glucose and mood, and ask about alcohol. The skin is the visible part of a systemic inflammatory disease.

2. Treatment

- **Topical:** generous emollient, with a **vitamin D analogue and a potent corticosteroid** as the mainstay, plus coal tar and salicylic acid preparations, and specific scalp formulations. Quantity and site-appropriate potency as in Case 71.
- **Phototherapy:** narrowband ultraviolet B for extensive disease.
- **Systemic:** methotrexate; **acitretin — teratogenic, with pregnancy avoidance required for three years afterwards**; ciclosporin for short-term control. **Then biologics — tumour necrosis factor, interleukin-17 and interleukin-23 inhibitors — which have transformed severe disease**, with tuberculosis and hepatitis screening beforehand.

- **Never oral corticosteroids.** Address smoking, alcohol and weight, all of which worsen the disease and reduce treatment response.

3. The Papulosquamous Differential

Condition	What identifies it
Psoriasis	Extensor, well-demarcated, silvery scale, nail and scalp involvement
Lichen planus	Violaceous flat-topped polygonal papules with Wickham striae, on the wrists and shins; oral involvement is common; scarring alopecia and nail destruction. Associated with hepatitis C — and a lichenoid drug eruption is the mimic
Pityriasis rosea	A herald patch, then oval scaly lesions along the lines of cleavage on the trunk — the "Christmas tree" pattern. Self-limiting over six to eight weeks; reassurance is the treatment
Seborrhoeic dermatitis	Greasy scale in the scalp, eyebrows, nasolabial folds and behind the ears. Florid, extensive disease should prompt an HIV test
Pityriasis versicolor	Fine scale with pigment change on the trunk (Case 74)
Secondary syphilis	A non-itchy coppery papulosquamous rash involving the palms and soles. Always in the differential, and diagnosed by serology (Case 79)
Cutaneous T-cell lymphoma	Persistent, fixed, atypical patches in an older patient that do not respond to adequate treatment. Biopsy rather than escalate the steroid
Discoid lupus and subacute cutaneous lupus	Scarring, photodistribution, follicular plugging (Case 59)

4. Teaching Points and Viva Questions

- Never give oral steroids for psoriasis — withdrawal can precipitate pustular or erythrodermic disease.
- Look at the scalp margin, natal cleft, umbilicus and nails.
- Ask about joints and screen the cardiovascular risk at every visit.
- A scaly rash involving the palms and soles should prompt syphilis serology.
- A fixed atypical patch in an older patient that resists treatment needs a biopsy.

Questions you should be able to answer:

- What caused his flare, and what will you tell the doctor who prescribed the prednisolone?
- What does the swollen finger signify and what does it change?
- Name four drugs that worsen psoriasis.
- Distinguish psoriasis from lichen planus at the bedside.
- A young man has an itchy scaly trunk rash six weeks after a sore throat. What is the likely diagnosis?

Case 76 · Blistering Disease and the Cutaneous Drug Emergencies

CLINICAL VIGNETTE

A **68-year-old man** has had three weeks of intensely itchy urticarial plaques on the trunk and limbs. Over the past week **tense blisters** have appeared on the plaques; they are difficult to rupture and leave intact skin around them. **The mouth and other mucosae are unaffected.** No new drugs. Nikolsky sign negative.

Biopsy with direct immunofluorescence: linear IgG and C3 at the basement membrane.

1. The Two Autoimmune Blistering Diseases

	Bullous pemphigoid	Pemphigus vulgaris
Age	Elderly	Middle-aged
Blister	Tense and subepidermal, difficult to rupture	Flaccid and intraepidermal, rupturing to leave painful erosions
Preceding phase	Weeks of intensely itchy urticarial plaques before any blister appears	Often begins with erosions rather than blisters
Mucosa	Usually spared	Prominently involved, and frequently the first site — painful mouth erosions
Nikolsky sign	Negative	Positive
Antibody	Anti-BP180 and BP230	Anti-desmoglein 1 and 3
Treatment	Potent topical corticosteroid, oral corticosteroid, doxycycline, immunosuppressants	Systemic corticosteroid with rituximab — historically a fatal disease

- **Diagnosis: biopsy of a fresh lesion for histology, plus a perilesional biopsy for direct immunofluorescence**, with serum indirect immunofluorescence or enzyme immunoassay. **Two biopsies, from two different places** — an important practical point.
- **Dermatitis herpetiformis** — intensely itchy grouped vesicles on the elbows, knees and buttocks. **It is coeliac disease of the skin:** check coeliac serology, prescribe a gluten-free diet, and use dapsone for rapid relief — **checking glucose-6-phosphate dehydrogenase status first**.
- Other causes of blisters: bullous impetigo, herpes simplex and zoster, insect bites, bullous erythema multiforme, porphyria cutanea tarda, bullosis diabeticorum, friction and burns.

2. Drug Eruptions — Benign or Dangerous?

- **The common, benign one** is the **morbilliform drug eruption**: a symmetrical itchy maculopapular rash appearing **7 to 14 days after a new drug**, with no mucosal involvement and no systemic upset. Stop the drug; it settles.

THE FEATURES THAT SEPARATE A RASH FROM AN EMERGENCY

Skin pain rather than itch · **mucosal involvement — mouth, eyes or genitals** · **blistering or skin detachment** · **a positive Nikolsky sign** · **facial oedema** · fever · lymphadenopathy · **eosinophilia** · deranged liver or renal function.

Any one of these turns a drug rash into a medical emergency. Stop the drug, escalate, and do not wait to see whether it settles.

Syndrome	Recognition and management
Stevens–Johnson syndrome and toxic epidermal necrolysis	One to four weeks after a new drug. Prodrome, then painful dusky macules, blistering and detachment, with mucosal erosions at two or more sites. Graded by the area of detachment. Culprits: allopurinol, lamotrigine, carbamazepine, phenytoin, sulfonamides including co-trimoxazole, nevirapine, NSAIDs. Management: stop the drug, transfer to a burns or specialist unit, meticulous supportive care — fluids, temperature control, analgesia, wound care, nutrition, and same-day ophthalmology because ocular scarring blinds. Consider ciclosporin or other immunomodulation; prognosticate with SCORTEN. Record the drug as an absolute lifelong contraindication and tell the patient in writing.
Drug reaction with eosinophilia and systemic symptoms	Later — two to eight weeks after the drug. Fever, widespread rash, facial oedema, lymphadenopathy, eosinophilia, and organ involvement: hepatitis, nephritis, myocarditis, and thyroiditis which may appear months later. Culprits: allopurinol, anticonvulsants, sulfonamides, vancomycin, minocycline. Stop the drug, give systemic corticosteroid with a slow taper, and monitor organ function — including thyroid function — for months.
Acute generalised exanthematous pustulosis	Rapid onset after an antibiotic: sterile pustules on a background of erythema, with fever and neutrophilia. Resolves on withdrawal.

ERYTHRODERMA

Erythema over more than 90% of the body surface, from any cause — psoriasis, eczema, a drug reaction, cutaneous T-cell lymphoma, or pityriasis rubra pilaris.

It is a medical emergency because the skin has stopped working: fluid loss and dehydration, heat loss and hypothermia, high-output cardiac failure, hypoalbuminaemia, electrolyte disturbance, and infection through a breached barrier.

Admit · keep the patient warm · rehydrate and monitor electrolytes and albumin · bland emollient and no irritants · stop every non-essential drug · treat infection · then treat the underlying cause.

- **Urticaria and angioedema:** acute versus chronic spontaneous urticaria; **non-sedating antihistamines up-titrated to several times the standard dose** rather than long-term corticosteroid; omalizumab in refractory chronic disease. **Angioedema involving the airway is an anaphylaxis emergency. Urticarial vasculitis** — individual lesions lasting more than 24 hours, bruising as they fade, with systemic features — needs a biopsy.

3. Teaching Points and Viva Questions

- Tense blisters and spared mucosa in an elderly patient is pemphigoid; flaccid blisters with mouth erosions is pemphigus.
- Two biopsies — one lesional for histology, one perilesional for immunofluorescence.
- Dermatitis herpetiformis is coeliac disease; check the serology and the G6PD.
- Skin pain, mucosal involvement, blistering, facial oedema, fever or eosinophilia turn a drug rash into an emergency.
- Severe drug reactions come one to four weeks later, and DRESS as late as eight.
- Erythroderma kills through the failure of the skin as an organ.

Questions you should be able to answer:

- Which two features of this man's blisters distinguish his diagnosis from pemphigus vulgaris?

- Which biopsies do you take, and from where?
- A patient develops a rash 12 days after starting allopurinol, with a swollen face, fever and eosinophils of 2.4. What is the diagnosis and what do you monitor for months?
- Name five drugs that commonly cause Stevens–Johnson syndrome.
- Why is an erythrodermic patient at risk of cardiac failure and hypothermia?

Case 77 · Skin Tumours and the Pigmented Lesion

CLINICAL VIGNETTE

A **62-year-old farm worker** with decades of outdoor sun exposure presents with three lesions.

On the nose: a slowly growing **pearly nodule with a rolled edge, surface telangiectasia and central ulceration**, present for about eighteen months and occasionally bleeding.

On the ear: a firm, tender, **keratotic nodule that has grown over three months**.

On the back: a pigmented lesion that his wife says has changed. It is **9 mm across, asymmetrical, with an irregular border and two shades of brown and black**.

1. The Three Common Malignancies

	Basal cell carcinoma	Squamous cell carcinoma	Melanoma
Appearance	Pearly nodule, rolled edge, telangiectasia, central ulcer	Keratotic or ulcerated nodule, often tender	Pigmented lesion that is changing
Growth	Slow, over months to years	Faster, over weeks to months	Variable; nodular type grows fast
Metastasis	Essentially never — but locally destructive	Yes — higher risk on ear, lip and scalp, in scars, and in the immunosuppressed	Yes, and early
Management	Excision, or Mohs surgery at high-risk sites; topical or destructive therapy for superficial lesions	Excision with margins, and assessment of regional nodes	Excisional biopsy, then wide excision by Breslow thickness, sentinel node in selected cases

- **Premalignant and in situ disease: actinic keratoses** — rough scaly macules on sun-damaged skin, treated as a field rather than lesion by lesion; **Bowen disease** — squamous carcinoma in situ, a persistent scaly plaque often on the lower leg; and **keratoacanthoma**, which grows rapidly and may regress but is managed as a squamous carcinoma.

2. The Pigmented Lesion

ASSESSING A PIGMENTED LESION

A — **A**symmetry · **B** — **B**order irregularity · **C** — **C**olour variation · **D** — **D**iameter over 6 mm · **E** — **E**volution or change.

Plus the ugly duckling sign: the lesion that looks unlike all the patient's others. **And the most important single feature is change**, which is why the history from the patient or their family matters more than the photograph.

Do not shave or punch a suspected melanoma. Perform an excisional biopsy with a narrow margin, so that the Breslow thickness — which determines the definitive excision margin, the staging and the prognosis — can be measured.

- **Subtypes:** superficial spreading; **nodular — fast-growing and sometimes amelanotic, so a rapidly growing pink nodule is not automatically benign**; lentigo maligna; and **acral lentiginous and subungual melanoma**.

THE LESIONS THAT GET MISSED

Melanoma is less common in darker skin — and it presents later and at sites that are not routinely examined.

Acral and subungual melanoma occur on the soles, palms and nail beds. So **examine the soles, the palms and the nails**, and treat **pigment spreading onto the nail fold — Hutchinson sign — as melanoma until proved otherwise** rather than as a bruise or a fungal nail.

The consequence of the assumption that pigmented skin does not get melanoma is that when it does, it is found late.

- **Modern systemic therapy — immune checkpoint inhibitors and BRAF/MEK inhibitors — has transformed advanced melanoma**, which is a further reason to biopsy properly and stage accurately rather than treating a suspicious lesion destructively.

3. Benign Lesions Worth Recognising

- **Seborrhoeic keratosis** — "stuck-on", warty, greasy; **naevi**; dermatofibroma; skin tag; cherry angioma; epidermoid cyst; **pyogenic granuloma** — a rapidly growing friable bleeding nodule, which must be distinguished from amelanotic melanoma by histology.

- **And one sign to know: the sudden eruption of multiple seborrhoeic keratoses — the sign of Leser–Trélat — suggests an internal malignancy** (Case 70).

4. Assessment and Prevention

- **Examine the whole skin, not only the lesion the patient points at** — including scalp, behind the ears, soles, between the toes and the nails. Measure and photograph; use dermoscopy where available; **palpate the regional lymph nodes.**

- **Prevention, which matters particularly in this climate:** avoid the midday sun, cover with clothing and a hat, use broad-spectrum sunscreen, avoid sunbeds, and protect children — cumulative childhood exposure drives adult risk.

- **Surveillance of organ transplant recipients and other chronically immunosuppressed patients**, who develop multiple and aggressive squamous cell carcinomas.

5. Teaching Points and Viva Questions

- Pearly with a rolled edge and telangiectasia is basal cell; keratotic, tender and fast-growing is squamous.
- Basal cell carcinoma does not metastasise but destroys locally.
- Change is the most important feature of a pigmented lesion.
- Excisional biopsy, never a shave, for suspected melanoma.
- Examine the soles, palms and nails — that is where melanoma is missed in darker skin.
- Examine all the skin, not just the lesion shown to you.

Questions you should be able to answer:

- Describe each of his three lesions and give your diagnosis for each.

- Why is the lesion on the ear of more concern than the one on the nose?
- The surgeon offers a shave biopsy of the pigmented lesion today. What do you say and why?
- A dark-skinned patient has a pigmented streak in the thumbnail extending onto the cuticle. What is your concern?
- A renal transplant recipient has four scaly nodules on the forearms. What is the diagnosis and what does he need?

Case 78 · Acne, Rosacea, and Disorders of Pigmentation, Hair and Nails

CLINICAL VIGNETTE

A **24-year-old woman** has had acne for four years. It now involves painful deep nodules on both cheeks and along the jawline, and she has developed pitted scars. It is worse before each period. Her periods are irregular, she has noticed coarse hair on the chin and upper lip, and she has gained weight.

She has used several creams and **two long courses of oral antibiotics bought from a pharmacy**.

She also reports **patches of complete pigment loss on the backs of both hands and around the mouth** appearing over six months, and **diffuse hair shedding for the past three months**, which began about two months after a febrile illness.

1. Acne

- **Lesions:** comedones, papules, pustules, nodules and cysts. **Grade by severity and, crucially, by the presence of scarring.**
- **Associations to look for: polycystic ovary syndrome — investigate any woman with acne plus hirsutism and menstrual irregularity, as here**; congenital adrenal hyperplasia; Cushing syndrome; and **drugs — corticosteroids, anabolic steroids, lithium, phenytoin, some progestogens and epidermal growth factor receptor inhibitors.**

THE PRINCIPLE THAT GOVERNS ACNE TREATMENT

Scarring is permanent and preventable, so escalate early rather than repeating antibiotic courses.

Foundation: a topical retinoid with benzoyl peroxide. **Topical antibiotics are used only in combination, never alone**, because of resistance. **Oral antibiotics for no more than about three months** — not repeated courses over years, which is what this patient has had.

In women: a combined oral contraceptive or spironolactone. **For severe, nodular, scarring or refractory acne: isotretinoin** — with the pregnancy prevention programme, and monitoring of lipids, liver function and mood.

And ask about the psychological impact, which is substantial and correlates poorly with the clinical severity. A patient with mild acne may be seriously distressed by it.

2. Rosacea and the Adnexal Disorders

- **Rosacea:** central facial erythema and flushing, telangiectasia, papules and pustules **without comedones** — the feature that separates it from acne. **Ocular rosacea with blepharitis and gritty eyes is common and needs ophthalmology referral.** Rhinophyma in longstanding disease.
- Triggers: heat, sunlight, alcohol, spicy food, hot drinks. Treatment: **sun protection**, topical ivermectin, metronidazole or azelaic acid, oral doxycycline, brimonidine for erythema, and vascular laser.
- **Hidradenitis suppurativa** — painful recurrent nodules, sinus tracts and scarring in the axillae, groin and inframammary folds, associated with obesity and smoking. **It is repeatedly managed as recurrent boils with repeated antibiotics and incisions.** Treatment: antiseptic washes, doxycycline, clindamycin with rifampicin, anti-tumour-necrosis-factor therapy, and surgery — with weight loss and smoking cessation.

3. Pigmentation

- **Vitiligo** — symmetrical, sharply demarcated depigmented macules, characteristically acral and periorificial, accentuated under a Wood's lamp. **Screen for associated autoimmune disease: thyroid function above all, and consider diabetes, pernicious anaemia and adrenal insufficiency.** Treatment: topical corticosteroid or calcineurin inhibitor, phototherapy, and camouflage.

> DO NOT CALL IT COSMETIC
> **The psychological and social impact of vitiligo is severe, and it is greatest in patients with darker skin, where the contrast is most visible.**
> It affects marriage prospects, employment and mood, and patients are frequently told it is "only cosmetic". **Ask about it, treat the distress as part of the disease, and offer camouflage and psychological support alongside any topical treatment.**

- **Melasma** — symmetrical facial hyperpigmentation associated with pregnancy, oral contraception and sun exposure. **Rigorous sun protection is the treatment**, with topical depigmenting agents; it recurs readily.

- **Post-inflammatory hyperpigmentation and hypopigmentation** — very common in darker skin and **slow to resolve, often over many months.** Explain the timescale explicitly, or the patient will assume the treatment failed and seek harmful skin-lightening products.

- Also: drug-induced pigmentation, acanthosis nigricans and Addison pigmentation (Cases 26 and 70).

4. Hair

Pattern	Diagnosis
Diffuse shedding 2–4 months after a trigger — fever, surgery, childbirth, rapid weight loss, severe illness	Telogen effluvium — self-limiting, with full recovery. This patient. Reassure, and check ferritin and thyroid function
Gradual patterned recession or vertex thinning	Androgenetic alopecia — topical minoxidil, finasteride in men
Well-circumscribed smooth bald patches with exclamation-mark hairs, sometimes with nail pitting	Alopecia areata — autoimmune; screen thyroid; topical or intralesional corticosteroid, and newer targeted therapy in severe disease
Loss of follicular openings, scarring	Scarring alopecia — irreversible, so it must be recognised early: lichen planopilaris, discoid lupus, and traction alopecia and central centrifugal cicatricial alopecia related to hairstyling and chemical practices

- **Investigate diffuse hair loss with ferritin and thyroid function**, and with androgen studies where there is hirsutism or virilisation.

5. Nails

- **Pitting and onycholysis** — psoriasis; **onychomycosis** — confirm with clippings before a long oral course (Case 74); **clubbing**; **koilonychia**; **splinter haemorrhages**; **Beau lines** after a systemic illness; leuconychia; half-and-half nails of renal failure; **melanonychia with Hutchinson sign — subungual melanoma** (Case 77); and ingrowing and pincer nails.

6. Teaching Points and Viva Questions

- Acne with hirsutism and irregular periods means investigate for polycystic ovary syndrome.
- Scarring is permanent — escalate early rather than repeating antibiotics.
- Papules and pustules without comedones is rosacea, and the eyes are often involved.
- Hidradenitis is not recurrent boils.
- Screen thyroid function in vitiligo and alopecia areata, and never call vitiligo cosmetic.
- Telogen effluvium follows a trigger by two to four months and recovers.
- Scarring alopecia is irreversible — recognise it before the follicles are gone.

Questions you should be able to answer:

- Which features of her history should prompt endocrine investigation, and what would you send?
- Why is repeating a third course of oral antibiotics the wrong answer?
- What do you check in a patient presenting with vitiligo?
- Explain her hair loss and its prognosis.
- How would you distinguish rosacea from acne on examination?

Case 79 · Sexually Transmitted Infections

CLINICAL VIGNETTE

A **27-year-old man** presents with a widespread rash. Three weeks ago he noticed a **single painless ulcer on the penis**, which healed without treatment. For the past week he has had a **non-itchy rash of coppery-red scaly papules over the trunk and limbs, including the palms and the soles**.

On examination: generalised non-tender lymphadenopathy, **greyish mucous patches on the buccal mucosa**, and patchy "moth-eaten" loss of scalp hair. He feels mildly feverish and tired.

Treponemal antibody test positive; rapid plasma reagin titre 1:128.

BEFORE THE EXAMINATION

Take the sexual history plainly, without assumptions and without embarrassment, because the patient's willingness to answer determines whether the diagnosis is made.

Cover: partners in the last three months and their gender · the sites of exposure · condom use · symptoms in partners · previous infections · HIV status and last test · vaccination · and, in women, contraception and pregnancy.

Confidentiality must be explicit and it must be real. In this setting the social and legal consequences of disclosure can be serious, and a patient who fears them will not return — so explain what will and will not be recorded and who will and will not be told, before you ask the questions.

1. Think in Syndromes, Not Organisms

Syndrome	Causes and management
Urethritis and discharge	Chlamydia — commonest, and frequently asymptomatic; gonorrhoea — purulent, short incubation; *Mycoplasma genitalium*; *Trichomonas*. Diagnose by nucleic acid amplification testing from first-void urine or the relevant site — including throat and rectum where exposure occurred. Treat gonorrhoea with ceftriaxone according to local resistance data — quinolone resistance is widespread and cephalosporin resistance is emerging — and chlamydia with doxycycline. Complications: epididymo-orchitis, pelvic inflammatory disease and tubal infertility, reactive arthritis (Case 60), disseminated gonococcal infection (Seminar 6).
Genital ulceration	Herpes simplex — the commonest cause: multiple painful shallow ulcers, with systemic symptoms in a primary episode. Aciclovir, with suppressive therapy for frequent recurrence, and counselling about transmission and about pregnancy. Syphilis — a single painless indurated chancre. Also chancroid, lymphogranuloma venereum, Behçet disease (Case 61), trauma and malignancy.
Genital lumps	Anogenital warts — human papillomavirus; treated destructively or with topical agents. Human papillomavirus vaccination prevents them, and prevents cervical, anal and oropharyngeal cancer. Molluscum contagiosum.
Vaginal discharge	Bacterial vaginosis, candidiasis and trichomoniasis — not all of which are sexually transmitted, which matters for how the conversation is handled.

2. Syphilis — the Great Imitator

Stage	Features
Primary	A single painless indurated ulcer at the site of inoculation, with regional lymphadenopathy. It heals spontaneously, which is why patients present later.
Secondary (6–12 weeks)	A generalised non-itchy papulosquamous rash characteristically involving the palms and soles, mucous patches, condylomata lata, moth-eaten alopecia, lymphadenopathy and fever. Highly infectious — and it also resolves spontaneously. This patient.
Latent	Asymptomatic, detected only serologically.
Tertiary (years later)	Gummata; cardiovascular syphilis with aortitis and aortic regurgitation (Case 16); neurosyphilis — tabes dorsalis, general paralysis, Argyll Robertson pupils, meningovascular disease.
Congenital	Prevented by antenatal screening and treatment — which is why the screening programme exists.

- **Serology: a treponemal test (enzyme immunoassay or TPPA) remains positive for life and tells you the patient has had syphilis. A non-treponemal test (RPR or VDRL) titre reflects disease activity and is used to confirm the response to treatment.** Dark-ground microscopy or polymerase chain reaction from a lesion where available.

- **Treatment: benzathine penicillin — a single dose in early disease, a longer course in late or neurosyphilis. Warn about the Jarisch–Herxheimer reaction** in the first 24 hours, and follow the RPR titre to confirm a fall.

WHAT MUST HAPPEN FOR EVERY DIAGNOSIS

Every patient with one sexually transmitted infection is tested for the others: HIV, syphilis, hepatitis B and C, gonorrhoea and chlamydia. A diagnosis of one is a marker of exposure risk, not a complete assessment (Case 45).

Then: partner notification and treatment · abstinence until treatment is complete and partners are treated · follow-up serology or a test of cure · vaccination against hepatitis A and B and human papillomavirus · and consideration of HIV pre-exposure prophylaxis where the risk continues.

Partner notification is a clinical duty and a skill. It is done with the patient's cooperation, and handled badly it prevents future presentation — by them and by everyone they talk to.

3. Teaching Points and Viva Questions

- A non-itchy papulosquamous rash involving the palms and soles is secondary syphilis until serology says otherwise.
- Both the primary ulcer and the secondary rash resolve without treatment — spontaneous resolution is not cure.
- The treponemal test stays positive for life; the RPR titre tracks activity and treatment response.
- Test for all the others when you find one.
- Painless single ulcer is syphilis; multiple painful ulcers are herpes.
- Explain confidentiality before you take the history, not after.

Questions you should be able to answer:

- What was the painless ulcer three weeks ago, and why did he not present then?
- Which single feature of the rash makes you think of this diagnosis?
- Explain the difference between the two serological tests and what each one tells you.
- What else must be tested for, and what happens about his partners?
- He becomes febrile with rigors four hours after his injection. What has happened?

Approach to the Patient

Sixteen seminars that start from the presenting problem rather than the diagnosis — jaundice, anasarca, chest pain, dyspnoea, headache, arthritis, chronic cough, hypertensive emergencies, PUO, coma, venous thromboembolism, shock, chronic diarrhoea, ascites, dementia and acute poisoning.

Seminars 1–16 · 18,015 words

How Part II Differs

In Part I you were told the diagnosis in the title and the case taught you how to confirm and manage it. **That is not how patients arrive.** A patient arrives with a symptom, and the diagnosis is the thing you are trying to produce.

These cases therefore run in a different order. **The differential comes first, before any history is taken**, because the differential is what the history is for. A student who takes a history before generating a differential is collecting facts without knowing which ones matter.

Section	What it does
1. The presentation	The patient as they actually appear — usually incomplete and sometimes misleading.
2. Think first	The differential, organised by mechanism or anatomy rather than as a list. Generated before the history.
3. What could kill in the next hour	The small number of diagnoses that must be excluded or treated immediately, regardless of how likely they are.
4. The history that discriminates	Only the questions that move you between the possibilities. Not a systems review.
5. The examination that discriminates	The same principle applied to the physical examination.
6. Investigations, in tiers	Bedside, then first-line, then targeted — with the pivotal test identified.
7. Management while you are still deciding	What to do before the diagnosis is secure, which is most of the time.
8. Teaching points and viva questions	As in Part I.

Case	Seminar it serves
Seminar 1 — Jaundice	Approach to the patient with jaundice
Seminar 2 — Generalised anasarca	Approach to the patient with generalised anasarca
Seminar 3 — Acute chest pain	Approach to the patient with acute chest pain
Seminar 4 — Acute dyspnoea	Approach to the patient with acute dyspnoea; respiratory failure and hypoxaemia
Seminar 5 — Headache	Approach to the patient with headache
Seminar 6 — Arthritis	Approach to the patient with arthritis; polyarthritis
Seminar 7 — Chronic cough	Approach to the patient with chronic cough
Seminar 8 — Hypertensive urgencies and emergencies	Hypertensive urgencies and emergencies
Seminar 9 — Pyrexia of unknown origin	Approach to the patient with pyrexia of unknown origin
Seminar 10 — Coma	Approach to the patient with coma
Seminar 11 — Venous thromboembolism	Approach to the patient with venous thromboembolism; pulmonary thromboembolism
Seminar 12 — Shock	Shock, its types and management
Seminar 13 — Chronic diarrhoea	Approach to the patient with chronic diarrhoea
Seminar 14 — Ascites	Approach to the patient with ascites
Seminar 15 — Dementia	Approach to the patient with dementia
Seminar 16 — Acute poisoning	Approach to the patient with acute poisoning

Seminar 1 · Approach to the Patient with Jaundice

THE PRESENTATION

A **58-year-old man** has become progressively yellow over three weeks. He itches intolerably, particularly at night. His stools have become pale and his urine dark. He has lost 8 kg without trying. **He has had no pain and no fever.**

On examination: deeply jaundiced with scratch marks over the trunk. **The gallbladder is palpable and non-tender.** The liver edge is firm. There are **no spider naevi, no palmar erythema and no ascites**. He is fully alert with no asterixis.

Bilirubin 280 µmol/L, predominantly conjugated · alkaline phosphatase 640 · gamma-glutamyl transferase 780 · alanine aminotransferase 92 · albumin 34 g/L · INR 1.1.

1. Think First — Three Compartments, Three Questions

Compartment	Bilirubin	Causes
Pre-hepatic	Unconjugated	Haemolysis of any cause, ineffective erythropoiesis, Gilbert syndrome. Liver enzymes are normal, the stools are normal in colour, and there is no bilirubin in the urine because unconjugated bilirubin is not water-soluble.
Hepatic	Mixed, hepatitic enzyme pattern	Viral hepatitis, drugs and toxins, alcohol, autoimmune hepatitis, ischaemic hepatitis, Wilson disease, haemochromatosis, cirrhosis, infiltration, severe sepsis.
Post-hepatic	Conjugated, cholestatic pattern	Gallstones, carcinoma of the head of the pancreas, cholangiocarcinoma, benign stricture, primary biliary cholangitis, primary sclerosing cholangitis, drug-induced cholestasis, nodal compression.

Answer three questions in order, and the diagnosis narrows at each step:

- **Is the bilirubin conjugated or unconjugated?** This separates haemolysis and Gilbert syndrome from everything else, and it costs one extra box on the request form.
- **Is the enzyme pattern hepatitic or cholestatic?** Aminotransferases out of proportion means the hepatocytes; alkaline phosphatase and gamma-glutamyl transferase out of proportion means the biliary tree.
- **Are the bile ducts dilated?** This is what the ultrasound is for, and it is the pivotal investigation in the whole assessment.

2. What Could Kill in the Next Hour

ASCENDING CHOLANGITIS

Charcot triad: fever, right upper quadrant pain and jaundice. Add hypotension and confusion and it becomes **Reynolds pentad**, which carries a high mortality.

An obstructed, infected biliary tree is a closed-space infection under pressure. **Antibiotics alone do not treat it — it must be drained**, urgently by endoscopic retrograde cholangiopancreatography or percutaneously, within hours in a septic patient.

This patient is afebrile and painless, which is precisely why he is **not** in this category — but you establish that deliberately rather than by default.

- **Acute liver failure** — jaundice with encephalopathy and a rising INR. See Case 35.
- **Paracetamol toxicity** — check a level in every jaundiced patient regardless of the history.

- **Severe haemolysis**, and **sepsis** with jaundice as a manifestation rather than a cause.

3. The History That Discriminates

Ask	What the answer tells you
Is there pain, and what kind?	Colicky right upper quadrant pain radiating to the back or shoulder suggests stones. Painless progressive jaundice with weight loss is malignant obstruction until proved otherwise.
Pale stools, dark urine and itch?	Cholestasis — bile is not reaching the gut. Their absence with dark urine but normal stools suggests haemolysis.
Fever or rigors?	Cholangitis, or hepatitis with a systemic illness.
Every drug, herbal and traditional preparation, and paracetamol	Drug-induced liver injury is common and under-recognised, and the culprit is often not prescribed.
Alcohol quantified; travel; unpasteurised dairy; transfusion; tattoos; sexual history	Alcoholic liver disease, viral hepatitis, brucellosis.
Previous biliary surgery, pancreatitis, inflammatory bowel disease	Stricture; primary sclerosing cholangitis, which is associated with ulcerative colitis.
Family history of jaundice, anaemia or liver disease; age under 40	Gilbert syndrome, hereditary haemolytic anaemia, Wilson disease.

4. The Examination That Discriminates

COURVOISIER'S SIGN

A palpable, non-tender gallbladder in a jaundiced patient makes gallstones an unlikely cause.

The reasoning is sound: a gallbladder chronically diseased by stones is fibrotic and cannot distend. A gallbladder that distends is therefore obstructed by something **downstream and recent** — characteristically a carcinoma of the head of the pancreas.

It is not infallible, but in this patient it points the assessment firmly towards malignant obstruction.

- **The presence or absence of chronic liver disease stigmata** — spider naevi, palmar erythema, gynaecomastia, ascites. Their **absence**, as here, argues against cirrhosis and for an acute obstructive process in a previously normal liver.
- **Mental state and asterixis**, which convert this from a diagnostic problem into an emergency.
- Liver edge — smooth and tender in hepatitis, hard and irregular in malignancy or cirrhosis; splenomegaly (portal hypertension or haemolysis); **left supraclavicular node**; abdominal masses; ascites.
- Pallor in haemolysis; **Kayser–Fleischer rings** in any patient under 40; scratch marks; xanthelasma in chronic cholestasis.

5. Investigations, in Tiers

- **Bedside:** urinalysis — **bilirubin in the urine means it is conjugated**; capillary glucose.
- **First line:** split bilirubin, full liver enzyme profile, **INR and albumin as the measures of function**, complete blood count with reticulocytes and blood film, haptoglobin and lactate dehydrogenase, direct

antiglobulin test if unconjugated, amylase, renal function, **paracetamol level**, viral hepatitis serology, autoimmune screen with immunoglobulins, and — under 40 — caeruloplasmin and iron studies.

THE PIVOTAL TEST

Ultrasound of the abdomen is the investigation that divides the problem in two, and it should be obtained early.

Ducts dilated → the obstruction is mechanical. Proceed to magnetic resonance cholangiopancreatography or endoscopic ultrasound to define the level and cause, and computed tomography for staging.

Ducts not dilated → the problem is within the hepatocytes or the small intrahepatic ducts. Pursue serology, autoantibodies and, where necessary, liver biopsy.

- **Magnetic resonance cholangiopancreatography is diagnostic; endoscopic retrograde cholangiopancreatography is therapeutic.** Do not use the latter as a purely diagnostic test — it carries a real risk of post-procedure pancreatitis and should be reserved for when you intend to intervene.
- CA 19-9 rises in biliary obstruction of any cause, including benign, so **interpret it only after the obstruction is relieved** and never as a screening test.

6. Management While You Are Still Deciding

- **Vitamin K** for a prolonged prothrombin time — in obstructive jaundice the deficiency is of absorption, and it corrects.
- **Cholangitis: broad-spectrum antibiotics and urgent biliary drainage.** Do not wait for the fever to settle before referring for drainage.
- **Maintain hydration and monitor renal function.** Jaundiced patients are prone to acute kidney injury, particularly around contrast and procedures.
- **Treat the itch** — it is genuinely disabling and is often ignored. Cholestyramine, with other agents where that fails.
- Nutrition, including fat-soluble vitamins; stop hepatotoxic drugs; and refer to the multidisciplinary team where malignancy is suspected, for staging and for **biliary stenting**, which relieves symptoms whether or not resection is possible.

7. Teaching Points and Viva Questions

- Split the bilirubin, read the enzyme pattern, then ask the ultrasound whether the ducts are dilated.
- Painless jaundice with weight loss is malignancy until proved otherwise.
- A palpable non-tender gallbladder points away from stones.
- Fever plus pain plus jaundice means the biliary tree needs draining, not just antibiotics.
- The INR and albumin tell you how the liver is working. The bilirubin does not.
- Endoscopic retrograde cholangiopancreatography is a treatment, not an investigation.

Questions you should be able to answer:

- His urine contains bilirubin. What does that exclude?
- Explain the reasoning behind Courvoisier's sign.
- The ultrasound shows no duct dilatation. How does your plan change?
- A different patient has jaundice, fever and rigors with a blood pressure of 84/50. What are your first three actions?
- A 24-year-old has an isolated unconjugated bilirubin of 45 with normal enzymes after a period of fasting. What is the diagnosis?

Seminar 2 · Approach to the Patient with Generalised Anasarca

THE PRESENTATION

A **42-year-old man** describes six weeks of progressive swelling. He first noticed **puffiness around his eyes on waking**; over the following weeks his legs, scrotum and abdomen have swollen. His urine has been **frothy**. He is breathless lying flat and has gained 12 kg.

On examination: periorbital oedema, pitting oedema to the sacrum, scrotal oedema, and ascites with shifting dullness. Blood pressure 152/94 mmHg. **The jugular venous pressure is not raised.** There are no spider naevi and no palmar erythema. Chest: dullness at both bases.

Urine dipstick: protein ++++, no blood. Urine albumin-to-creatinine ratio grossly raised · serum albumin 18 g/L · cholesterol markedly raised · creatinine normal.

1. Think First — Four Mechanisms

Oedema forms when the Starling forces are disturbed. There are only four ways to do that, and every cause sits in one of them.

Mechanism	Causes
Raised hydrostatic pressure	Heart failure, constrictive pericarditis, venous obstruction, renal failure with fluid overload, drugs — calcium channel blockers, non-steroidal anti-inflammatory drugs, thiazolidinediones
Reduced oncotic pressure	Nephrotic syndrome, cirrhosis, protein-losing enteropathy, severe malnutrition
Increased capillary permeability	Sepsis, anaphylaxis and angioedema, burns, systemic inflammatory states
Lymphatic obstruction	Malignancy, post-surgical or post-radiotherapy lymphoedema, filariasis

Add two that fit awkwardly: **hypothyroid myxoedema**, which is non-pitting, and pregnancy.

THE JUGULAR VENOUS PRESSURE IS THE SINGLE MOST USEFUL DISCRIMINATOR

Look at the neck before you look at the ankles.

Raised → the problem is on the venous side: heart failure, constrictive pericarditis, fluid overload from renal failure, or tamponade.

Normal or low → the problem is oncotic or permeability: **nephrotic syndrome, cirrhosis, malnutrition, protein-losing enteropathy**.

Then add the timing: **periorbital oedema worst on waking suggests a renal cause**; ankle oedema worst by evening suggests a cardiac or venous one; and unilateral swelling is local until proved otherwise.

2. What Could Kill in the Next Hour

- **Pulmonary oedema** with hypoxia; **cardiac tamponade**; **massive pulmonary embolism** — for which the nephrotic patient is at high risk; **severe hyponatraemia**; **sepsis**; and anasarca with **acute kidney injury and hyperkalaemia**.

3. The History That Discriminates

- **Where did it start and when is it worst?** Face on waking versus ankles by evening. This one question separates the renal from the cardiac patient more efficiently than any test.

- **Frothy urine, haematuria, reduced urine output** — renal. **Orthopnoea, paroxysmal nocturnal dyspnoea, chest pain, palpitations** — cardiac.
- **Jaundice, alcohol, known liver disease, abdominal swelling preceding leg swelling** — hepatic.
- **Diarrhoea, weight loss, malabsorption** — protein-losing enteropathy or malnutrition.
- **Drugs** — calcium channel blockers are a very common and entirely reversible cause of ankle oedema, and anti-inflammatory drugs cause fluid retention and worsen every other cause.
- **Underlying disease that causes nephrotic syndrome:** diabetes, hepatitis B and C, human immunodeficiency virus, systemic lupus erythematosus, amyloidosis, myeloma, malignancy, and recent infection.

4. The Examination That Discriminates

- **Jugular venous pressure**, weight, blood pressure, and **the urine dipstick — which you perform yourself rather than waiting for**.
- Distribution of oedema: periorbital, sacral in a bedbound patient, scrotal, and whether it pits.
- Ascites and shifting dullness; pleural effusions; third heart sound and murmurs; pulsatile hepatomegaly; **Kussmaul sign** for constrictive pericarditis.
- Stigmata of chronic liver disease; thyroid examination; lymphadenopathy; and xanthelasma, which accompanies the hyperlipidaemia of nephrotic syndrome.

5. Investigations, in Tiers

- **Bedside: urine dipstick, and a urine protein-to-creatinine or albumin-to-creatinine ratio.** This single test immediately separates the renal cause from all the others, and it is available within minutes.
- **First line:** serum albumin and total protein, liver and renal function, lipids, complete blood count, C-reactive protein, thyroid function, glucose, **natriuretic peptide**, chest radiograph, electrocardiogram.
- **Targeted — if nephrotic:** hepatitis B and C, human immunodeficiency virus, antinuclear antibody, anti-double-stranded DNA and complement, antineutrophil cytoplasmic antibodies, **serum immunoglobulins with protein electrophoresis and serum free light chains** to exclude myeloma and amyloidosis, and **renal biopsy — which in an adult determines the treatment** and is not optional.
- **Targeted — otherwise:** echocardiography, abdominal ultrasound, and faecal alpha-1 antitrypsin clearance for protein-losing enteropathy.

NEPHROTIC SYNDROME — DEFINITION AND CONSEQUENCES

Proteinuria above 3.5 g in 24 hours · serum albumin below 30 g/L · oedema · usually with hyperlipidaemia.

The complications are what harm the patient, and they are predictable:

Venous thromboembolism, including **renal vein thrombosis** — loss of antithrombin in the urine makes these patients strikingly prothrombotic · **infection**, particularly pneumococcal, from urinary loss of immunoglobulins · acute kidney injury · hyperlipidaemia · vitamin D deficiency.

6. Management While You Are Still Deciding

- **Salt restriction and fluid restriction**, with **daily weights** as the measure of response.
- **Loop diuretic — and expect to need more than usual.** Gut wall oedema impairs absorption of oral diuretics, so intravenous administration or a higher dose is frequently required, sometimes combined with a thiazide for sequential blockade.
- **An angiotensin-converting enzyme inhibitor or receptor blocker to reduce proteinuria**, with monitoring of potassium and creatinine.
- **Statin** for the hyperlipidaemia; **thromboprophylaxis, and formal anticoagulation where the albumin is very low** or there is another risk factor.
- **Vaccination**, including pneumococcal; treat infection promptly and with a low threshold.
- **Then treat the cause**, which in an adult means acting on the biopsy — immunosuppression for the primary glomerular diseases, and treatment of the underlying disorder in secondary causes.

7. Teaching Points and Viva Questions

- Look at the neck before the ankles. The jugular venous pressure divides the differential in two.
- Puffy eyes in the morning is a renal history; swollen ankles in the evening is a cardiac one.
- Dipstick the urine yourself, in the first five minutes.
- Nephrotic patients clot, and they get infected. Anticipate both.
- Oral diuretics are poorly absorbed through an oedematous gut.
- In an adult, the biopsy determines the treatment.

Questions you should be able to answer:

- His jugular venous pressure is normal. Which half of your differential does that remove?
- Why is he at risk of thrombosis, and what would you do about it?
- He is not responding to 40 mg of oral furosemide. Give two reasons and your next step.
- What must be excluded before you attribute this to a primary glomerular disease?
- A different patient has ankle oedema, a normal albumin and a normal jugular venous pressure, and takes amlodipine. What is your first move?

Seminar 3 · Approach to the Patient with Acute Chest Pain

THE PRESENTATION

A **62-year-old woman** presents with two hours of central chest discomfort which she describes as a heaviness radiating to her left arm. She is sweaty and nauseated. She also reports that it is worse on deep inspiration, and she has felt breathless since it began.

She had a knee replacement three weeks ago and flew home last week.

On examination: heart rate 108/min, blood pressure 132/84 mmHg in the right arm and 128/82 mmHg in the left, respiratory rate 24/min, **oxygen saturation 93% on air**. Chest is clear. Heart sounds normal. The right calf is slightly swollen.

Electrocardiogram: sinus tachycardia with T wave inversion in V1–V4. High-sensitivity troponin mildly raised.

1. Think First — The Six That Kill, Then Everything Else

Diagnosis	The story and the sign	The test
Acute coronary syndrome	Heavy, exertional, radiating to arm or jaw, with sweating and nausea	Electrocardiogram and serial troponin
Aortic dissection	Tearing pain, maximal at the very onset, radiating to the back; pulse or blood pressure differential; new aortic regurgitation; widened mediastinum	Computed tomographic aortogram
Pulmonary embolism	Pleuritic pain with breathlessness; hypoxia with a clear chest; risk factors; tachycardia	Computed tomographic pulmonary angiography
Tension pneumothorax	Sudden, unilateral hyper-resonance with absent breath sounds, tracheal deviation, shock	None — this is a clinical diagnosis. Decompress first
Oesophageal rupture	Severe pain after forceful vomiting; surgical emphysema; pleural effusion	Computed tomography with contrast
Cardiac tamponade	Raised jugular venous pressure, muffled heart sounds, hypotension, pulsus paradoxus	Echocardiography

Then the rest: pericarditis, myocarditis, pneumonia and pleurisy, gastro-oesophageal reflux and oesophageal spasm, musculoskeletal and costochondral pain, **herpes zoster before the rash appears**, biliary and pancreatic pain referred to the chest, and anxiety — which is a diagnosis of exclusion, not a first impression.

2. What Could Kill in the Next Hour

- **Electrocardiogram within 10 minutes**, repeated if the first is unremarkable and the pain continues.
- Oxygen only if hypoxic; intravenous access; continuous monitoring beside a defibrillator; analgesia.

BEFORE THE ASPIRIN

Take the blood pressure in both arms and feel all the peripheral pulses before you give aspirin, an antiplatelet or an anticoagulant.

Giving antithrombotic therapy to a patient with an aortic dissection is among the most damaging errors in acute medicine, and dissection presents as "chest pain radiating down the arm" often enough to catch people out.

Features that should stop you: tearing pain that was maximal at onset, radiation to the back, a pulse or pressure differential, a new early diastolic murmur, neurological signs, or a widened mediastinum.

3. The History That Discriminates

- **How quickly did it reach its worst?** Instantaneous and maximal at onset suggests dissection or pneumothorax. Crescendo over minutes suggests ischaemia.
- **Character and radiation.** Heaviness to the arm or jaw suggests ischaemia; tearing to the back suggests dissection; sharp and pleuritic suggests pleura, pericardium or embolism.
- **What changes it?** Worse on inspiration — pleuritic. Relieved by sitting forward — pericarditis. Reproduced by movement or palpation — musculoskeletal, though this does **not** exclude a serious cause. Related to food or lying flat — oesophageal.
- **What came with it?** Sweating, nausea and vomiting favour ischaemia. Syncope raises dissection, embolism and arrhythmia. **Vomiting immediately before the pain began** raises oesophageal rupture.
- **Risk factors for each of the six**, taken deliberately — including **recent surgery, immobility and long-haul travel** for embolism, as in this patient, and cocaine use in a younger one.

4. The Examination That Discriminates

- **Both arms, all pulses, respiratory rate and oxygen saturation**, perfusion and conscious level.
- **Jugular venous pressure** — raised in tamponade, right ventricular infarction and massive embolism.
- Heart sounds: a **new early diastolic murmur** suggests dissection into the aortic root; a **rub** suggests pericarditis; muffled sounds suggest tamponade. Test for pulsus paradoxus.
- Chest: tracheal position, asymmetry of expansion, percussion note, breath sounds, and **surgical emphysema**.
- Calves; abdomen; chest wall palpation; and the skin over the dermatomes for early zoster.

5. Investigations, in Tiers

- **Bedside:** electrocardiogram within 10 minutes and repeated; oxygen saturation; glucose.
- **First line:** high-sensitivity troponin using the local pathway with a repeat sample; complete blood count, renal function, coagulation; **chest radiograph**.
- **Targeted: D-dimer only where pulmonary embolism is being considered and the pre-test probability is low or intermediate** — a positive result in a high-probability patient adds nothing and a negative one cannot be relied on. Then computed tomographic pulmonary angiography, or computed tomographic aortogram, or echocardiography, as the differential dictates.

THE TRAP IN THIS CASE

A raised troponin means myocardial injury. It does not mean myocardial infarction, and it certainly does not mean coronary occlusion.

Troponin rises in **pulmonary embolism**, sepsis, heart failure, renal impairment, myocarditis, tachyarrhythmia, and after stroke or major exertion.

In this patient, a mildly raised troponin with **anterior T wave inversion, hypoxia, a clear chest, a swollen calf and recent surgery and air travel** is right heart strain from pulmonary embolism — not an anterior myocardial infarction. Anchoring on the first plausible diagnosis is the error the case is built to demonstrate.

6. Management While You Are Still Deciding

- Monitored area, oxygen to target, analgesia, and treatment of the specific diagnosis once identified — thrombolysis or thrombectomy for infarction, anticoagulation for embolism, urgent surgical referral for dissection or rupture, needle decompression for tension pneumothorax.
- **Where the diagnosis remains uncertain, the disposition decision is the clinical act.** Use a validated pathway, and if discharging, provide explicit safety-netting and arranged follow-up rather than an instruction to return if worse.
- **Remember that a patient may have two diagnoses at once** — an embolism and demand ischaemia, or pneumonia and an arrhythmia. Do not stop looking once the first explanation is found.

7. Teaching Points and Viva Questions

- Electrocardiogram in ten minutes, and repeat it if the pain persists.
- Both arms before the aspirin.
- Hypoxia with a clear chest is pulmonary embolism until proved otherwise.
- Tension pneumothorax is treated before it is imaged.
- Troponin is a marker of injury, not of a diagnosis.
- Reproducible chest wall tenderness lowers the probability of a dangerous cause but never excludes it.

Questions you should be able to answer:

- Give the six immediately life-threatening causes and one discriminating feature of each.
- Why is her troponin raised, and what does the T wave inversion represent?
- When is a D-dimer useful, and when is it worse than useless?
- What features in a history would make you withhold aspirin?
- A patient collapses with chest pain, a blood pressure of 70/40, a raised jugular venous pressure and a clear chest. Give three diagnoses.

Seminar 4 · Approach to the Patient with Acute Dyspnoea

THE PRESENTATION

A **74-year-old man** has become progressively breathless over three days and is now breathless at rest. He sleeps on four pillows and his ankles have swollen. He has also had a productive cough with green sputum and has felt feverish.

He has documented chronic obstructive pulmonary disease and documented heart failure, and takes inhalers, furosemide and bisoprolol.

On examination: speaking in short phrases. Respiratory rate 30/min, **oxygen saturation 86% on air**, heart rate 118/min and **irregularly irregular**, blood pressure 108/68 mmHg, temperature 38.1 °C. **The jugular venous pressure is raised.** There are widespread crackles **and** expiratory wheeze. Pitting oedema to both knees.

1. Think First — Follow the Oxygen

Level	Causes
Airway	Foreign body, anaphylaxis and angioedema, epiglottitis, laryngeal tumour — stridor is the sign
Lungs	Asthma, chronic obstructive pulmonary disease, pneumonia, pneumothorax, pleural effusion, acute respiratory distress syndrome, interstitial lung disease
Circulation	Pulmonary oedema, acute coronary syndrome, arrhythmia, pulmonary embolism, tamponade, valve disease
Blood	Anaemia, carbon monoxide poisoning, methaemoglobinaemia
Metabolic and neuromuscular	Metabolic acidosis — ketoacidosis, sepsis, renal failure, salicylate; neuromuscular weakness; chest wall restriction
Psychogenic	Hyperventilation — a diagnosis of exclusion and never a first impression

Four questions sort most patients within a minute of walking to the bedside:

- **Is there stridor, or wheeze, or neither?** Stridor is upper airway and is an emergency; wheeze is lower airway; neither points elsewhere.
- **Is the chest clear despite hypoxia?** Then think pulmonary embolism, anaemia, acidosis, or shunt.
- **Is the jugular venous pressure raised?** Cardiac, embolic or tamponade.
- **Is it unilateral?** Pneumothorax, effusion or consolidation.

2. What Could Kill in the Next Hour

- **Sit the patient up. Give oxygen to an explicit target** — 94–98%, or **88–92% where there is a risk of carbon dioxide retention**, written on the chart. Monitoring, intravenous access, and senior help early.
- **Look immediately for the causes that are reversible within minutes:** tension pneumothorax, anaphylaxis, upper airway obstruction, and opioid toxicity.

3. The History That Discriminates

- **Speed of onset is the most informative single item.** Seconds to minutes — pneumothorax, embolism, aspiration, anaphylaxis, arrhythmia. Hours — asthma, pulmonary oedema, pneumonia. Days to weeks — effusion, anaemia, interstitial disease, malignancy.

- **Orthopnoea and paroxysmal nocturnal dyspnoea** favour a cardiac cause; **fever and purulent sputum** an infective one; **pleuritic pain and unilateral leg swelling** an embolic one; **wheeze with a known diagnosis** an airways one.
- **Weight gain, ankle swelling, and any recent change to diuretic dose or adherence** — a very common and entirely correctable precipitant.
- Exposure history, occupational history, drugs, and the patient's **baseline exercise tolerance**, without which "breathless" cannot be quantified.

4. The Examination That Discriminates

- Respiratory rate counted, saturation **on air** with the device and flow recorded, ability to complete a sentence, accessory muscle use, cyanosis, conscious level.
- **Jugular venous pressure**; tracheal position; percussion and auscultation comparing sides; heart sounds, third sound and murmurs; peripheral oedema and calves; peak flow; temperature; capillary glucose.

5. Investigations, in Tiers

- **Bedside:** arterial or venous blood gas — which tells you the **type of respiratory failure, whether there is acidosis, the lactate, and the bicarbonate as a marker of chronicity**; electrocardiogram; glucose; peak flow.
- **First line:** chest radiograph, complete blood count, renal function, C-reactive protein, **natriuretic peptide**, troponin.
- **Targeted:** computed tomographic pulmonary angiography where embolism is suspected; echocardiography; sputum and blood cultures; carboxyhaemoglobin.
- **Bedside ultrasound** is increasingly the fastest discriminator available — B-lines of pulmonary oedema, pleural effusion, absent lung sliding in pneumothorax, gross cardiac function and inferior vena cava filling, all in a few minutes at the trolley.

THE POINT OF THIS CASE

This man has **at least three simultaneous problems**: an infective exacerbation of his airways disease, decompensated heart failure, and new atrial fibrillation — each worsening the others.

The commonest error in the breathless elderly patient is to find one diagnosis and stop. **Treat the contributors in parallel** — controlled oxygen, bronchodilators, antibiotics, diuresis, rate control — and reassess frequently, rather than debating which single label is correct.

Decide and **document the ceiling of care early**, while the patient can still participate in the conversation.

6. Management While You Are Still Deciding

- Controlled oxygen to a written target, with a repeat gas after 30–60 minutes.
- Treat the most likely and the most dangerous simultaneously, then **subtract** treatments as the picture clarifies rather than adding indefinitely.

- Continuous positive airway pressure for cardiogenic pulmonary oedema, or non-invasive ventilation for hypercapnic acidosis, with early critical care involvement.
- Reassess after every intervention. Improvement or its absence is itself diagnostic information.

7. Teaching Points and Viva Questions

- Write the target saturation range on the chart. "Give oxygen" is not a prescription.
- Speed of onset narrows the differential faster than any investigation.
- Hypoxia with a clear chest, and the jugular venous pressure, are the two highest-yield observations.
- Elderly patients are allowed more than one diagnosis, and usually have them.
- Hyperventilation is what you conclude at the end, never what you assume at the start.

Questions you should be able to answer:

- What oxygen target would you set for this man, and why?
- Name the three processes contributing to his breathlessness and the treatment for each.
- His gas shows pH 7.28, carbon dioxide 8.4 kPa, bicarbonate 31. Interpret it.
- A 24-year-old is acutely breathless with a clear chest and normal saturations. What must you exclude before diagnosing hyperventilation?
- Which four bedside ultrasound findings would you look for, and what would each tell you?

Seminar 5 · Approach to the Patient with Headache

THE PRESENTATION

A **48-year-old woman** developed a severe occipital headache while lifting a heavy box. **It reached its maximum intensity within seconds** and she describes it as the worst headache of her life. She vomited twice and now dislikes the light. Six hours later it has eased somewhat but has not gone.

On examination: Glasgow Coma Scale 15, no focal neurological deficit. There is neck stiffness. Blood pressure 168/96 mmHg, temperature 36.9 °C. Fundoscopy shows no papilloedema.

THE SINGLE MOST IMPORTANT QUESTION IN THIS CONSULTATION

"How long did it take to reach its worst?" is the question that matters — not "how bad is it?"

Almost everybody with a severe headache says it is the worst they have had. **Thunderclap headache — maximum intensity within about one minute — is the feature that demands investigation**, and it means subarachnoid haemorrhage until proved otherwise.

Partial improvement over hours is entirely compatible with subarachnoid haemorrhage and provides no reassurance at all.

1. Think First — Primary and Secondary

- **Primary headache disorders:** migraine with and without aura, tension-type headache, and the trigeminal autonomic cephalalgias including cluster headache.
- **Secondary headache** is where the danger lies:

Cause	The pattern that suggests it
Subarachnoid haemorrhage	Thunderclap onset, vomiting, neck stiffness, may have no focal signs at all
Meningitis or encephalitis	Fever, neck stiffness, rash, altered consciousness, seizures, personality change
Giant cell arteritis	Age over 50, new headache, scalp tenderness, jaw claudication, visual symptoms, raised inflammatory markers
Raised intracranial pressure or a mass lesion	Worse on waking, worse on coughing, bending or straining; vomiting; papilloedema; focal signs; new seizure
Cerebral venous sinus thrombosis	Subacute progressive headache, pregnancy or the puerperium, prothrombotic state, seizures, papilloedema
Arterial dissection	Neck pain, Horner syndrome, after trauma or neck manipulation
Acute angle-closure glaucoma	Painful red eye, haloes around lights, fixed mid-dilated pupil, vomiting
Carbon monoxide poisoning	Other members of the household also unwell; heaters and poor ventilation
Medication overuse headache	Daily analgesia for more than 10–15 days per month
	THE RED FLAGS — SNOOP **S** — **S**ystemic features: fever, weight loss, malignancy, immunosuppression, pregnancy **N** — **N**eurological deficit, seizure, or altered consciousness **O** — **O**nset sudden: thunderclap **O** — **O**lder: a new headache over the age of 50 **P** — **P**attern change or **P**rogression; **P**ositional variation; **P**recipitated by Valsalva; **P**apilloedema

2. What Could Kill in the Next Hour

- **Bacterial meningitis** — antibiotics immediately, before imaging and before lumbar puncture (Case 44).
- **Subarachnoid haemorrhage** with rebleeding or hydrocephalus.
- **Giant cell arteritis with visual symptoms — start high-dose corticosteroids on suspicion, before the biopsy**, because the visual loss is sudden, painless and irreversible.
- Raised intracranial pressure with impending herniation; carbon monoxide poisoning; hypertensive emergency with encephalopathy.

3. The History That Discriminates

- **Time to maximum intensity**, as above. Then duration, frequency and whether the pattern has changed.
- **Positional variation:** worse lying flat and on waking suggests raised pressure; worse on standing and relieved by lying suggests low cerebrospinal fluid pressure, as after a dural puncture.
- **Triggers:** exertion, coughing, straining and sexual activity all raise the concern for haemorrhage on a first occurrence.
- **Associated features:** fever, rash, visual disturbance, diplopia, weakness, seizure, jaw pain on chewing, lacrimation and nasal congestion with a strictly unilateral orbital pain (cluster), and aura.
- **Analgesic use — how many days per month**, which identifies medication overuse headache, a very common and entirely reversible cause of daily headache.
- **Pregnancy or recent delivery; anticoagulation; immunosuppression; malignancy; recent trauma or neck manipulation; and whether anyone else at home has a headache.**

4. The Examination That Discriminates

- **Temperature and blood pressure**, conscious level, and a full neurological examination.
- **Fundoscopy for papilloedema** — omitted far more often than it is performed, and the finding changes the plan entirely.
- Neck stiffness; the skin for a non-blanching rash; **temporal artery tenderness, thickening and absent pulsation in anyone over 50**; the eye itself for redness and a mid-dilated pupil; visual acuity, fields and colour vision; and pupillary responses including Horner syndrome.

5. Investigations, in Tiers

SUSPECTED SUBARACHNOID HAEMORRHAGE — THE PATHWAY

Non-contrast computed tomography of the head, as soon as possible. Its sensitivity is very high when performed **within 6 hours** of onset and falls progressively thereafter as the blood degrades.

If the computed tomogram is negative and more than 6 hours have elapsed since onset, proceed to lumbar puncture — performed at least 12 hours after the headache began, so that **xanthochromia** has had time to develop. It is measured by spectrophotometry, not by eye.

A negative scan alone does not exclude the diagnosis in a patient presenting late, and this is the point at which the diagnosis is most often missed.

Where haemorrhage is confirmed, or suspicion persists, proceed to **computed tomographic or catheter angiography** to find the aneurysm.

- **Giant cell arteritis:** erythrocyte sedimentation rate and C-reactive protein **urgently**, then temporal artery ultrasound or biopsy within days — **the biopsy remains informative for a week or two after starting steroids, so treatment is never delayed for it.** Same-day ophthalmology assessment if there are visual symptoms.
- **Meningitis:** blood cultures, polymerase chain reaction, and lumbar puncture — with antibiotics given first.
- **Cerebral venous sinus thrombosis:** computed tomographic or magnetic resonance venography — plain imaging is frequently normal.
- **Dissection:** angiography with fat-suppressed sequences. **Glaucoma:** intraocular pressure and immediate ophthalmology referral. **Carbon monoxide:** carboxyhaemoglobin on a blood gas.
- **Magnetic resonance imaging** for a suspected mass lesion or where the picture is progressive.

6. Management While You Are Still Deciding

- Analgesia and antiemetics while investigation proceeds — treating the pain does not obscure the diagnosis.
- **Avoid opioids in primary headache disorders**, which promote medication overuse headache and rarely work well.
- Treat the specific cause: neurosurgical referral and nimodipine for subarachnoid haemorrhage; antibiotics for meningitis; corticosteroids for arteritis; anticoagulation for venous thrombosis.
- **For primary headache:** acute treatment with a triptan or an anti-inflammatory drug, consideration of prophylaxis where attacks are frequent, a **headache diary**, attention to sleep, hydration and caffeine, and explicit review of analgesic frequency.

7. Teaching Points and Viva Questions

- Ask how long it took to peak, not how severe it is.
- Computed tomography sensitivity falls after six hours; xanthochromia needs twelve.
- Start steroids in suspected giant cell arteritis before the biopsy, not after.

- Do fundoscopy. Papilloedema changes everything that follows.
- Take the temperature and the blood pressure in every headache.
- Ask how many days a month she takes painkillers, and whether anyone else at home has a headache.

Questions you should be able to answer:

- Her computed tomogram at 7 hours is normal. What do you do, and when?
- What is xanthochromia and why must you wait 12 hours?
- A 72-year-old has a new headache and pain in her jaw when chewing. What do you do, in what order?
- Give five red flags from the SNOOP list and the diagnosis each suggests.
- A patient has daily headache and takes codeine most days. What is the likely diagnosis and the treatment?

Seminar 6 · Approach to the Patient with Arthritis

THE PRESENTATION

A **58-year-old man** presents with two days of a hot, swollen, exquisitely painful right knee. He cannot bear weight and will not let you move the joint at all. He has had three previous attacks of sudden severe pain and swelling in his left great toe over the past two years, each settling within a week.

He has type 2 diabetes and chronic kidney disease, and takes a thiazide diuretic.

On examination: temperature 37.9 °C. The right knee is hot, red, and holds a tense effusion. Movement is restricted **in every direction**. No other joint is involved. There is no rash and no psoriasis.

C-reactive protein 180 · white cells 14.2 × 10^9/L · serum urate 340 µmol/L (within the normal range).

BEFORE ANYTHING ELSE

A single hot, swollen joint is septic arthritis until proved otherwise, and the joint must be aspirated. An infected joint can be destroyed within days, and the cartilage does not come back.

Two errors this case is built to prevent:

1. A history of gout does not protect against sepsis. **Crystals and infection coexist**, and finding crystals in the fluid does not exclude a co-existing septic arthritis.

2. A normal serum urate does not exclude gout. Urate levels commonly fall during an acute attack, so a normal value taken at presentation is uninformative — measure it again several weeks later.

1. Think First — By Number of Joints and Tempo

Pattern	Causes
Acute monoarthritis	Septic arthritis · crystal arthritis — gout and calcium pyrophosphate disease · haemarthrosis and trauma · reactive arthritis · the first joint of what will become a polyarthritis · avascular necrosis
Oligoarthritis (2–4 joints)	The spondyloarthritides — psoriatic, reactive, inflammatory bowel-associated, axial · crystal disease · sarcoidosis · Behçet disease · brucellosis · disseminated gonococcal infection
Acute polyarthritis	Viral — parvovirus B19, hepatitis B and C, chikungunya, dengue, rubella · reactive · early rheumatoid arthritis · systemic lupus erythematosus · drug-induced
Chronic polyarthritis	Rheumatoid arthritis · psoriatic arthritis · connective tissue disease · osteoarthritis (non-inflammatory) · chronic tophaceous gout

Then refine by **symmetry, joint size, axial involvement, and whether the distal interphalangeal joints are affected** — as set out in the rheumatology system opener.

2. What Could Destroy or Kill

- **Septic arthritis** — including of a prosthetic joint, which has a different microbiology and needs orthopaedic involvement immediately.
- **Disseminated gonococcal infection** — migratory arthralgia, tenosynovitis and pustular skin lesions in a sexually active patient.
- **Necrotising fasciitis** — pain out of proportion, rapid spread, systemic toxicity. Not a joint problem, but it presents as one.
- **Giant cell arteritis** in an older patient with a polymyalgic presentation — because untreated it blinds.

3. The History That Discriminates

- **Speed of onset and number of joints**, and whether previous episodes followed the same pattern.
- **Risk factors for sepsis:** diabetes, immunosuppression, chronic kidney disease, a **prosthetic joint**, intravenous drug use, a skin breach or ulcer, and **recent joint injection or aspiration**.
- **Risk factors for gout:** diuretics, alcohol, chronic kidney disease, obesity, previous podagra, family history, and a diet high in purines.
- **Preceding infection** — gastrointestinal or genitourinary, one to four weeks earlier, for reactive arthritis. **Sexual history** for gonococcal disease.
- **Unpasteurised milk and animal contact — brucellosis causes sacroiliitis and large joint arthritis and is a realistic cause here.** Recent travel for chikungunya and dengue.
- Psoriasis, inflammatory bowel disease, red eye, urethral discharge, oral and genital ulcers, rash, and every drug.

4. The Examination That Discriminates

- **Fever — but its absence does not exclude sepsis**, particularly in the elderly and the immunosuppressed.
- **Restriction of movement in every direction with severe pain** indicates the joint itself. **Bursitis and cellulitis over a joint preserve most passive movement** — this distinction is made at the bedside in thirty seconds and prevents an unnecessary aspiration or, worse, a missed one.
- Examine **all** the other joints, the entheses, and the spine; look for psoriasis in the scalp, natal cleft, umbilicus and nails; look for tophi, pustules, erythema nodosum and conjunctivitis.

5. Investigations, in Tiers

THE PIVOTAL INVESTIGATION

Aspirate the joint, and do it before antibiotics are given. One sample answers the question.

Send: cell count with differential · Gram stain · culture · **polarised light microscopy for crystals**.

Interpretation: over 50,000 white cells per mm^3 with a neutrophil predominance strongly suggests sepsis — but **lower counts do not exclude it**, especially early or in the immunosuppressed. 2,000–50,000 indicates inflammation; under 2,000 is non-inflammatory; frank blood suggests trauma, a bleeding disorder, or pseudogout.

Negatively birefringent needle-shaped crystals are urate; **positively birefringent rhomboid crystals** are calcium pyrophosphate.

- **Blood cultures before antibiotics**; complete blood count, C-reactive protein and erythrocyte sedimentation rate, renal and liver function, glucose, and serum urate — interpreted with the caution above.
- **Radiograph** as a baseline, and to look for chondrocalcinosis, erosions or avascular necrosis. **Ultrasound** to confirm an effusion and guide aspiration; **magnetic resonance imaging** where osteomyelitis or spondylodiscitis is suspected.

- **Targeted:** rheumatoid factor and anti-cyclic citrullinated peptide antibody, antinuclear antibody, **brucella serology**, parvovirus and hepatitis serology, and nucleic acid amplification testing for gonorrhoea and chlamydia from the appropriate sites.

6. Management While You Are Still Deciding

- **Aspirate, culture, then start empirical antibiotics** covering staphylococci according to local resistance patterns, adjusted once cultures return. **Do not wait for the culture result to start treatment, and do not start treatment before taking the sample.**
- **Refer to orthopaedics for washout or arthroscopic lavage**, with repeated aspiration where surgery is delayed. Splint briefly for comfort, then mobilise early to preserve function.
- **If it proves to be crystal disease:** an anti-inflammatory drug, colchicine, or corticosteroid — oral or intra-articular — chosen according to renal function and comorbidity. In this patient, with chronic kidney disease, anti-inflammatory drugs are a poor choice.
- **Do not start urate-lowering therapy during an acute attack — but do not stop it if the patient is already taking it.** Begin allopurinol or febuxostat several weeks later, with colchicine or anti-inflammatory cover for the first months, and treat to a target urate level.
- Review the thiazide, which is contributing, and address alcohol, weight and renal function.

7. Teaching Points and Viva Questions

- Aspirate every hot joint. It is the investigation, and it takes minutes.
- Crystals in the fluid do not exclude infection in the same joint.
- A normal urate during an attack tells you nothing.
- Bursitis and cellulitis preserve passive movement; septic arthritis does not.
- Ask about milk, animals, sexual history and recent joint injections.
- Never start urate-lowering therapy in an acute attack, and never stop it either.

Questions you should be able to answer:

- The aspirate shows 30,000 white cells and urate crystals. Have you excluded sepsis?
- Why is his urate normal, and when should you measure it?
- He has chronic kidney disease. How does that change your choice of anti-inflammatory treatment?
- Distinguish septic arthritis from prepatellar bursitis at the bedside.
- A 26-year-old has migratory arthralgia, tenosynovitis and pustules. What is the diagnosis and what do you send?

Seminar 7 · Approach to the Patient with Chronic Cough

THE PRESENTATION

A **52-year-old woman** has coughed for four months. The cough is dry, worse at night and when she lies down, and it interrupts conversation and has twice caused stress incontinence. She is not breathless. She has never smoked.

She was started on **ramipril five months ago** for hypertension. She also describes a sensation of mucus dripping at the back of her throat and frequent throat clearing, and occasional heartburn.

On examination: entirely normal. **Chest radiograph normal. Spirometry normal with no reversibility.**

1. Think First

Chronic cough means more than eight weeks. Under three weeks is acute, and three to eight weeks subacute — most often post-infectious and self-limiting.

Category	Causes
The three commonest in a non-smoker with a normal chest radiograph	Upper airway cough syndrome (post-nasal drip, rhinosinusitis) · asthma, including cough-variant asthma and non-asthmatic eosinophilic bronchitis · gastro-oesophageal reflux
Drugs	Angiotensin-converting enzyme inhibitors — in up to one in seven patients, beginning anywhere from days to months after starting
Must not be missed	Lung cancer · tuberculosis · bronchiectasis · interstitial lung disease · heart failure · inhaled foreign body · chronic infection
Others	Smoking and chronic obstructive pulmonary disease · obstructive sleep apnoea · chronic aspiration · cough hypersensitivity syndrome · habit cough
	RED FLAGS — INVESTIGATE RATHER THAN TREAT EMPIRICALLY **Haemoptysis · weight loss · fever or night sweats · hoarseness · dysphagia · breathlessness · chest pain · recurrent pneumonia · an abnormal examination or chest radiograph · a smoker over 40 · immunosuppression.** **And the standing regional rule: any cough lasting more than two to three weeks, particularly with weight loss or night sweats, means send three sputum samples for tuberculosis** before you begin an empirical trial for reflux. The empirical pathway below applies only once tuberculosis and malignancy have been considered and excluded.

2. The History That Discriminates

- **Check the drug chart before you take the history.** An angiotensin-converting enzyme inhibitor explains a large number of chronic coughs, and **the temporal link is often missed because the cough may begin months after the drug was started.**
- **Dry or productive, and how much.** Large daily volumes of purulent sputum means bronchiectasis until proved otherwise.
- **Timing and triggers:** worse at night suggests asthma, reflux or heart failure; worse on lying flat suggests reflux; provoked by cold air, exercise or laughing suggests airway hyper-responsiveness; provoked by eating or talking suggests reflux or aspiration.
- **Nasal symptoms and throat clearing** for upper airway cough syndrome; heartburn and regurgitation for reflux — **although reflux-related cough frequently occurs with no heartburn at all**.

- **Exposures:** smoking including waterpipe, occupational dusts, **biomass fuel and incense smoke**, birds and moulds, and tuberculosis contact.

3. The Examination That Discriminates

- **Expect it to be normal, and record that it is.** A normal examination in chronic cough is the usual finding, not a failure to examine properly.
- Examine the nose and post-nasal space, the throat, and the **ears** — impacted wax against the drum stimulates the auricular branch of the vagus and causes cough.
- Cervical lymph nodes, clubbing, the chest, the heart, and — importantly — **watch the patient use her inhaler** if she has one.

4. Investigations, in Tiers

- **First line for everyone: chest radiograph**, spirometry with reversibility testing, and a complete blood count looking for eosinophilia.
- **Where tuberculosis is possible — which is often, here: three sputum specimens for smear, nucleic acid amplification testing and culture.**
- **Targeted:** fractional exhaled nitric oxide or bronchial provocation testing for cough-variant asthma; **computed tomography of the chest** for suspected bronchiectasis, malignancy or interstitial disease; ear, nose and throat assessment with nasendoscopy; oesophageal pH and impedance monitoring where reflux is suspected and empirical treatment has failed; bronchoscopy for a suspected foreign body or endobronchial lesion; echocardiography.

5. Management While You Are Still Deciding

> THE FIRST THERAPEUTIC STEP IN THIS PATIENT
>
> **Stop the ramipril and substitute an angiotensin receptor blocker** — and tell the patient that **resolution takes up to four weeks and occasionally longer**.
>
> The commonest error is to stop the drug, review at one week, find the cough unchanged, and conclude that the drug was not responsible. **Do not judge it before four weeks have passed.**

- **Then treat the likely causes one at a time, each for long enough to be a fair trial.** Treating three things simultaneously means that when the cough settles you will not know why, and when it does not you will not know what to change.
- **Upper airway cough syndrome:** intranasal corticosteroid, with an antihistamine where there is an allergic component. **Asthma or eosinophilic bronchitis:** a trial of inhaled corticosteroid. **Reflux:** a proton pump inhibitor with dietary and postural measures, recognising that the evidence for acid suppression in cough is modest.
- **Smoking cessation** where relevant, which alone resolves a substantial proportion of coughs within weeks.
- **Refractory chronic cough:** speech and language therapy with cough suppression techniques, and neuromodulator therapy such as gabapentin or low-dose morphine, under specialist supervision.

- **Acknowledge the impact.** Chronic cough causes urinary incontinence, sleep loss, social embarrassment, exhaustion and occasionally rib fractures. Patients are frequently told it is nothing.

6. Teaching Points and Viva Questions

- Eight weeks defines chronic cough. Read the drug chart before the history.
- Angiotensin-converting enzyme inhibitor cough can start months after the drug and takes weeks to settle after stopping.
- A normal examination and a normal film are expected — but red flags and regional tuberculosis risk override the empirical pathway.
- Reflux cough often occurs without heartburn.
- Treat one cause at a time, for long enough to know whether it worked.

Questions you should be able to answer:

- Name the three commonest causes in a non-smoker with a normal film.
- She stopped the ramipril a week ago and is no better. What do you tell her?
- Which findings in this history would make you send sputum before starting any trial?
- Why should you not start a nasal steroid, an inhaler and a proton pump inhibitor together?
- A 63-year-old smoker has coughed for three months and has lost 5 kg. What is your first investigation?

Seminar 8 · Hypertensive Urgencies and Emergencies

THE PRESENTATION

A **54-year-old man** attends after a pharmacy reading of 226/128 mmHg. For two days he has had a persistent headache and blurred vision. He has no chest pain and no breathlessness. He was prescribed antihypertensives two years ago and **stopped taking them several months ago** because he felt well.

On examination: blood pressure 224/126 mmHg in both arms, correctly measured and repeated. **Fundoscopy shows flame haemorrhages, cotton wool spots and bilateral papilloedema.** No focal neurological deficit. Chest clear, no murmur, no radio-femoral delay.

Creatinine 168 µmol/L · urine dipstick: blood and protein · haemoglobin 112 g/L · platelets 96 × 10^9/L · blood film: red cell fragments · lactate dehydrogenase raised.

THE DISTINCTION THAT GOVERNS EVERYTHING THAT FOLLOWS

The blood pressure number does not tell you which of these you are dealing with. The end-organ assessment does.

Hypertensive emergency — severe hypertension **with acute end-organ damage**. Requires immediate, **controlled** parenteral treatment in a monitored bed.

Hypertensive urgency — severe hypertension **without** acute end-organ damage. Treated with oral therapy and gradual reduction over days, usually as an outpatient. **Rapid lowering in this group causes harm and no benefit.**

This patient has retinopathy with papilloedema, acute kidney injury and a thrombotic microangiopathy on the film. **That is an emergency.**

1. Think First — Where Is the End-Organ Damage?

Organ	What to look for
Brain	Hypertensive encephalopathy — headache, confusion, seizures, visual loss; ischaemic stroke; intracerebral haemorrhage; posterior reversible encephalopathy syndrome
Eye	Flame haemorrhages, cotton wool spots and papilloedema — which defines accelerated or malignant hypertension
Heart and aorta	Acute coronary syndrome, acute pulmonary oedema, aortic dissection
Kidney	Acute kidney injury, haematuria and proteinuria, and thrombotic microangiopathy with fragments and thrombocytopenia
Pregnancy	Pre-eclampsia and eclampsia — a separate pathway entirely, and to be considered in any pregnant or recently delivered woman

2. How Fast, and With What — the Targets Differ by Situation

WHY YOU DO NOT SIMPLY NORMALISE THE BLOOD PRESSURE

In chronic hypertension the cerebral autoregulatory curve **shifts to the right**. The brain, kidney and retina are perfused adequately at pressures that would be dangerous in a normotensive person — and they lose perfusion at pressures that appear entirely acceptable on the chart.

Dropping the pressure too quickly therefore causes watershed cerebral infarction, blindness, acute kidney injury and myocardial ischaemia. More harm has been done by treating the number aggressively than by treating it gradually.

Situation	Target and agent
General hypertensive emergency	Reduce mean arterial pressure by no more than 20–25% in the first hour, then to around 160/100 over the next 2–6 hours, then normalise over 24–48 hours. Intravenous labetalol or nicardipine, titrated.
Aortic dissection	The exception — lower fast and hard: systolic below 120 mmHg and heart rate below 60 within about 20 minutes. Give the beta blocker first, then the vasodilator, so that reflex tachycardia does not increase aortic wall shear stress.
Acute ischaemic stroke	Do not lower unless above about 220/120, or thrombolysis is planned — in which case below 185/110. See Case 64.
Intracerebral haemorrhage	Early lowering towards a systolic of about 140 mmHg.
Acute pulmonary oedema	Intravenous nitrate with a loop diuretic; non-invasive ventilation as needed.
Phaeochromocytoma, cocaine or amphetamine	Alpha blockade first. Never a beta blocker alone — unopposed alpha stimulation raises the pressure further.
Pre-eclampsia and eclampsia	Labetalol, nifedipine or hydralazine, plus magnesium sulfate, with obstetric involvement and delivery as the definitive treatment.

Sublingual short-acting nifedipine has been abandoned because it produces an uncontrolled and unpredictable fall in pressure. It should not be used.

3. The History That Discriminates

- **Ask what medication was stopped, and when.** Non-adherence, or an abrupt withdrawal — particularly of clonidine or a beta blocker — is among the commonest precipitants, and it is entirely correctable.
- Symptoms of each organ system: headache, visual change, confusion, seizure, chest pain, breathlessness, oliguria, frothy or bloody urine.
- **Drugs:** anti-inflammatory drugs, decongestants, corticosteroids, the combined oral contraceptive, ciclosporin, erythropoietin, liquorice — and **cocaine and amphetamines**, which change the treatment.
- **Features of a secondary cause**, as in Case 14 — because severe hypertension in a young patient, or hypertension that suddenly becomes uncontrolled, is far more likely to be secondary.
- **Pregnancy or recent delivery** in any woman of childbearing age.

4. The Examination That Discriminates

- **Blood pressure measured properly, in both arms, and repeated** — with the correct cuff size, after rest. Severe readings are frequently artefactual.
- **Fundoscopy in every patient. This is the examination that most often converts an urgency into an emergency**, and it is the one most often skipped.
- Full neurological examination; heart and lungs; **radio-femoral delay and peripheral pulses**; abdominal and renal bruits; volume status.

5. Investigations, in Tiers

- **Bedside: urinalysis** — blood and protein indicate renal involvement and are available in a minute; electrocardiogram.
- **First line:** urea, electrolytes and creatinine, **complete blood count with a blood film for fragments**, lactate dehydrogenase, troponin, natriuretic peptide, glucose, chest radiograph, **pregnancy test**.
- **Targeted:** computed tomography of the head where there are neurological features; **computed tomographic aortogram where dissection is suspected**; echocardiography; renal imaging.
- **Once stabilised, screen for a secondary cause** — aldosterone-to-renin ratio, plasma metanephrines, renal artery imaging, and a sleep study.

6. Management While You Are Still Deciding

- **Monitored bed with continuous blood pressure monitoring**, ideally intra-arterial, and an intravenous agent titrated to a defined target that is written down.
- **Identify and remove the precipitant**, and restart oral therapy early so that the infusion can be weaned.
- Expect the **creatinine to rise transiently** as the pressure falls — this is haemodynamic and is not a reason to stop treating, provided the fall is controlled.
- **In a hypertensive urgency:** do not treat in the emergency department with repeated intravenous boluses. Restart or adjust oral therapy, arrange review within days, and address why the medication stopped.

7. Teaching Points and Viva Questions

- The organs define the emergency, not the number.
- Do fundoscopy. Papilloedema changes the diagnosis and the disposition.
- Twenty to twenty-five per cent in the first hour — except in dissection, and except in acute ischaemic stroke where you do not lower it at all.
- Beta blocker before vasodilator in dissection; alpha before beta in cocaine and phaeochromocytoma.
- Always ask which tablets were stopped and why.

Questions you should be able to answer:

- Is this an urgency or an emergency, and what exactly makes it so?
- What is your target pressure at one hour, and why not lower?
- Why do the fragments on his blood film matter?
- A patient with the same pressure has tearing interscapular pain. How does your plan change, and in what order do you give the drugs?

- A 22-year-old with a pressure of 230/130 has taken cocaine. What must you avoid?

Seminar 9 · Approach to the Patient with Pyrexia of Unknown Origin

THE PRESENTATION

A **47-year-old man** has had intermittent fever for six weeks, reaching 38.8 °C most evenings, with **drenching night sweats** and 9 kg of weight loss. He has had two courses of antibiotics from different doctors, each followed by a few days of apparent improvement.

He keeps sheep and goats and drinks fresh unboiled milk.

On examination: thin and tired. Temperature 38.4 °C with a pulse of 82/min. There is **mild hepatosplenomegaly** and a soft systolic murmur that has not previously been documented.

Erythrocyte sedimentation rate 88 · normocytic anaemia · white cell count normal with relative lymphocytosis · mildly raised transaminases · chest radiograph, urine culture and first blood cultures all negative.

1. Think First — Four Categories

Pyrexia of unknown origin is conventionally fever above 38.3 °C on several occasions for more than three weeks, remaining undiagnosed after appropriate initial investigation. The causes fall into four groups, and the proportions differ substantially by region.

Category	The causes that matter here
Infection	Tuberculosis — especially extrapulmonary: miliary, abdominal, spinal, nodal · brucellosis · infective endocarditis, including culture-negative from *Coxiella*, *Brucella* and *Bartonella* · occult abscess — dental, hepatic, subphrenic, psoas, pelvic · osteomyelitis and spondylodiscitis · human immunodeficiency virus · typhoid · visceral leishmaniasis · malaria
Malignancy	Lymphoma above all · leukaemia · renal cell and hepatocellular carcinoma · atrial myxoma · metastatic disease
Non-infectious inflammatory	Adult-onset Still disease · giant cell arteritis and polymyalgia rheumatica — a major and treatable cause over the age of 50 · systemic lupus erythematosus and vasculitis · sarcoidosis · inflammatory bowel disease · Behçet disease · familial Mediterranean fever and other periodic fever syndromes, worth considering where there is consanguinity and a lifelong history
Miscellaneous	Drug fever · venous thromboembolism · subacute thyroiditis · adrenal insufficiency · haematoma · factitious fever · and a substantial group that resolve without ever being diagnosed

2. The Method — Which Matters More Than the List

HOW TO ACTUALLY APPROACH IT

1. Confirm the fever is real. Documented, measured by staff, with a chart. Suspect factitious fever if there is no tachycardia, no diurnal variation, and normal inflammatory markers.

2. Stop every non-essential drug. Drug fever occurs with almost any agent, typically one to three weeks after starting, in a patient who looks surprisingly well, and it settles within 72 hours of withdrawal. It costs nothing to test.

3. Repeat the history and the full examination every single day. In pyrexia of unknown origin the diagnosis is found more often by re-examining than by ordering another test. A new murmur, a new node, a rash, a tender vertebra, a joint — these appear over days.

4. Take the exposure history again, from the beginning. Travel, animals, **unpasteurised milk**, contacts, occupation, sexual history, dental work, prostheses, previous surgery.

5. Stop the antibiotics and re-culture. Prior antibiotic exposure is the commonest reason blood cultures are sterile in endocarditis — and this patient has had two courses.

3. What Could Kill

- Infective endocarditis; disseminated tuberculosis; an occult abscess progressing to sepsis; aggressive lymphoma; **giant cell arteritis with impending visual loss**; and adrenal crisis.

4. Investigations, in Tiers

- **First tier:** complete blood count **with a blood film**, erythrocyte sedimentation rate and C-reactive protein, renal and liver function, lactate dehydrogenase, **three sets of blood cultures taken off antibiotics**, urinalysis and culture, chest radiograph, human immunodeficiency virus and hepatitis serology, antinuclear antibody and rheumatoid factor, protein electrophoresis, thyroid function, creatine kinase, and **ferritin**.

ONE TEST WORTH ADDING EARLY

A markedly raised ferritin — many times the upper limit — in a febrile patient points to adult-onset Still disease or to haemophagocytic lymphohistiocytosis. The latter is rapidly fatal if missed and is diagnosed by a specific combination of fever, cytopenias, splenomegaly, hypertriglyceridaemia, hypofibrinogenaemia and very high ferritin.

It is a cheap test that is frequently omitted from the standard panel.

- **Regionally targeted: brucella serology with prolonged blood cultures** — and tell the laboratory; **tuberculin or interferon-gamma release assay with sputum and tissue for tuberculosis**; *Coxiella* and *Bartonella* serology; malaria films; leishmania serology.
- **Imaging: echocardiography, proceeding to transoesophageal study** where endocarditis is possible; computed tomography of chest, abdomen and pelvis; **magnetic resonance imaging of the spine** for spondylodiscitis; dental panoramic radiograph; and **fluorodeoxyglucose positron emission tomography where available**, which has a high diagnostic yield in this setting.
- **Tissue, when imaging is unrevealing:** lymph node biopsy; **bone marrow aspirate and trephine sent for culture as well as histology**, which has a good yield for tuberculosis, lymphoma and leishmaniasis; liver biopsy; and **temporal artery biopsy or ultrasound in anyone over 50 with a raised erythrocyte sedimentation rate**.

5. Management While You Are Still Deciding

THE HARDEST DISCIPLINE IN THIS PRESENTATION

Avoid empirical antibiotics and empirical corticosteroids. Both blunt the fever, obscure the picture, sterilise the cultures, and can make a definitive diagnosis impossible — sometimes permanently.

The exceptions, where you treat before you know: suspected endocarditis in a haemodynamically compromised patient · suspected giant cell arteritis with visual symptoms · suspected tuberculous meningitis · neutropenic sepsis · any patient who is deteriorating.

Otherwise: supportive care, daily review, daily examination, and patience. A proportion of patients defervesce spontaneously without a diagnosis ever being made, and that is an acceptable outcome once the dangerous causes have been excluded.

6. Teaching Points and Viva Questions

- Re-examine the patient every day. That is where the diagnosis usually comes from.
- Stop the drugs. Drug fever is common and free to exclude.

- Three sets of blood cultures, off antibiotics.
- In this region, tuberculosis and brucellosis head the list — and both need the laboratory to be told.
- Check the ferritin.
- Empirical treatment feels active and usually destroys the diagnosis.

Questions you should be able to answer:

- Define pyrexia of unknown origin and give the four diagnostic categories.
- Which two diagnoses does this man's occupation and diet put at the top of your list?
- He has had two courses of antibiotics. How does that affect your investigation?
- A colleague wants to start empirical antituberculous therapy. Argue both sides.
- Which single investigation would you request if a positron emission tomogram were unavailable and the computed tomogram was normal?

Seminar 10 · Approach to the Patient in Coma

THE PRESENTATION

A **62-year-old woman** is brought in by ambulance having been found unresponsive at home by her son, who last spoke to her the previous evening. She has type 2 diabetes treated with gliclazide, and takes an antidepressant.

On arrival: Glasgow Coma Scale 7 — **eyes 1, verbal 2, motor 4**. Pupils 2 mm and reactive **bilaterally**. No lateralising signs; tone symmetrical; plantars flexor. Temperature 35.8 °C, blood pressure 148/86 mmHg, heart rate 62/min, respiratory rate 10/min and shallow.

Capillary glucose 3.1 mmol/L.

BEFORE THE DIFFERENTIAL

Airway first. A Glasgow Coma Scale of 8 or less does not protect the airway. Position, suction, adjunct, and call for anaesthetic help.

Then, in this order, and within the first two minutes:

Glucose — check it and correct it. **In anyone malnourished or alcohol-dependent, give thiamine before or with the glucose**, to avoid precipitating Wernicke encephalopathy.

Oxygen and ventilation — hypoxia and hypercapnia are both causes and consequences.

Naloxone if opioid toxicity is conceivable — look at the pupils and the respiratory rate.

Everything else can wait a few minutes. These cannot.

1. Think First — Two Mechanisms

Consciousness requires **both cerebral hemispheres** and the **reticular activating system in the brainstem**. Coma therefore means either diffuse bilateral hemispheric dysfunction or a brainstem lesion — and the examination tells you which.

	Diffuse / metabolic-toxic	Structural
Findings	Symmetrical, with preserved pupillary reflexes and preserved brainstem reflexes; may have tremor, myoclonus, asterixis	Asymmetry, focal signs, cranial nerve and brainstem abnormalities, abnormal pupils, gaze deviation
Causes	Hypoglycaemia and hyperglycaemia · hyponatraemia, hypercalcaemia · uraemia, hepatic encephalopathy · hypoxia, hypercapnia · hypothermia and hyperthermia · sepsis · myxoedema, adrenal crisis · thiamine deficiency · drugs and toxins — opioids, benzodiazepines, alcohol, antidepressants, salicylate, carbon monoxide · post-ictal state and non-convulsive status epilepticus	Intracerebral and subarachnoid haemorrhage · large infarct with oedema · subdural and extradural haematoma · tumour · abscess · hydrocephalus · basilar artery occlusion · herniation

Infection sits across both: meningitis, encephalitis and cerebral malaria can produce either picture, and they are treated before imaging.

2. The History — From Everybody Except the Patient

- **The circumstances in which she was found**, and **when she was last known to be well** — which determines the treatment window if this proves to be a stroke.
- **Access to drugs: what is in the house, and what is missing.** Ask the ambulance crew about empty packets, bottles and syringes, and about the state of the room.

- Preceding headache, fever, confusion, focal symptoms, seizures, vomiting or trauma — including a fall days earlier, which raises subdural haematoma.
- Comorbidity: diabetes, liver disease, kidney disease, epilepsy, psychiatric illness, malignancy, and alcohol use.
- **Whether anyone else in the household is unwell or has a headache** — carbon monoxide poisoning affects the whole house, and is repeatedly missed.

3. The Coma Examination

- **Record the Glasgow Coma Scale as its three components**, not as a total. "GCS 7" hides whether the patient is deteriorating in eye opening or in motor response, and the motor score is the most prognostically important.
- **Respiratory pattern and temperature**, both of which are diagnostic clues and both of which are frequently omitted.

Pupils	Suggests
Pinpoint and reactive	Opioids, or a pontine lesion
Mid-position and fixed	Midbrain lesion
Unilateral fixed and dilated	Third nerve compression — uncal herniation. A neurosurgical emergency
Bilateral fixed and dilated	Severe hypoxic-ischaemic injury, profound drug toxicity, or hypothermia
Equal and reactive	Favours a metabolic or toxic cause — pupillary reflexes are remarkably resistant to metabolic insult

- **Eye movements:** spontaneous movement, gaze deviation (**towards the lesion in a hemispheric stroke, away from it in a seizure focus**), corneal reflexes, and oculocephalic testing — **only once the cervical spine has been cleared**.
- **Fundoscopy** for papilloedema and for the subhyaloid haemorrhage of subarachnoid bleeding.
- Motor response to a standardised stimulus, tone, reflexes, plantars, **asymmetry**, and abnormal posturing.
- Neck stiffness — with caution if trauma is possible. Skin for rash, needle marks, jaundice, cyanosis, bruising, and **signs of head injury including periorbital and mastoid bruising and cerebrospinal fluid leak**. Smell the breath. Look for a medical alert bracelet.

4. Investigations, in Tiers

- **Bedside:** glucose, arterial blood gas **including carboxyhaemoglobin and lactate**, electrocardiogram, temperature.
- **First line:** urea and electrolytes, calcium, magnesium, liver function, ammonia, complete blood count, C-reactive protein, coagulation, creatine kinase, thyroid function, **cortisol**, blood and urine cultures, **paracetamol and salicylate levels**, toxicology screen, and **serum osmolality with an osmolar gap** where a toxic alcohol is possible.

- **Computed tomography of the head** in all but the most obvious metabolic cases; **lumbar puncture after imaging** where infection is suspected — with antibiotics given first.

THE CAUSE THAT IS INVISIBLE WITHOUT ASKING FOR IT

Consider non-convulsive status epilepticus in any patient whose coma is unexplained, particularly after a witnessed seizure, in a known epileptic, or where there are subtle twitching movements of the face or eyes.

It is invisible without an **electroencephalogram**, it is treatable, and it is one of the commonest missed causes of persistent unexplained coma. If the imaging and the metabolic screen are normal, ask for an electroencephalogram rather than waiting.

5. Management While You Are Still Deciding

- **Secure the airway** — intubate for a score of 8 or less, an absent gag, or a rising carbon dioxide. Maintain oxygenation and normocapnia.
- **Treat the reversible causes empirically in sequence:** glucose, thiamine, naloxone; then antibiotics and aciclovir if infection is possible, before imaging.
- Nurse head-up at 30 degrees; maintain normothermia, normoglycaemia and normal sodium; treat seizures; **treat raised intracranial pressure** and involve neurosurgery urgently for a mass lesion or herniation.
- Eye care, pressure area care, nutrition, thromboprophylaxis, and a urinary catheter.
- **Talk to the family early and honestly**, and establish what the patient would have wanted before decisions become urgent.

6. Teaching Points and Viva Questions

- Airway, glucose, thiamine, naloxone — in that order, in the first two minutes.
- Record the coma score in its three components.
- Symmetrical signs with reactive pupils point to a metabolic cause; asymmetry points to a structural one.
- A unilateral fixed dilated pupil is a neurosurgical emergency.
- Ask whether anyone else at home is unwell.
- If nothing explains it, ask for an electroencephalogram.

Questions you should be able to answer:

- What is the likely cause here, and what would you give first — and in what order?
- Why does she need thiamine considered before glucose?
- Her pupils are equal and reactive. What does that make more likely?
- The glucose is corrected but she does not wake. What are your next three steps?

- A patient has a right pupil of 6 mm that does not react. What has happened and whom do you call?

Seminar 11 · Approach to the Patient with Venous Thromboembolism

THE PRESENTATION

A **34-year-old woman** presents with three days of pain and swelling in the left calf. Since this morning she has had right-sided pleuritic chest pain and has felt breathless climbing stairs.

She takes the combined oral contraceptive pill. She returned four days ago from a 14-hour car journey. Her mother had a deep vein thrombosis at the age of 40.

On examination: heart rate 104/min, blood pressure 118/74 mmHg, respiratory rate 22/min, **oxygen saturation 94% on air**. The left calf is **4 cm greater in circumference** than the right, with tenderness along the deep venous system and pitting oedema. Chest is clear. Heart sounds normal.

1. Think First

Deep vein thrombosis and pulmonary embolism are one disease presenting in two places. This patient has both, and finding one is sufficient reason to treat.

- **Differential for the leg:** cellulitis, ruptured Baker cyst, calf muscle tear or haematoma, superficial thrombophlebitis, chronic venous insufficiency, lymphoedema, compartment syndrome.
- **Differential for the chest:** as in Seminar 3.

Generate the risk factors from Virchow's triad rather than memorising a list:

Element	Risk factors
Stasis	Immobility, long-distance travel, surgery, plaster cast, paralysis, heart failure, obesity, pregnancy
Endothelial injury	Surgery, trauma, central venous catheter, previous venous thromboembolism
Hypercoagulability	Malignancy · pregnancy and the puerperium · oestrogen — combined oral contraceptive and hormone replacement · inherited thrombophilia · antiphospholipid syndrome · nephrotic syndrome · inflammatory disease · acute infection · dehydration

2. What Could Kill in the Next Hour

HIGH-RISK PULMONARY EMBOLISM

A patient with pulmonary embolism who is hypotensive, shocked or arresting does not go down a diagnostic pathway.

Persistent hypotension or shock with right ventricular strain defines **high-risk pulmonary embolism**, and it requires **immediate reperfusion — systemic thrombolysis**, or catheter-directed therapy or surgical embolectomy where thrombolysis is contraindicated.

Bedside echocardiography showing a dilated, poorly functioning right ventricle is enough to act on in a peri-arrest patient. Waiting for a computed tomogram in this situation costs lives.

3. Score Before You Test

THE CENTRAL PRINCIPLE OF THIS CASE

Calculate the pre-test probability first, using a validated score. The correct next test depends entirely on the answer.

D-dimer is useful only where the probability is low or intermediate, and its value lies **entirely in its negative predictive value** — it excludes, it never confirms. It is raised by age, pregnancy, infection, malignancy, surgery, trauma and inflammation, so a positive result on its own means almost nothing.

In a high-probability patient, a negative D-dimer does not exclude the diagnosis. Go straight to imaging. Requesting a D-dimer in this patient, whose probability is high, would be an error whichever way it came back.

Age-adjusted thresholds improve specificity in older patients without losing sensitivity.

4. Investigations

- **Suspected deep vein thrombosis: proximal leg vein compression ultrasound.** If negative but the probability is high, repeat it after about a week, or proceed to further imaging.
- **Suspected pulmonary embolism: computed tomographic pulmonary angiography.**

THE IMAGING CHOICE THAT IS REGULARLY GOT WRONG

Use **ventilation–perfusion scanning** in preference to computed tomography where the chest radiograph is normal and the patient is **pregnant or a young woman**, because it delivers substantially less radiation to breast tissue. It is also preferred in significant renal impairment and in contrast allergy.

In pregnancy, start with bilateral leg ultrasound. If a deep vein thrombosis is confirmed, the treatment is the same and chest imaging can be avoided altogether — sparing both mother and fetus.

- **Supporting tests, none of which diagnose:** electrocardiogram — sinus tachycardia is the commonest finding, and the classical S1Q3T3 pattern is uncommon; chest radiograph, whose main role is to exclude alternatives; blood gas; and **troponin and natriuretic peptide, which are used for risk stratification and not for diagnosis**.
- **Echocardiography** for right ventricular strain in the haemodynamically unstable patient.

5. Management

- **Start anticoagulation on clinical suspicion while awaiting imaging** where the probability is high and the bleeding risk is acceptable. Do not wait several hours for a scan with the patient untreated.

Situation	Anticoagulant
Most patients	A direct oral anticoagulant, which is now first line and needs no monitoring
Antiphospholipid syndrome, particularly triple-positive	Warfarin — direct oral anticoagulants are inferior and are avoided
Pregnancy	Low-molecular-weight heparin. Warfarin and direct oral anticoagulants are contraindicated
Severe renal impairment	Low-molecular-weight heparin or warfarin, with dose adjustment
Cancer-associated thrombosis	A direct oral anticoagulant or low-molecular-weight heparin, weighing bleeding risk — particularly with gastrointestinal and genitourinary tumours

- **Duration:** three months where the event was provoked by a major transient risk factor that has now resolved; at least three to six months if unprovoked, with a considered decision about extended therapy weighing recurrence risk against bleeding risk; indefinite therapy in active cancer, antiphospholipid syndrome, and recurrent unprovoked events.
- **Low-risk pulmonary embolism can be managed as an outpatient** using a validated severity score, which is safe and avoids admission.

TWO INVESTIGATIONS THAT ARE DONE TOO OFTEN

Do not perform a thrombophilia screen acutely, and do not perform one while the patient is anticoagulated — the results are unreliable and, in most cases, would not change management. The duration of anticoagulation is decided by whether the event was provoked, not by a genetic result.

Antiphospholipid antibodies are the exception, and are worth testing in a young patient with unprovoked thrombosis, recurrent pregnancy loss, or both arterial and venous events — because a positive result **does** change the drug.

And do not scan the whole body looking for cancer after an unprovoked event. A careful history and examination, basic bloods, and **age-appropriate screening only** — extensive occult malignancy screening finds little and improves nothing.

- **Stop the combined oral contraceptive** and counsel on alternative contraception — a progestogen-only method or a non-hormonal method — and on future pregnancy, which will require thromboprophylaxis.
- Graduated compression for post-thrombotic symptoms; explain the risk of recurrence and the symptoms that should bring her back; and **follow up persisting breathlessness at three to six months for chronic thromboembolic pulmonary hypertension**, which is treatable and easily missed.

6. Teaching Points and Viva Questions

- Score the probability before you choose the test.
- D-dimer excludes; it never confirms — and it is useless in a high-probability patient.
- Ventilation–perfusion scanning in pregnancy and in young women; leg ultrasound first in pregnancy.
- Anticoagulate on suspicion when the probability is high.
- The exceptions to direct oral anticoagulants are antiphospholipid syndrome, pregnancy and severe renal impairment.
- No thrombophilia screen, and no whole-body cancer hunt.

Questions you should be able to answer:

- Would you send a D-dimer on this patient? Justify your answer.
- Which imaging would you choose for her, and why not computed tomography?
- She is 8 weeks pregnant. How does everything change?
- When is a thrombophilia screen actually useful?
- Six months later she remains breathless on exertion. What must you exclude?

Seminar 12 · Approach to the Patient in Shock

THE PRESENTATION

A **58-year-old man** is brought in drowsy. His wife reports two days of vomiting and diarrhoea, and that he has passed no urine today. He takes ramipril and metformin.

On arrival: heart rate 128/min, blood pressure 74/44 mmHg, respiratory rate 28/min, oxygen saturation 96% on air, temperature 36.2 °C. **The peripheries are cold with a capillary refill of five seconds. The jugular venous pressure is not visible.** He is rousable but confused.

Lactate 5.8 mmol/L · glucose 6.4 · no rash · abdomen soft.

THE DEFINITION THAT MATTERS

Shock is inadequate tissue perfusion, not a blood pressure reading.

A patient with a "normal" blood pressure, cold peripheries, oliguria, confusion and a lactate of 5 is shocked. A young person compensates by vasoconstriction and tachycardia and maintains their pressure until they decompensate suddenly.

Judge perfusion by: mental state · capillary refill and peripheral temperature · urine output · and the lactate and its trend — which is the single most useful marker of both severity and response.

1. Think First — Four Mechanisms

Mechanism	Causes
Hypovolaemic	Haemorrhage — gastrointestinal, ruptured aortic aneurysm, ectopic pregnancy, trauma, retroperitoneal · fluid loss — vomiting and diarrhoea, burns, ketoacidosis, pancreatitis, third-space losses
Distributive	Sepsis — the commonest · anaphylaxis · neurogenic after spinal cord injury · adrenal crisis · liver failure · vasodilating drugs and toxins
Cardiogenic	Myocardial infarction · arrhythmia · myocarditis · acute valve failure or papillary muscle rupture · cardiomyopathy · beta blocker and calcium channel blocker overdose
Obstructive	Massive pulmonary embolism · tension pneumothorax · cardiac tamponade · dynamic hyperinflation in severe asthma

	Jugular venous pressure	Peripheries	Other clues
Hypovolaemic	Low	Cold	Obvious loss; collapsed inferior vena cava on ultrasound. This patient
Distributive / septic	Low or normal	Warm early, cold late	Fever, bounding pulse, wide pulse pressure, a source
Cardiogenic	Raised	Cold	Crackles, third heart sound, murmur, abnormal electrocardiogram
Obstructive	Raised	Cold	Tamponade — muffled sounds, pulsus paradoxus. Tension pneumothorax — unilateral hyper-resonance, tracheal shift. Embolism — hypoxia with a clear chest

The jugular venous pressure and the temperature of the hands divide the four mechanisms in about ten seconds, and they are available before any test.

2. What Could Kill in the Next Minutes

THE REVERSIBLE CAUSES

Act on these **before** the diagnosis is complete:

Tension pneumothorax — needle decompression, not imaging · **anaphylaxis** — intramuscular adrenaline · **haemorrhage** — stop the bleeding and give blood · **tamponade** — pericardiocentesis · **arrhythmia** — cardioversion or pacing · **adrenal crisis** — intravenous hydrocortisone · **sepsis** — antibiotics within the hour · **hypoglycaemia** — glucose.

Immediate actions in every shocked patient: airway and high-flow oxygen · two large-bore cannulae · continuous monitoring · bloods including **lactate and cross-match** · urinary catheter · **an early call to a senior and to critical care** — made while you are still resuscitating, not after.

3. The History and Examination That Discriminate

- **From whoever is available:** onset and course; bleeding of any kind; fever; chest pain; breathlessness; vomiting and diarrhoea; **drugs — antihypertensives, beta blockers, insulin, anticoagulants, and recently stopped corticosteroids**; allergies and exposures; recent surgery or procedure; immobility; and the possibility of pregnancy.

- **Examination:** full vital signs **including the respiratory rate**, capillary refill, peripheral temperature, conscious level; **jugular venous pressure**; heart sounds, murmurs and pulsus paradoxus; chest; abdomen for peritonism, a pulsatile mass or distension; **rectal examination**; calves; **the whole skin for a non-blanching rash, urticaria or cellulitis**; every line and wound; and **a pregnancy test in any woman of childbearing age**.

4. Investigations, in Tiers

- **Bedside: lactate, blood gas, glucose, electrocardiogram, pregnancy test — and bedside ultrasound**, which in a few minutes gives cardiac function, inferior vena cava filling, free intraperitoneal fluid, pneumothorax and the aorta.

- **First line:** complete blood count, coagulation, **cross-match**, urea and electrolytes, liver function, amylase, C-reactive protein, blood cultures, troponin, urinalysis, chest radiograph.

- **Targeted:** echocardiography, computed tomography of the aorta, chest or abdomen, random cortisol, and toxicology.

5. Management While You Are Still Deciding

HOW TO GIVE FLUID

Give balanced crystalloid in boluses of 250 to 500 mL and reassess after each one. Prescribing a litre over an hour and walking away is not resuscitation.

Reassess with: blood pressure, heart rate, capillary refill, urine output, mental state and the lactate.

Three important exceptions:

In haemorrhage, give blood rather than crystalloid — activate the major haemorrhage protocol, give tranexamic acid where indicated, and **accept permissive hypotension until surgical control** in trauma.

In cardiogenic shock, fluid may make things worse — small cautious challenges only, with inotropic support and treatment of the cause.

In obstructive shock, no amount of fluid will work until the obstruction is relieved.

- **Vasopressors once fluid responsiveness is exhausted** — noradrenaline first line. A central line is preferable, but **peripheral administration while one is being placed is better than delay**.
- **Sepsis: antibiotics within one hour, and source control** — remembering that no antibiotic treats an undrained collection (Cases 32 and 48).
- **Anaphylaxis: intramuscular adrenaline, repeated as needed**, plus fluid, and observation for a biphasic reaction.
- Correct calcium, potassium and severe acidosis; **give hydrocortisone if adrenal crisis is conceivable, including in any patient on long-term steroids** (Case 26); and actively rewarm the hypothermic.
- **Document the escalation plan and ceiling of care early**, while the patient or family can still participate.

6. Teaching Points and Viva Questions

- Shock is a perfusion diagnosis. A normal blood pressure does not exclude it.
- The jugular venous pressure and the hands divide the four mechanisms.
- Treat the reversible causes before the diagnosis is complete.
- Fluid in boluses with reassessment after each — never a bag prescribed and forgotten.
- Blood, not crystalloid, in haemorrhage; caution with fluid in cardiogenic shock.
- Follow the lactate.

Questions you should be able to answer:

- Which mechanism is this, and which two bedside findings told you?
- A shocked patient has a raised jugular venous pressure and a clear chest. Give three diagnoses.
- Why is a lactate of 5.8 more useful to you than the blood pressure?
- A trauma patient is hypotensive from abdominal bleeding. How does your fluid strategy differ?
- He does not respond to two litres. What do you do next, and where?

Seminar 13 · Approach to the Patient with Chronic Diarrhoea

THE PRESENTATION

A **34-year-old woman** describes eight months of loose stool four to six times daily, with bloating, and 7 kg of weight loss. **In the last two months she has begun waking at night to open her bowels.** She feels persistently exhausted.

On examination: pale, body mass index 19 kg/m^2, angular stomatitis, mild abdominal distension, no mass, normal perianal examination.

Haemoglobin 96 g/L microcytic · ferritin 4 µg/L · folate low · albumin 34 g/L · C-reactive protein normal · faecal calprotectin normal.

1. Think First — Define It, Then Classify by Mechanism

- **Chronic means more than four weeks.** First distinguish it from **faecal incontinence** and from **overflow diarrhoea with underlying constipation** — patients call all three "diarrhoea", and the management of each is entirely different.

Mechanism	Causes and clues
Osmotic	Lactose intolerance, sugar alcohols, laxatives, magnesium salts. Improves with fasting.
Secretory	Bile acid diarrhoea, microscopic colitis, hormone-secreting tumours (VIPoma, carcinoid, gastrinoma), some infections. Persists with fasting and occurs at night.
Inflammatory	Inflammatory bowel disease, coeliac disease, infection, radiation, ischaemic colitis. Blood, fever, raised inflammatory markers or calprotectin.
Malabsorptive	Coeliac disease, pancreatic exocrine insufficiency, small intestinal bacterial overgrowth, giardiasis, short bowel. Steatorrhoea and nutritional deficiency.
Dysmotility	Irritable bowel syndrome, diabetic autonomic neuropathy, thyrotoxicosis, drugs.

- **Regionally: giardiasis, amoebiasis, intestinal tuberculosis, schistosomiasis, tropical sprue and brucellosis.** Chronic diarrhoea with weight loss here requires stool parasitology and active consideration of tuberculosis (Case 39).

RED FLAGS — INVESTIGATE RATHER THAN LABEL

Weight loss · nocturnal diarrhoea · blood in the stool · anaemia · raised inflammatory markers · onset after the age of 50 · a family history of colorectal cancer or inflammatory bowel disease · fever · steatorrhoea · a short history in an older patient.

This patient has three of them, which is why she needs investigating rather than reassuring.

And irritable bowel syndrome is a positive diagnosis, made on symptom criteria in the absence of red flags — not a label applied when the tests come back normal.

2. The History That Discriminates

- Frequency, consistency, volume, **blood, mucus, urgency, tenesmus, incontinence**, and **nocturnal symptoms**.
- **Steatorrhoea** — pale, bulky, offensive stool that floats and is difficult to flush.
- **Does it stop when she does not eat?** This single question separates osmotic from secretory diarrhoea.

- **The drug chart, which is a common and entirely reversible cause: metformin, magnesium-containing antacids, proton pump inhibitors, antibiotics, laxatives — including covert use — non-steroidal anti-inflammatory drugs, colchicine, selective serotonin reuptake inhibitors, orlistat and chemotherapy.**
- **Previous surgery: cholecystectomy or ileal resection causes bile acid diarrhoea**; gastrectomy and bariatric surgery cause malabsorption. Also radiotherapy.
- **Extraintestinal clues:** an itchy vesicular rash on the elbows and knees (**dermatitis herpetiformis** — Case 76), arthritis, mouth and eye lesions, thyroid symptoms, flushing, diabetes.
- Travel, water source, unpasteurised dairy, contacts, and human immunodeficiency virus risk. Family history of coeliac disease, inflammatory bowel disease and colorectal cancer.

3. Examination

- Weight and nutritional state; pallor; **angular stomatitis and glossitis**; clubbing; mouth ulcers; thyroid; abdominal masses and tenderness; **perianal inspection and rectal examination**; skin, joints and lymph nodes.

4. Investigations, in Tiers

- **First line:** complete blood count, ferritin, B12, folate, urea and electrolytes, liver function, albumin, calcium, C-reactive protein, **thyroid function**, **faecal calprotectin**, **stool culture with ova and parasites on three samples and *Clostridioides difficile* toxin**, and a human immunodeficiency virus test.

COELIAC SEROLOGY, DONE PROPERLY

Send tissue transglutaminase antibody with a total IgA level, in a patient who is still eating gluten.

Two ways this test is wasted: selective IgA deficiency — present in a small but significant minority, and it makes the antibody falsely negative, which is why the total IgA must be requested alongside it; and **a patient who has already started a gluten-free diet**, in whom both the serology and the biopsy may normalise.

Confirm with duodenal biopsy while the patient is still on gluten, then start the diet — not the other way round.

- **Second line, by suspicion: faecal elastase** for pancreatic insufficiency; **bile acid testing or a therapeutic trial of a sequestrant**; breath testing for bacterial overgrowth and lactose intolerance; gut hormones and urinary 5-hydroxyindoleacetic acid; **duodenal biopsy for coeliac disease and giardia**; **colonoscopy with ileal intubation**; computed tomography or magnetic resonance enterography; and a **faecal laxative screen** where surreptitious use is suspected.

TWO DIAGNOSES MISSED BECAUSE THE COLON LOOKS NORMAL

Microscopic colitis — watery secretory diarrhoea, often nocturnal, in a middle-aged or older patient, with **a completely normal-looking colon at endoscopy.** It is diagnosed only on **random biopsies of normal mucosa**, so the biopsies must be taken. It is frequently **drug-induced — proton pump inhibitors, non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors** — and responds to budesonide.

Bile acid diarrhoea — after cholecystectomy, ileal resection or Crohn disease, and often idiopathic. Urgent watery diarrhoea, frequently postprandial. **It responds dramatically to a bile acid sequestrant**, and a therapeutic trial is a reasonable diagnostic test.

Both are common, both are treatable, and both are routinely labelled as irritable bowel syndrome.

5. Management While You Are Still Deciding

- Rehydrate, correct electrolytes, and replace deficiencies — **iron, B12, folate, calcium, vitamin D, magnesium and zinc**.
- **Stop the culprit drug**, which may be the entire treatment.
- **Avoid antidiarrhoeal agents until infection and inflammatory colitis have been excluded** (Case 39).
- **Then treat the cause:** a **gluten-free diet with dietetic support, coeliac follow-up, pneumococcal vaccination and bone density assessment** in coeliac disease; pancreatic enzyme replacement; antimicrobials for giardiasis or overgrowth; a sequestrant for bile acid diarrhoea; budesonide for microscopic colitis; and the therapy of Case 39 for inflammatory bowel disease.
- **In coeliac disease, explain the timescale:** symptoms improve over weeks, the serology falls over many months, and adherence must be lifelong — with first-degree relatives offered testing.

6. Teaching Points and Viva Questions

- Four weeks defines chronic. Distinguish diarrhoea from incontinence and from overflow.
- Nocturnal diarrhoea, weight loss, blood and anaemia are red flags, not features of irritable bowel syndrome.
- Read the drug chart before ordering anything.
- Send total IgA with the coeliac serology, and biopsy before starting the diet.
- Biopsy a normal-looking colon — microscopic colitis is invisible to the eye.
- Think of bile acid diarrhoea after a cholecystectomy, and try a sequestrant.

Questions you should be able to answer:

- Which three red flags does she have, and what do they exclude?
- Her tissue transglutaminase is negative. What must you check before accepting that?
- A 62-year-old has watery nocturnal diarrhoea and a normal colonoscopy. What was not done?
- A patient develops urgent watery diarrhoea after a cholecystectomy. What is the diagnosis and how would you test it?
- Why should the biopsy come before the gluten-free diet?

Seminar 14 · Approach to the Patient with Ascites

THE PRESENTATION

A **46-year-old woman** describes six weeks of increasing abdominal distension with early satiety and weight gain, and is now breathless lying flat. She drinks no alcohol and has no risk factors for liver disease. For three months she has had vague pelvic discomfort and irregular vaginal bleeding.

On examination: tense ascites with shifting dullness. **There are no spider naevi, no palmar erythema and no jaundice. The jugular venous pressure is normal.** There is a firm irregular mass in the pelvis, and **a hard nodule at the umbilicus**.

Ascitic tap: serum-ascites albumin gradient 6 g/L · ascitic protein 42 g/L · neutrophils 40/mm³ · cytology: malignant cells. CA-125 markedly raised. Computed tomography: ovarian mass with peritoneal deposits.

THE POINT OF THIS CASE

Not all ascites is cirrhosis — and the assumption that it is delays the diagnoses that are treatable.

This patient has **no stigmata of chronic liver disease, a normal jugular venous pressure, a low albumin gradient and malignant cytology.** Started on spironolactone and furosemide as "decompensated liver disease", she would have lost months.

Tap the fluid. It is safe under ultrasound, it takes ten minutes, and it answers the question.

1. Think First — the Albumin Gradient Divides It in Two

Serum-ascites albumin gradient = serum albumin minus ascitic albumin, on samples taken at the same time.

Gradient 11 g/L or more — portal hypertension	Gradient below 11 g/L — not portal hypertension
Cirrhosis — the commonest cause overall	Peritoneal malignancy — ovarian, gastric, colorectal, pancreatic, mesothelioma
Alcoholic hepatitis; acute liver failure	Tuberculous peritonitis — important in this region
Heart failure and constrictive pericarditis	Pancreatic ascites
Budd–Chiari syndrome; portal vein thrombosis	Nephrotic syndrome (Seminar 2)
Massive hepatic metastases	Serositis in lupus; chylous ascites
	A REFINEMENT WORTH KNOWING **Cirrhosis: high gradient, LOW ascitic protein.** **Heart failure: high gradient, HIGH ascitic protein.** Both raise the gradient, because both raise sinusoidal pressure — so the **protein** is what separates them. A patient with a high gradient, a high ascitic protein and a raised jugular venous pressure has a cardiac problem, and diuretics will work.

2. What Must Not Be Missed

- **Spontaneous bacterial peritonitis** — **ascitic neutrophils of 250/mm³ or more**, with or without fever, pain or a positive culture. **Every patient admitted with ascites is tapped** (Case 37).

- **Tense ascites causing respiratory compromise**; **hepatorenal syndrome**; a **surgical abdomen** — perforation or ischaemia — presenting as distension; and **malignancy or tuberculosis mistaken for cirrhosis**.

3. The History and Examination That Discriminate

- Speed of onset; abdominal pain and fever; **alcohol quantified and hepatitis risk**; **cardiac symptoms — orthopnoea, oedema, known heart disease**; **weight loss and night sweats, pointing to malignancy or tuberculosis**; **gynaecological history — pelvic pain, irregular bleeding, and family history of ovarian or breast cancer**; frothy urine; diarrhoea; previous abdominal surgery or peritoneal dialysis; tuberculosis contact and unpasteurised milk.

- **First confirm it is ascites:** shifting dullness requires about 1.5 litres, and a fluid thrill more. Distinguish it from obesity, a large ovarian cyst, a distended bladder, pregnancy and gross organomegaly — **ultrasound settles it in a minute**.

- **Then: the presence or absence of chronic liver disease stigmata · the jugular venous pressure · a pelvic and rectal examination, and in women a vaginal examination · the umbilicus for a Sister Mary Joseph nodule · the left supraclavicular fossa · the breasts · peripheral oedema · and the mental state for encephalopathy.**

4. Investigations, in Tiers

- **Diagnostic paracentesis, under ultrasound. Send: cell count and differential; culture in blood culture bottles inoculated at the bedside; albumin and total protein with a paired serum albumin; glucose; lactate dehydrogenase; cytology — and where indicated adenosine deaminase and mycobacterial culture, amylase, and triglycerides.**

- **Interpretation:** the gradient as above; **neutrophils ≥250 means peritonitis**; **a lymphocyte-predominant, high-protein fluid with a high adenosine deaminase suggests tuberculous peritonitis** — where the culture yield is low, so **laparoscopic peritoneal biopsy is often needed and empirical treatment is sometimes justified**; and **a negative cytology does not exclude malignancy**, since sensitivity is moderate at best.

- **Blood:** liver function, INR, albumin, renal function, complete blood count, C-reactive protein, natriuretic peptide, alpha-fetoprotein, and **CA-125 — which is raised in cirrhotic ascites as well, so interpret it with the imaging rather than alone**.

- **Imaging: ultrasound with Doppler** for liver texture, portal and hepatic vein patency, nodules and the pelvis; echocardiography where a cardiac cause is possible; computed tomography of chest, abdomen and pelvis; and **laparoscopy where the cause remains unexplained**.

5. Management While You Are Still Deciding

THE THERAPEUTIC ERROR

Do not diurese an undiagnosed ascites.

Malignant and tuberculous ascites respond poorly or not at all to diuretics, so treating them as cirrhosis produces months of ineffective treatment, electrolyte disturbance and renal impairment while the actual disease progresses. Establish the mechanism first — which takes one tap and one ultrasound.

- **Cirrhotic ascites:** sodium restriction, spironolactone with furosemide, daily weights, and large-volume paracentesis with albumin replacement — Case 37.
- **Malignant ascites:** treat the cancer; **repeated therapeutic paracentesis or an indwelling drain for symptom control**; diuretics help only where the mechanism is massive hepatic metastasis.
- **Tuberculous peritonitis:** standard antituberculous therapy.
- **Cardiac ascites:** treat the heart failure — here diuretics are the treatment (Case 12).
- Nutrition and symptom control; and where malignancy is confirmed, **early palliative care involvement** and an honest conversation.

6. Teaching Points and Viva Questions

- Tap every ascites, and tap it on admission.
- The albumin gradient divides the differential in two; the ascitic protein then separates cirrhosis from heart failure.
- Neutrophils of 250 or more is spontaneous bacterial peritonitis.
- A negative cytology does not exclude malignancy.
- Lymphocytic, high-protein fluid with a raised adenosine deaminase is tuberculosis.
- Examine the pelvis and the umbilicus, and do not diurese an undiagnosed ascites.

Questions you should be able to answer:

- What does her albumin gradient of 6 tell you, and what does it exclude?
- A patient has a gradient of 14 with an ascitic protein of 45 and a raised jugular venous pressure. What is the diagnosis?
- The cytology is negative but you still suspect malignancy. What next?
- What would make you suspect tuberculous peritonitis, and how would you prove it?
- Why is starting spironolactone before the tap a mistake?

Seminar 15 · Approach to the Patient with Dementia

THE PRESENTATION

A **74-year-old man** is brought by his daughter. Over two years he has become forgetful — repeating questions, losing possessions, missing appointments, and recently **becoming lost while driving a familiar route**. He struggles to find words. He has withdrawn from the mosque and from friends. In the last six months bills have gone unpaid and **he has twice left the gas on**.

There is no fluctuation, no hallucination, no falls and no tremor.

On examination: cognitive testing shows impaired recall and orientation with preserved attention. No focal neurological signs, normal gait. Blood pressure 148/86 mmHg. **Hearing is poor and he has no hearing aid.**

Thyroid function normal · B12 low-normal · calcium normal. Computed tomography: generalised atrophy with medial temporal predominance, no vascular lesions.

1. Think First — Three Questions in Order

	Delirium	Dementia	Depression
	QUESTION ONE: IS THIS DEMENTIA, DELIRIUM OR DEPRESSION? **This is the single most important step, and it is where the errors are made.**		
Onset	Hours to days	Months to years	Weeks to months
Course	Fluctuating, worse at night	Progressive	Persistent low mood
Attention	Impaired — the cardinal feature	Preserved until late	Variable, effort-dependent
Consciousness	Clouded	Clear	Clear
Hallucinations	Common	Late, or in Lewy body disease	Uncommon
Answers	Muddled	Confabulated or approximate	"I don't know"

- **Delirium is frequently superimposed on dementia. So a sudden change in someone with established dementia is delirium, and it needs a cause found** — infection, pain, constipation, urinary retention, drugs, metabolic disturbance — not an increase in the antipsychotic.
- **Depression can present as pseudodementia**, with prominent "don't know" answers, and it is reversible with treatment.

QUESTION TWO: IS ANY OF IT REVERSIBLE?

Reversible or contributory causes to exclude in every patient:

Drugs — and this is the highest-yield item on the list: anticholinergics, benzodiazepines, opioids, antipsychotics, antiepileptics, and polypharmacy generally.

Metabolic and deficiency: B12 and folate deficiency, hypothyroidism, hypercalcaemia, hyponatraemia, uraemia, liver disease, recurrent hypoglycaemia.

Structural: chronic subdural haematoma, **normal pressure hydrocephalus**, cerebral tumour.

Infective: human immunodeficiency virus, neurosyphilis.

Other: alcohol and Wernicke–Korsakoff syndrome, obstructive sleep apnoea, depression.

And sensory impairment: untreated deafness and poor vision both mimic and worsen cognitive impairment. In this patient a hearing aid may be part of the treatment, and it is the cheapest intervention available.

Question three: which dementia?

Type	What identifies it
Alzheimer disease	Insidious, episodic memory affected first, then language and visuospatial function; medial temporal atrophy. This patient.
Vascular dementia	Stepwise decline or focal neurological signs, vascular risk factors, imaging burden. Frequently mixed with Alzheimer disease.
Dementia with Lewy bodies	Fluctuating cognition, visual hallucinations, dream enactment, parkinsonism — and severe, sometimes fatal, neuroleptic sensitivity (Case 69).
Frontotemporal dementia	Younger patient, with personality and behavioural change or progressive language failure, and relatively preserved memory early. Frequently misdiagnosed as psychiatric illness.
Others	Parkinson disease dementia, progressive supranuclear palsy, Huntington disease, prion disease (rapid progression), alcohol-related, HIV-associated, normal pressure hydrocephalus.

2. The History — Which Must Come From an Informant

- **Always take a collateral history.** The patient's own account is unreliable by the nature of the condition, and a consultation conducted with the patient alone will underestimate the problem.
- **Which domain failed first** — memory, language, behaviour or visuospatial function — because that is what distinguishes the subtypes.
- **Function, in specifics rather than generalities: finances, medication, cooking, driving, appliances, getting lost, washing and dressing.** This is what determines risk and the support required, and it is more useful than any score.
- Behavioural and psychological symptoms; hallucinations and fluctuation; **dream enactment**; falls; continence; mood and sleep; alcohol; **the complete drug history**; vascular risk factors; family history.
- **Safety, asked explicitly: driving, gas and fire, wandering, and financial vulnerability and exploitation.** This patient has already left the gas on twice and become lost while driving.

3. Examination

- A validated cognitive assessment, noting **which domains** are impaired; **test attention specifically**, to exclude delirium; assess mood.
- **Hearing and vision.**
- Full neurological examination — focal signs, gait, parkinsonism; **postural blood pressure**; cardiovascular examination.
- **Evidence of self-neglect or of neglect by others:** weight loss, dehydration, poor dentition, unexplained bruising, pressure damage.

4. Investigations, in Tiers

- **First line:** complete blood count, urea and electrolytes, **calcium**, glucose or glycated haemoglobin, liver function, **thyroid function, B12 and folate**, C-reactive protein — and **human immunodeficiency virus**

and syphilis serology where there is risk or the picture is atypical.

- **Structural imaging — computed tomography, or preferably magnetic resonance imaging — to exclude a subdural haematoma, tumour or hydrocephalus, to assess vascular burden, and to look at the pattern of atrophy. It is not performed to "confirm dementia".**
- **Specialist:** neuropsychometry; electroencephalography where prion disease or non-convulsive status is suspected; dopamine transporter imaging in suspected Lewy body disease; cerebrospinal fluid or amyloid biomarkers in young-onset or atypical cases; genetic testing in familial disease.
- **Refer urgently rather than routinely if: the onset is before 65, progression is rapid, behaviour or language change dominates, or there are focal neurological signs.**

5. Management While You Are Still Deciding

- **Treat what is treatable first. A medication review — stopping anticholinergic and sedative drugs — is among the highest-yield interventions in the whole assessment.** Correct deficiencies, treat depression and sleep apnoea, **fit hearing aids and correct vision**, and manage vascular risk.
- **Cholinesterase inhibitors** — donepezil, rivastigmine or galantamine — in Alzheimer, Lewy body and Parkinson disease dementia; **memantine** in moderate to severe Alzheimer disease or where inhibitors are not tolerated. **The benefit is modest and symptomatic: say so, or the family will expect reversal.**

BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS

Look for a cause before you prescribe. Agitation, aggression and shouting are usually communication, not psychosis.

The usual causes: pain · constipation · urinary retention · infection · hunger or thirst · fear · boredom · too much noise · an unfamiliar place · a new carer. Look for each, and use non-pharmacological approaches first.

Antipsychotics increase the risk of stroke and death in dementia. They are a last resort, at the lowest dose, for a defined period, with a documented review date — and they are dangerous in dementia with Lewy bodies, where sensitivity can be fatal.

WHERE THE REAL WORK IS

Occupational therapy and a home assessment · a care package and day services · dementia-friendly environment · nutrition, dental and foot care · vaccination.

Carer health is a clinical issue. Carer strain predicts institutionalisation and carer illness; ask about it directly and offer support and respite.

Do the legal and financial planning while capacity remains — lasting power of attorney, advance decisions, a will, and an advance care plan. **Capacity is decision-specific and fluctuates: assess it for the decision in front of you.**

Driving must be discussed and documented, with the legal duty to notify the licensing authority explained.

Then an honest prognosis, a palliative approach in advanced disease, and an agreed plan that avoids futile hospital admission.

6. Teaching Points and Viva Questions

- Dementia, delirium or depression — decide that first, and test attention to do it.
- A sudden change in someone with dementia is delirium, and needs a cause.
- Always take an informant history, and ask about function in specifics.

- Review the drugs — it is the highest-yield intervention.
- Fit the hearing aid.
- Find the cause of agitation before prescribing an antipsychotic, and never use one lightly in Lewy body disease.
- Do the legal planning while capacity remains.

Questions you should be able to answer:

- How would you distinguish this from delirium at the bedside?
- Name six reversible contributors you would exclude, and the test for each.
- Why does his hearing matter to his cognition?
- His daughter reports he has become aggressive at bath time. What do you do before prescribing anything?
- What must be arranged while he still has capacity?

Seminar 16 · Approach to the Patient with Acute Poisoning

THE PRESENTATION

A **22-year-old woman** is brought in six hours after taking "a lot of tablets" following an argument. Empty packets of paracetamol and ibuprofen were found beside her, and she also drank vodka. She will not say how many she took.

On examination: drowsy but rousable, Glasgow Coma Scale 14. She has vomited twice. Respiratory rate 22/min, heart rate 104/min, blood pressure 112/70 mmHg, temperature 36.6 °C, pupils 3 mm and reactive, glucose 5.2 mmol/L.

Alanine aminotransferase normal · INR 1.1 · lactate 2.4 · salicylate not detected · paracetamol level pending.

1. Think First — Four Questions

- **What, how much, when, and with what else?** — and **the history in poisoning is frequently wrong**, whether through confusion, shame or intent. **Assume the worst plausible scenario and treat it.**
- **Is there a specific antidote or elimination strategy, and is there a time window?**
- **Does the toxidrome fit the story?** If it does not, believe the patient's physiology rather than their account.
- **Why did this happen, and what is the risk of it happening again?** The psychosocial assessment is part of the medical management, not an addendum to it.

Toxidrome	Features and immediate action
Opioid	Pinpoint pupils, respiratory depression, reduced consciousness → naloxone, by infusion for long-acting agents
Sedative — benzodiazepine, alcohol	Reduced consciousness with relatively preserved respiration early, normal pupils. Flumazenil is rarely used — it precipitates seizures
Anticholinergic	"Mad, hot, dry, red, blind and full" — delirium, dry skin, dilated pupils, urinary retention, tachycardia
Cholinergic — organophosphate	Salivation, lacrimation, urination, defaecation, bronchorrhoea, bradycardia, small pupils, fasciculation → atropine in large repeated doses titrated to drying of secretions, plus pralidoxime. Decontaminate, and protect yourself and the staff
Sympathomimetic — cocaine, amphetamine	Agitation, dilated pupils, tachycardia, hypertension, hyperthermia and sweating (which distinguishes it from anticholinergic) → benzodiazepines first; avoid a beta blocker alone
Serotonin syndrome	Clonus and hyperreflexia, agitation, hyperthermia, diarrhoea, rapid onset after a serotonergic drug → benzodiazepines, cooling, cyproheptadine
Salicylate	Tinnitus, hyperventilation, vomiting, sweating, a mixed respiratory alkalosis with metabolic acidosis

2. What Could Kill in the Next Hour

- **Airway and breathing** — the commonest cause of death in poisoning is airway obstruction and aspiration, not the drug itself.
- **Hypoglycaemia**; **arrhythmia** — check the electrocardiogram for **a wide QRS from sodium channel blockade, which is treated with sodium bicarbonate**, and for a prolonged QT interval; **seizures**; **hyperthermia**, which requires active cooling.

- **And the patient who looks well.** Paracetamol produces no symptoms for 24 hours and then destroys the liver. **The level, not the appearance, decides the treatment.**
- **Use the poisons information service or database in every significant case.** It is a core clinical resource, not a last resort, and it should be consulted early.

3. Decontamination and Elimination

- **Activated charcoal within about one hour of ingestion, in a patient who can protect their airway.** It is of limited value later, and **useless for iron, lithium, alcohols and corrosives**.
- **Gastric lavage and ipecac are obsolete.** Do not use them.
- **Whole bowel irrigation** for modified-release or enteric-coated preparations in selected cases.
- **Urinary alkalinisation** for salicylate; **haemodialysis for lithium, salicylate, toxic alcohols, metformin-associated lactic acidosis, valproate and theophylline**; **intravenous lipid emulsion** in refractory local anaesthetic and some lipophilic drug toxicity.

Poison	Antidote
Paracetamol	N-acetylcysteine
Opioid · benzodiazepine	Naloxone · flumazenil (rarely)
Tricyclic antidepressant	Sodium bicarbonate for a wide QRS
Beta blocker · calcium channel blocker	Glucagon · calcium; high-dose insulin with euglycaemia for both
Digoxin	Digoxin-specific antibody fragments
Iron · methanol and ethylene glycol	Desferrioxamine · fomepizole or ethanol, with haemodialysis
Organophosphate · warfarin	Atropine with pralidoxime · vitamin K and prothrombin complex concentrate
Isoniazid · sulfonylurea	Pyridoxine · glucose with octreotide (Case 21)
Carbon monoxide · cyanide · methaemoglobinaemia	High-flow oxygen · hydroxocobalamin · methylene blue — with caution in glucose-6-phosphate dehydrogenase deficiency
	PARACETAMOL — THE ONE TO GET RIGHT **Asymptomatic for the first 24 hours**, then right upper quadrant pain and vomiting, then hepatic failure at three to four days. **The patient who feels fine is the one who needs the level.** **Measure the level at four hours or later after a single acute ingestion and treat according to the nomogram.** **Start N-acetylcysteine without waiting for the level if: the overdose was staggered or the timing is unknown · the patient presents more than eight hours after ingestion · or the patient is unwell.** The antidote loses efficacy after eight hours, so the balance shifts firmly towards treating. **Monitor INR, alanine aminotransferase, creatinine, pH and lactate — and note that the INR and the pH are the markers of severity, not the aminotransferase.** Use the King's College criteria and refer to a liver unit early (Case 35). **Anaphylactoid reactions to N-acetylcysteine are common: slow the infusion, treat the reaction, and continue — do not abandon the antidote.**

4. Management While You Are Still Deciding

- Airway, breathing and circulation; oxygen; glucose; monitoring; intravenous access; **electrocardiogram with attention to the QRS width and the QT interval**; temperature; and a **pregnancy test**.
- Supportive care is the mainstay for most poisons: **most patients survive because of good airway and circulatory management, not because of an antidote.**
- Correct electrolytes and acid–base disturbance; treat seizures with benzodiazepines; cool the hyperthermic patient actively; and observe for the delayed effects of modified-release preparations.

THE HALF OF THE ASSESSMENT THAT IS NOT THE DRUG

Every patient presenting with self-poisoning requires a risk and mental health assessment before discharge, by someone competent to perform it.

Establish: intent and planning · precautions taken against discovery · ongoing suicidal ideation · the means available and the access to them · previous attempts · psychiatric and substance misuse history · **and the social circumstances, including abuse and coercion, which may be the reason for the presentation.**

Treat the physical and the psychiatric problem together. A patient discharged "medically fit" without an assessment has been half treated — and the risk of repetition and of completed suicide is highest in the weeks that follow.

Also consider the non-suicidal explanations: accidental ingestion, therapeutic error, drug interaction, recreational use, a child, an older person with cognitive impairment, and **deliberate poisoning by another person.**

Arrange safety planning, discuss means restriction with the family, and **arrange follow-up before discharge rather than after it.**

5. Teaching Points and Viva Questions

- Treat the patient, not the poison — supportive care saves more lives than antidotes.
- The history is often wrong. Let the toxidrome and the tests guide you.
- Use the poisons information service early.
- Charcoal only within the hour and with a protected airway; lavage is obsolete.
- Paracetamol is silent then lethal — treat on the level, or blind if staggered, late or unwell.
- The INR and the pH, not the aminotransferase, tell you how sick the liver is.
- Check the QRS width on the electrocardiogram.
- No self-poisoning is discharged without a mental health assessment.

Questions you should be able to answer:

- She cannot say how much she took or when. How does that change your management?
- Give three situations in which you would start N-acetylcysteine without a level.
- Her aminotransferase is normal at eight hours. Is that reassuring?
- A patient arrives drowsy with a QRS of 140 ms. What is the likely poison and the treatment?

- She is medically fit at 24 hours and wants to go home. What must happen first?

Interpretation

Reading the investigation itself — the ECG from first principles through the tachycardias and conduction block, the blood count, film and coagulation screen, renal function and urinalysis, liver function tests, the chest radiograph and pulmonary function, and rheumatological serology.

Chapters 1–11 · 5,794 words

How Part III Differs

Parts I and II are about patients. **Part III is about the four or five investigations that a physician must be able to read alone, at three in the morning, with no specialist available.** These are not cases and they are not numbered as cases — they are chapters, numbered separately, and they are meant to be returned to rather than read once.

THE PRINCIPLE OF THIS PART

Every chapter gives a systematic order in which to look, and the order matters more than the list of abnormalities. Pattern recognition finds the abnormality you were expecting. **A system finds the second abnormality — the one that was not the reason the test was ordered, and the one that changes the management.**

So each chapter begins with the sequence, and only then covers what can be found and the traps that mislead.

Chapter	Tutorial it serves
1 — Reading the electrocardiogram systematically	Interpretation of the normal 12-lead electrocardiogram
2 — Ischaemia, pericarditis and the electrolytes	Ischaemic heart disease, pericarditis and electrolyte abnormalities
3 — The narrow-complex tachycardias	Supraventricular tachyarrhythmias
4 — The broad-complex tachycardias	Ventricular arrhythmias
5 — Bradycardia and conduction block	Conduction blocks and bradyarrhythmias
6 — A reading drill	Revision with practical demonstration
7 — The blood count, film, coagulation screen and marrow	Complete blood count, film interpretation, coagulation screening, normal bone marrow
8 — Renal function and urinalysis	Assessment of renal function and urinalysis
9 — Liver function tests	Assessment of liver function and its interpretation
10 — The chest radiograph and pulmonary function tests	Chest radiograph, pulmonary function tests and others
11 — Rheumatological and immunological serology	Investigations in rheumatology

Chapter 1 · Reading the Electrocardiogram Systematically

BEFORE YOU INTERPRET ANYTHING

Name, date and time · calibration (10 mm per mV) and paper speed (25 mm per second) · lead placement · and — above all — the previous tracing.

Comparing with an old electrocardiogram is often the single most useful act in the whole interpretation. A left bundle branch block that is old is a different problem from one that is new.

Two placement errors to recognise: limb lead reversal, which produces a spurious inferior or lateral pattern with an inverted P in lead I; and **chest leads placed too high, which produces false anterior T wave changes and poor R wave progression.** If the tracing does not fit the patient, look at where the electrodes are before you believe it.

The sequence — same order, every time, out loud

Step	What to establish
1. Rate	300 divided by the number of large squares between R waves. For an irregular rhythm, count the complexes in 30 large squares and multiply by 10.
2. Rhythm	Regular or irregular. Is there a P wave before every QRS, and a QRS after every P? Is the P sinus in origin — upright in II, inverted in aVR?
3. Axis	Normal −30° to +90°. Look at leads I and II: both positive is normal; I positive with II negative is left axis deviation; I negative with II positive is right axis deviation.
4. P wave	Taller than 2.5 mm — P pulmonale, right atrial enlargement. Broader than 120 ms and bifid — P mitrale, left atrial enlargement (Case 10).
5. PR interval	120–200 ms. Long — first-degree block. Short with a slurred upstroke — pre-excitation.
6. QRS	Width under 120 ms; voltage; Q waves; R wave progression across the chest leads; bundle branch block.
7. ST segment	Elevation or depression — with its shape and its distribution by territory.
8. T wave	Inversion, flattening, peaking, biphasic change.
9. QT interval	Corrected for rate. Prolonged above about 440 to 460 ms.
10. Look again	For what hides: subtle ST depression, extra P waves, delta waves, and the review of the leads you skipped.

Bundle branch block

- **Right bundle branch block:** QRS above 120 ms with an **RSR′ pattern in V1** ("M" shape) and a broad slurred S wave in leads I and V6. Causes: normal variant, pulmonary embolism, right heart strain, ischaemia, congenital disease.
- **Left bundle branch block:** QRS above 120 ms with a **broad notched R wave in V6** ("M" shape) and a dominant S in V1. **In left bundle branch block the ST segments and T waves cannot be interpreted for ischaemia** — and **a new left bundle branch block in a patient with chest pain is managed as an infarction** (Case 11).

The QT interval

- **Prolonged by:** congenital long QT syndromes; **drugs — antipsychotics, macrolides, fluoroquinolones, antiarrhythmics, methadone, ondansetron, some antifungals and antiemetics**; **electrolytes — low potassium, magnesium and calcium**; bradycardia; hypothermia; raised intracranial pressure; and hypothyroidism.

- **It matters because of torsades de pointes** (Chapter 4). **Check the corrected QT before and after starting a QT-prolonging drug**, particularly where several are combined — which happens routinely in hospital.

And then look for the things that hide

- **Posterior infarction** — tall R waves with ST depression in V1–V2 (Chapter 2). **Flutter waves** hiding within T waves. **Delta waves.** Subtle widespread ST depression with elevation in aVR. **Epsilon waves and the Brugada pattern.** Electrical alternans. And the **review leads** — aVR, and V1, which are the two most often ignored.

Chapter 2 · Ischaemia, Pericarditis and the Electrolytes

1. Ischaemia and Infarction

- **Territory and artery** — the table in Case 11. **Every inferior infarct gets right-sided leads before anyone gives a nitrate**, and tall R waves with ST depression in V1–V2 get posterior leads V7–V9.
- **Evolution:** hyperacute tall T waves → ST elevation → Q wave formation → T wave inversion → resolution with a residual Q. **A single tracing is a snapshot: repeat it if the pain continues.**
- **Reciprocal ST depression** supports a true infarction and helps distinguish it from pericarditis and from early repolarisation.

FOUR PATTERNS THAT ARE MISSED BECAUSE THEY ARE NOT ST ELEVATION

Widespread ST depression with ST elevation in aVR — suggests left main or severe proximal three-vessel disease. This is a high-risk pattern, not a "non-specific" one.

Wellens syndrome — **deep symmetrical T wave inversion, or a biphasic T wave, in V2–V3 in a patient who is now pain-free**, with preserved R waves and no Q waves. It indicates **critical proximal left anterior descending stenosis**. The patient looks well and the temptation is to discharge them; they need admission and angiography.

De Winter pattern — upsloping ST depression with tall symmetrical T waves in the precordial leads, an equivalent of proximal left anterior descending occlusion.

Posterior infarction — the "ST depression" in V1–V2 that is really elevation seen from behind.

2. Pericarditis

- **Widespread concave (saddle-shaped) ST elevation with PR segment depression, crossing territories, without reciprocal change and without Q waves** — with ST depression and PR elevation in aVR. The full comparison with infarction is in Case 17.
- **Electrical alternans, low voltage and sinus tachycardia** suggest a large effusion with tamponade.

3. The Electrolytes

Abnormality	Electrocardiographic change
Hyperkalaemia	Tall tented T waves → flattened or absent P waves with a long PR → broadening QRS → sine wave → arrest. Any change is an indication for immediate treatment (Case 28).
Hypokalaemia	Flattened T waves, ST depression, prominent U waves, prolonged QT, and ventricular arrhythmia.
Hypercalcaemia · hypocalcaemia	Short QT · long QT.
Hypomagnesaemia	Prolonged QT and torsades de pointes — and it must be corrected alongside potassium, or the potassium will not stay corrected.

4. Other Patterns Worth Recognising

Pattern	Cause
Downsloping ST with a "reverse tick"	Digoxin effect. Toxicity is a different matter: any arrhythmia, classically with bidirectional ventricular tachycardia or atrial tachycardia with block.
J waves with bradycardia and prolonged intervals	Hypothermia
Sinus tachycardia with right axis deviation, right bundle branch block and T inversion in V1–V4	Pulmonary embolism — the classical S1Q3T3 pattern is uncommon and its absence means nothing (Seminars 3 and 11)
Deep, widely splayed T wave inversion with a long QT	Subarachnoid haemorrhage and other intracranial catastrophe
Voltage criteria with lateral ST depression and T inversion	Left ventricular hypertrophy with strain (Case 14)
Deep lateral T inversion, or giant negative T waves	Hypertrophic cardiomyopathy, including the apical variant (Case 18)
Coved ST elevation with T inversion in V1–V2	Brugada pattern — associated with sudden death; refer
Concave elevation with notched J points in a young, well patient	Early repolarisation — no reciprocal change and no evolution

Chapter 3 · The Narrow-Complex Tachycardias

THE FIRST QUESTION IN ANY TACHYCARDIA

Before you classify the rhythm, decide whether the patient can wait.

Adverse features: shock · syncope · myocardial ischaemia · heart failure. Any of these in a tachyarrhythmia means **synchronised cardioversion under sedation**, not a third drug.

The rhythm diagnosis is important. It is not more important than the patient.

1. What Narrow Means

A QRS under 120 ms means the ventricles are being depolarised through the normal conducting system, so **the origin is at or above the atrioventricular node.** Then divide by regularity.

Regular narrow	Irregular narrow
Sinus tachycardia — a sign, not a diagnosis. Find the cause — pain, fever, hypovolaemia, sepsis, anaemia, thyrotoxicosis, embolism, drugs, anxiety — and treat that	Atrial fibrillation — irregularly irregular with no discernible P waves
Atrial flutter with fixed block — saw-tooth baseline; a ventricular rate close to 150 should always make you think of flutter with 2:1 conduction	Atrial flutter with variable block
Atrioventricular nodal re-entrant tachycardia — abrupt onset and offset, 140–220/min, P waves absent or retrograde	Multifocal atrial tachycardia — varying P wave morphology; think of chronic obstructive pulmonary disease and theophylline
Atrioventricular re-entrant tachycardia with an accessory pathway; atrial tachycardia; junctional tachycardia	Frequent atrial ectopy

2. Managing the Stable Regular Narrow Tachycardia

- **Vagal manoeuvres first** — the modified Valsalva with a supine reposition and passive leg raise is substantially more effective than the standard version.
- **Then adenosine, given rapidly with a continuous electrocardiographic recording running** — because **the response is diagnostic as well as therapeutic**: termination suggests a re-entrant circuit involving the node; transient block revealing flutter waves diagnoses flutter; and no effect suggests an atrial or ventricular origin. **Warn the patient about the brief and very unpleasant sensation**, and avoid it in asthma.
- Then a rate-limiting calcium channel blocker or a beta blocker; and cardioversion if drugs fail or the patient deteriorates.

THE ONE CONTRAINDICATION TO REMEMBER

In atrial fibrillation with pre-excitation — an irregular broad-complex tachycardia in a patient with a delta wave — do not give adenosine, verapamil, diltiazem, digoxin or a beta blocker.

Blocking the node diverts conduction down the accessory pathway and can precipitate **ventricular fibrillation**. Use procainamide, or cardiovert, and get expert help.

3. Atrial Fibrillation

- **Rate control or rhythm control**, according to symptoms, duration, age and structural disease; and **anticoagulation decided by the stroke risk score, independently of whether the rhythm has been controlled** — restoring sinus rhythm does not remove the need for anticoagulation.
- **Two exceptions to direct oral anticoagulants: rheumatic mitral stenosis, which requires warfarin** (Case 10), and **antiphospholipid syndrome** (Case 63).
- **Always look for the cause:** thyrotoxicosis, sepsis, alcohol, electrolyte disturbance, ischaemia, valve disease, pulmonary embolism, and obstructive sleep apnoea.
- Consider referral for ablation, and for assessment of any accessory pathway.

Chapter 4 · The Broad-Complex Tachycardias

THE RULE THAT PREVENTS DEATHS

A broad-complex tachycardia is ventricular tachycardia until proved otherwise — and overwhelmingly so in a patient with previous myocardial infarction or known structural heart disease.

Haemodynamic stability does not exclude ventricular tachycardia. A patient can sit up and talk through it, and the temptation is then to treat it as a supraventricular rhythm with a bundle branch block.

Giving verapamil to ventricular tachycardia can be fatal. If you are not certain, treat it as ventricular tachycardia — the treatment for that is safe in supraventricular tachycardia, and the reverse is not true.

1. Features Favouring Ventricular Tachycardia

- A very broad QRS; an extreme or bizarre axis; **concordance of the QRS across all the precordial leads**; **fusion beats and capture beats**; **atrioventricular dissociation**; and **a history of ischaemic heart disease or cardiomyopathy**, which alone makes ventricular tachycardia far more likely than anything else.

2. Management

- **Pulseless: defibrillate and follow the advanced life support algorithm**, seeking the reversible causes — the four Hs and four Ts.
- **Unstable with a pulse: synchronised cardioversion under sedation.**
- **Stable monomorphic ventricular tachycardia:** amiodarone or procainamide, correction of potassium and magnesium, treatment of ischaemia, and expert help. Cardiovert if drugs fail.

TORSADES DE POINTES

Polymorphic ventricular tachycardia with a prolonged QT. Often self-terminating, often recurrent, and it degenerates into ventricular fibrillation.

Treatment: intravenous magnesium sulfate · stop every QT-prolonging drug · correct potassium, magnesium and calcium · and increase the heart rate with pacing or isoprenaline if the episodes are bradycardia-dependent — because pauses precipitate it.

Amiodarone is not the answer here — it prolongs the QT further.

3. The Broad Rhythms That Are Not Ventricular Tachycardia

Rhythm	Recognition
Supraventricular tachycardia with pre-existing bundle branch block	A previous tracing showing the same QRS morphology in sinus rhythm
Pre-excited tachycardia	Irregular, very fast, with delta waves in sinus rhythm — and the drug contraindications of Chapter 3
Hyperkalaemia	A slow, broad, sine-wave rhythm with absent P waves — check the potassium in every broad-complex rhythm (Case 28)
Sodium channel blocker toxicity	Tricyclic antidepressant overdose — a wide QRS treated with sodium bicarbonate (Seminar 16)
Paced rhythm; artefact	Pacing spikes; and a "rhythm" with palpable pulses that do not match it

- **After the event:** treat the cause, correct electrolytes, revascularise where appropriate, and **assess for an implantable defibrillator** (Cases 11 and 18).

Chapter 5 · Bradycardia and Conduction Block

AGAIN, THE PATIENT BEFORE THE RHYTHM

Adverse features: shock · syncope · myocardial ischaemia · heart failure.

If present: atropine, then transcutaneous pacing or an isoprenaline or adrenaline infusion while transvenous pacing is arranged. If absent, look for the risk of progression — which is what the block type tells you.

1. The Blocks

Block	Recognition and significance
First degree	PR above 200 ms with no dropped beats. Usually benign in isolation.
Second degree, Mobitz I (Wenckebach)	Progressive PR lengthening, then a dropped beat. Usually at the node, often vagal or drug-related, and generally benign.
Second degree, Mobitz II	A constant PR interval with sudden unheralded dropped beats. Infranodal, unpredictable, and it progresses to complete block — it needs pacing. The distinction from Mobitz I is the whole point of the classification.
2:1 block	Can be either type. Needs assessment — look at the QRS width and the response to exercise or atropine.
Third degree (complete)	No relationship between P waves and QRS complexes, with a slow escape rhythm. Cannon a waves in the neck. Pacing.

2. The Causes — and the Reversible Ones First

- **Drugs, which are the commonest reversible cause: beta blockers, verapamil and diltiazem, digoxin, amiodarone, ivabradine, and cholinesterase inhibitors** — and combinations of them, especially in the elderly with declining renal function.
- **Hyperkalaemia** — check it in every bradycardia.
- **Ischaemia: inferior infarction causes atrioventricular block that is usually transient and atropine-responsive**, because the node is supplied by the right coronary artery; **anterior infarction causing block implies extensive septal damage and carries a much worse prognosis**, and generally needs pacing.
- **Metabolic and other:** hypothyroidism, hypothermia, raised intracranial pressure with the Cushing reflex, and obstructive sleep apnoea.
- **Infective and infiltrative: an aortic root abscess in infective endocarditis — a new atrioventricular block in a febrile patient with a murmur is an emergency** (Case 13); Lyme disease; diphtheria; Chagas disease; **sarcoidosis and amyloidosis** (Case 18); and rheumatic disease.
- Degenerative conduction system disease; and **high vagal tone in athletes and during sleep, which is normal.**

3. Sinus Node Disease

- **Sick sinus syndrome** — inappropriate sinus bradycardia, sinus arrest, and the **tachycardia–bradycardia syndrome**, in which treating the tachycardia unmasks the bradycardia and vice versa. Ambulatory

monitoring correlates symptoms with rhythm.

- **Before implanting a permanent pacemaker, exclude a reversible cause — almost always a drug or hyperkalaemia.** A patient paced for a bradycardia caused by their beta blocker has been given a lifelong device for a prescribing problem.

Chapter 6 · A Reading Drill

Interpretation is a skill of repetition. Work through these, saying the sequence from Chapter 1 aloud each time, and give the finding, the diagnosis and the **action**.

THE FIVE ELECTROCARDIOGRAMS YOU MUST NEVER MISS

1. ST elevation in a territory, with reciprocal depression — an infarct.

2. Complete heart block — or Mobitz II, which will become it.

3. A broad-complex tachycardia — ventricular tachycardia until proved otherwise.

4. Hyperkalaemia — tented T waves through to the sine wave.

5. A prolonged QT — the substrate for torsades.

And three more that are missed rather than mistaken: **Wellens pattern · posterior infarction · the Brugada pattern.**

The tracing	Diagnosis and action
62-year-old with chest pain: ST elevation in II, III and aVF with ST depression in I and aVL	Inferior infarct. Right-sided leads before any nitrate; reperfusion (Case 11).
58-year-old with chest pain: tall R waves and ST depression in V1–V2	Posterior infarct. Record V7–V9 and treat as an ST-elevation infarct.
Pain-free 55-year-old after an episode of chest pain: biphasic T waves in V2–V3, preserved R waves	Wellens syndrome — critical proximal left anterior descending stenosis. Admit; do not discharge.
34-year-old with positional chest pain: widespread saddle ST elevation with PR depression, no reciprocal change	Pericarditis. Anti-inflammatory drug plus colchicine; check troponin (Case 17).
Dialysis patient, missed a session: tall tented T waves, absent P waves, broad QRS	Hyperkalaemia. Calcium gluconate, insulin–dextrose, salbutamol — now (Case 28).
70-year-old, dizzy: regular P waves at 90, regular QRS at 38, no relationship between them	Complete heart block. Atropine, pacing; stop the rate-limiting drugs; check potassium.
Post-infarct patient, rate 170, broad QRS, concordant precordial leads, blood pressure 105/70	Ventricular tachycardia. Stability does not change the diagnosis. Amiodarone or cardioversion — not verapamil.
Rate exactly 150, regular, narrow, saw-tooth baseline in II	Atrial flutter with 2:1 block. Adenosine may unmask the flutter waves.
Palpitations, rate 190, narrow, regular, abrupt onset	Nodal re-entrant tachycardia. Modified Valsalva, then adenosine with the trace running.
Irregularly irregular, no P waves, rate 130	Atrial fibrillation. Rate control, look for the cause, score the stroke risk.
Young patient, syncope: short PR with a slurred upstroke, now in an irregular broad tachycardia	Pre-excited atrial fibrillation. No adenosine, verapamil, digoxin or beta blocker. Procainamide or cardioversion.
Collapsed patient, QRS 150 ms, sinus tachycardia, dilated pupils, drowsy	Tricyclic overdose with sodium channel blockade. Sodium bicarbonate (Seminar 16).

Chapter 7 · The Blood Count, Film, Coagulation Screen and Marrow

1. Reading the Blood Count

- **Haemoglobin with the mean cell volume and the reticulocyte count** — the reticulocyte count is the first branch of the whole anaemia algorithm (Case 50), and it is frequently not requested.
- **Read the white cell differential, not the total.** A normal total can conceal a neutropenia with a lymphocytosis.

Abnormality	Common causes
Neutrophilia	Infection, inflammation, tissue damage, corticosteroids, smoking, malignancy, myeloproliferative disease. A left shift and toxic granulation suggest infection rather than steroid effect.
Neutropenia	Drugs — carbimazole, clozapine, chemotherapy, co-trimoxazole — viral infection, marrow disease, hypersplenism, autoimmune, B12 and folate deficiency, and ethnic benign neutropenia
Lymphocytosis	Viral infection, pertussis, chronic lymphocytic leukaemia (Case 54), lymphoma, tuberculosis
Lymphopenia	Corticosteroids, HIV, sepsis, lymphoma, radiotherapy, malnutrition
Eosinophilia	Parasitic infestation — first on the list in this region · drug reaction and DRESS (Case 76) · atopy · eosinophilic granulomatosis with polyangiitis (Case 61) · adrenal insufficiency · malignancy
Thrombocytosis	Reactive — infection, inflammation, iron deficiency, bleeding, post-splenectomy — or clonal (Case 57)
Thrombocytopenia	Case 52 — and always look at the film first
Pancytopenia	Marrow failure or infiltration, B12 or folate deficiency, hypersplenism, drugs, and in this region visceral leishmaniasis, brucellosis and tuberculosis (Seminar 9)

2. The Film — What to Ask For and What It Shows

THE FILM FINDINGS WORTH KNOWING BY NAME

Request a film on any unexplained abnormal count, and look at the report properly. These findings are diagnostic in themselves:

Blasts and Auer rods → acute leukaemia (Case 53) · **hypersegmented neutrophils and oval macrocytes** → B12 or folate deficiency (Case 50) · **spherocytes** → hereditary spherocytosis or warm autoimmune haemolysis · **schistocytes** → microangiopathy — **with a low platelet count this is a haematological emergency** · **sickle cells** · **target cells and basophilic stippling** → thalassaemia, lead · **tear-drop poikilocytes with a leucoerythroblastic picture** → marrow infiltration or myelofibrosis (Case 57) · **rouleaux** → paraproteinaemia (Case 56) · **bite cells and Heinz bodies** → glucose-6-phosphate dehydrogenase deficiency (Case 50) · **malaria parasites** — with the species and the percentage parasitaemia (Case 42) · **smudge cells** → chronic lymphocytic leukaemia.

THE RESULTS THAT ARE NOT REAL

Pseudothrombocytopenia — platelet clumping in the EDTA tube. Not a disease; repeat in citrate (Case 52).

Spurious hyperkalaemia — haemolysis of the sample, a clenched fist, delayed transport, or a very high platelet or white cell count.

Pseudohyponatraemia — severe hyperlipidaemia or paraproteinaemia (Case 27).

A falsely normal glycated haemoglobin — haemoglobinopathy, haemolysis, recent transfusion (Case 20).

And the general rule: repeat a single surprising result before acting on it, and look at the trend rather than the value.

3. The Coagulation Screen

- **Prothrombin time and INR · activated partial thromboplastin time · fibrinogen · thrombin time · D-dimer.** The interpretation table — prolonged prothrombin time alone, prolonged partial thromboplastin time alone, both prolonged, or both normal with clear bleeding — is in Case 52, together with the **mixing study**, which separates a factor deficiency from an inhibitor.

- **Two traps:** a **lupus anticoagulant** prolongs the partial thromboplastin time in a patient who thromboses rather than bleeds (Case 63); and **the INR does not measure bleeding risk in liver disease**, where procoagulant and anticoagulant factors fall together (Case 38).

4. The Bone Marrow

- **The aspirate** gives cellular morphology, differential counts, iron stores, cytogenetics and flow cytometry. **The trephine biopsy** gives architecture, cellularity, fibrosis and infiltration — and is the part that shows a lymphoma or a granuloma.

- **Send it for culture as well as histology whenever infection is possible** — marrow culture has a good yield for tuberculosis, brucellosis and leishmaniasis (Case 41 and Seminar 9).

- Indications: unexplained cytopenias, suspected leukaemia, lymphoma or myeloma, staging, suspected infiltration, and pyrexia of unknown origin.

Chapter 8 · Renal Function and Urinalysis

THE LIMITATION OF THE NUMBER EVERYONE USES

Creatinine is a product of muscle. A frail, elderly, cachectic or amputee patient can lose most of their renal function with a creatinine that never leaves the reference range.

And the estimating equations are not valid in acute kidney injury, at extremes of body size, in pregnancy, or in amputees — exactly the patients in whom the number is most likely to be relied upon.

So interpret the creatinine against the patient's own previous values, not against the reference range (Case 28). Cystatin C where available.

1. The Numbers

- **The urea-to-creatinine relationship:** urea raised disproportionately in **gastrointestinal bleeding** (Case 38), volume depletion, a high protein load, catabolism and corticosteroids; and low in liver disease, malnutrition and pregnancy.
- **Potassium, bicarbonate, calcium, phosphate and parathyroid hormone** in chronic disease (Case 29).

2. Urinalysis, Done Properly

- **The dipstick:** protein, blood, leucocytes, nitrites, glucose, ketones, pH and specific gravity. **Two limitations to hold on to: it does not detect Bence Jones protein** (Case 56), and **it is unreliable in the elderly and in catheterised patients**, in whom bacteriuria is common and does not mean infection (Case 32).

ASK FOR THE MICROSCOPY

Microscopy is the part of urinalysis that is routinely skipped, and it is the part that localises the disease.

Dysmorphic red cells and red cell casts → glomerular bleeding, which redirects the whole investigation from urology to immunology and biopsy (Case 33).

Granular muddy-brown casts → acute tubular necrosis · white cell casts → pyelonephritis or interstitial nephritis · eosinophils → interstitial nephritis · crystals → stones, urate, oxalate or drug crystals.

3. Quantifying and Localising

- **Albumin-to-creatinine and protein-to-creatinine ratios** on an early morning sample; the thresholds of Case 29 and the nephrotic range of Seminar 2. Twenty-four-hour collections are cumbersome and frequently inaccurate.
- **In hyponatraemia: paired serum and urine osmolality with a urine sodium, taken before any fluid is given** (Case 31).
- **In metabolic alkalosis: the urine chloride**, which separates the chloride-responsive from the chloride-resistant causes. **In a normal-anion-gap acidosis: the urinary anion gap**, which separates renal from gastrointestinal bicarbonate loss (Case 30).
- Fractional excretion of sodium and of urea in distinguishing pre-renal from intrinsic injury — useful, but unreliable on diuretics.

- **Ultrasound: size, symmetry, cortical thickness, obstruction and cysts** — and remember that **small echogenic kidneys mean chronic disease whatever the history says** (Cases 28 and 29).

Chapter 9 · Liver Function Tests

THE NAME IS MISLEADING

Most of what is called a "liver function test" measures injury, not function.

The aminotransferases and alkaline phosphatase tell you that hepatocytes or bile ducts are being damaged. They do not tell you how much liver is working.

Function is measured by the albumin, the prothrombin time or INR, the bilirubin — and clinically, by the mental state. A falling aminotransferase in a deteriorating jaundiced patient means there is little liver left to leak enzymes (Case 35).

1. Read the Pattern First

- **Hepatitic** — aminotransferases raised out of proportion to alkaline phosphatase. **Cholestatic** — alkaline phosphatase and gamma-glutamyl transferase raised out of proportion. **Mixed.** This single decision narrows the differential more than anything else (Case 35).

- **An alanine aminotransferase above 1000** has a short differential: viral hepatitis, drugs and toxins (**check a paracetamol level in everyone**), ischaemic hepatitis, autoimmune hepatitis, a passing stone, acute Budd–Chiari, and Wilson disease under 40.

2. The Individual Tests

Test	What it actually means
Alanine aminotransferase	Relatively liver-specific.
Aspartate aminotransferase	Also present in muscle, heart and red cells — so check the creatine kinase before investigating a raised AST as liver disease. An AST:ALT ratio above 2 suggests alcohol; above 1 suggests cirrhosis.
Alkaline phosphatase	Liver or bone. Confirm the source with the gamma-glutamyl transferase: a raised alkaline phosphatase with a normal GGT is bone — Paget disease, metastases, osteomalacia, a healing fracture, childhood growth — or placental in pregnancy.
Gamma-glutamyl transferase	Sensitive and very non-specific. Raised in isolation by alcohol and by enzyme-inducing drugs; useful mainly to confirm that a raised alkaline phosphatase is hepatobiliary.
Bilirubin	Split it into conjugated and unconjugated (Seminar 1). An isolated unconjugated hyperbilirubinaemia with normal enzymes, a normal film and no haemolysis, provoked by fasting or illness, is Gilbert syndrome — which needs reassurance, not investigation.
Albumin	Falls in chronic liver disease — but also in inflammation, nephrotic syndrome, protein-losing enteropathy and malnutrition. It is a good acute-phase marker and a poor nutritional one.
Prothrombin time / INR	The best single marker of synthetic function — and in obstructive jaundice it corrects with vitamin K, whereas in hepatocellular failure it does not.

3. Working Up an Abnormal Result

- **Repeat it first** — transient abnormalities are common. Then take an alcohol, drug and herbal history, and calculate the body mass index and metabolic risk.

- **The non-invasive panel:** hepatitis B and C serology; autoantibodies with immunoglobulins; **ferritin and transferrin saturation**; **caeruloplasmin under the age of 40**; alpha-1 antitrypsin; coeliac serology; thyroid function; lipids and glucose; and an ultrasound.

- **Then assess fibrosis non-invasively — FIB-4 and APRI from routine bloods, or transient elastography** (Case 36).

THE RESULT THAT LOOKS REASSURING AND IS NOT

Normal liver enzymes do not exclude cirrhosis. Enzymes frequently normalise as the liver becomes fibrotic.

A falling platelet count may be the only abnormality, appearing long before ascites or varices — so a patient with a low platelet count and a risk factor for liver disease deserves a fibrosis assessment rather than a repeat count (Case 36).

Chapter 10 · The Chest Radiograph and Pulmonary Function Tests

1. Reading the Chest Radiograph

- **Details and adequacy first:** name and date; **projection** — posteroanterior or anteroposterior, since an anteroposterior film magnifies the heart and cannot be used to judge its size; erect or supine; **inspiration** (count the ribs); **penetration**; and **rotation** — the clavicles should be equidistant from the spinous process.

Step	What to inspect
A — Airway	Tracheal position and calibre, the carina, and the main bronchi.
B — Breathing	Both lung fields, zone by zone, comparing right with left; the pleura; the apices; the costophrenic angles; the horizontal fissure.
C — Circulation	Heart size (cardiothoracic ratio above 0.5 on a posteroanterior film), the cardiac and mediastinal borders, the aortic knuckle, and the pulmonary vasculature.
D — Diaphragm	Position and contour of both hemidiaphragms; free air beneath them; the gastric bubble.
E — Everything else	Bones and soft tissues; breast shadows; surgical emphysema; and every line, tube and device — including confirming the nasogastric tube position before anything is fed through it.
Review areas	The apices · behind the heart · below the diaphragm · the costophrenic angles · the periphery of the lung fields. These are where lesions hide.

- **The signs to know, with their cases:** the **silhouette sign** for localising consolidation (Case 1); the **air bronchogram**; the **meniscus** of an effusion and the tracheal rule in a white-out — **pushed away means effusion, pulled towards means collapse** (Case 6); **hyperinflation with flattened hemidiaphragms** (Case 3); **Kerley B lines, upper lobe diversion and bat's-wing shadowing** (Case 12); **cavitation** and **upper zone predilection** (Case 43); **tramline and ring shadows** (Case 4); a **widened mediastinum** (Seminar 3); and free air under the diaphragm.

2. Pulmonary Function Tests

- **The first question is obstructive or restrictive.** A **forced expiratory volume to forced vital capacity ratio below 0.7** is obstructive. A **normal or high ratio with a reduced forced vital capacity and a reduced total lung capacity** is restrictive.

- **Reversibility testing** distinguishes asthma from fixed airflow obstruction — with the caveat that a single negative test does not exclude asthma.

THE MEASUREMENT THAT DECIDES WHAT A RESTRICTIVE PATTERN MEANS

A restrictive pattern has two quite different causes, and the gas transfer separates them.

Reduced gas transfer → the lung parenchyma is diseased — interstitial lung disease, and it is also reduced in emphysema, pulmonary vascular disease and anaemia.

Normal or raised gas transfer with a restrictive pattern → the lungs are normal and the problem is the pump — chest wall deformity, obesity, pleural disease, or **neuromuscular weakness** (Case 5).

Gas transfer is raised in alveolar haemorrhage and in polycythaemia, and must be corrected for haemoglobin.

- **Flow–volume loops:** a flattened inspiratory limb indicates **extrathoracic upper airway obstruction**; a flattened expiratory limb indicates intrathoracic obstruction.
- **Peak expiratory flow** and its diurnal variation in asthma — measured before and after every intervention in an acute attack (Case 2).
- **Vital capacity in neuromuscular disease, measured serially** — and the point from Case 66: act on the falling vital capacity rather than waiting for the blood gas, because hypercapnia is a pre-terminal finding.
- **Six-minute walk distance with oximetry**, which detects the exertional desaturation that a resting saturation misses (Cases 8 and 45).

Chapter 11 · Rheumatological and Immunological Serology

THE RULE THAT GOVERNS THE WHOLE CHAPTER

These tests have poor specificity, and their usefulness depends entirely on the probability of disease before they are sent.

A positive antinuclear antibody in a patient with fatigue and nothing else is far more likely to be a false positive than lupus — and once it is in the record, the patient may spend years carrying a diagnosis that is very difficult to remove.

So order these tests to answer a specific question raised by the history and examination. Do not use them to screen an undifferentiated symptom.

1. The Tests

Test	How to interpret it
Rheumatoid factor	Poor specificity — positive in healthy older people, hepatitis C, infective endocarditis, Sjögren syndrome, sarcoidosis and chronic infection. Anti-cyclic citrullinated peptide antibody is far more specific and predicts erosive disease (Case 58).
Antinuclear antibody	Sensitive, poorly specific; positive at low titre in many healthy people. Its value lies in the negative: a negative result makes lupus very unlikely (Case 59).
The specific antinuclear antibodies	Anti-double-stranded DNA and anti-Sm — specific for lupus, and the former tracks activity. Anti-Ro and anti-La — Sjögren, and neonatal lupus with congenital heart block, so essential before pregnancy. Anti-RNP. Anti-centromere — limited systemic sclerosis; anti-topoisomerase (Scl-70) — diffuse disease with lung fibrosis. Myositis panel including anti-Jo-1. Anti-histone — drug-induced lupus.
Complement C3 and C4	Consumed in active immune complex disease. The pattern is diagnostically useful: low C3 with normal C4; low C3 and C4; or normal complement — the table in Case 33.
ANCA — proteinase-3 and myeloperoxidase	Supports but does not prove, and the titre tracks relapse unreliably. False positives in infection — including endocarditis and tuberculosis — and in drug-induced disease (Case 61).
Antiphospholipid antibodies	Lupus anticoagulant, anticardiolipin, anti-beta-2 glycoprotein I. Must be confirmed on a repeat sample at least 12 weeks later, and the assays are distorted by acute thrombosis and by anticoagulation (Case 63).

2. The Inflammatory Markers

- **C-reactive protein** rises and falls within hours to days. **The erythrocyte sedimentation rate** is slower and is confounded by **anaemia, age, sex, pregnancy and a paraprotein** — so a very high sedimentation rate with a normal C-reactive protein should prompt a myeloma screen.

- **The lupus exception, which is worth its own sentence: in active lupus the sedimentation rate rises and the C-reactive protein characteristically does not — so a high C-reactive protein in a febrile lupus patient means infection until proved otherwise** (Case 59).

- **Ferritin** is an acute-phase protein, so it is unreliable as an iron marker in inflammation (Case 49) — and **a very high ferritin in a febrile patient suggests adult-onset Still disease or haemophagocytic syndrome** (Seminar 9).

3. The Rest, and Their Practical Traps

- **HLA-B27** supports axial spondyloarthritis but does not diagnose it, and it is common in healthy people (Case 60).
- **Serum urate** — normal during an acute attack of gout and raised in many people who never get it (Case 62).
- **Creatine kinase** in suspected myositis — and remember it also explains a raised aspartate aminotransferase (Chapter 9).
- **Immunoglobulins with protein electrophoresis and serum free light chains** — for myeloma, amyloidosis and paraprotein-associated neuropathy (Cases 56 and 67).
- **Cryoglobulins must be transported to the laboratory at body temperature.** Sent in a cold tube, the test is destroyed, and a negative result means nothing. Telephone the laboratory before taking the sample.
- **Coeliac serology requires a total IgA level and a patient still eating gluten** (Seminar 13).

THE SENTENCE TO END ON

Serology supports a clinical diagnosis. It does not create one, and — with a few defined exceptions such as anti-double-stranded DNA and complement in lupus nephritis — it does not measure disease activity.

A patient improving clinically with a persistently positive antibody is improving. A patient deteriorating with a negative one is deteriorating. **Treat the patient, not the titre.**