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.