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?