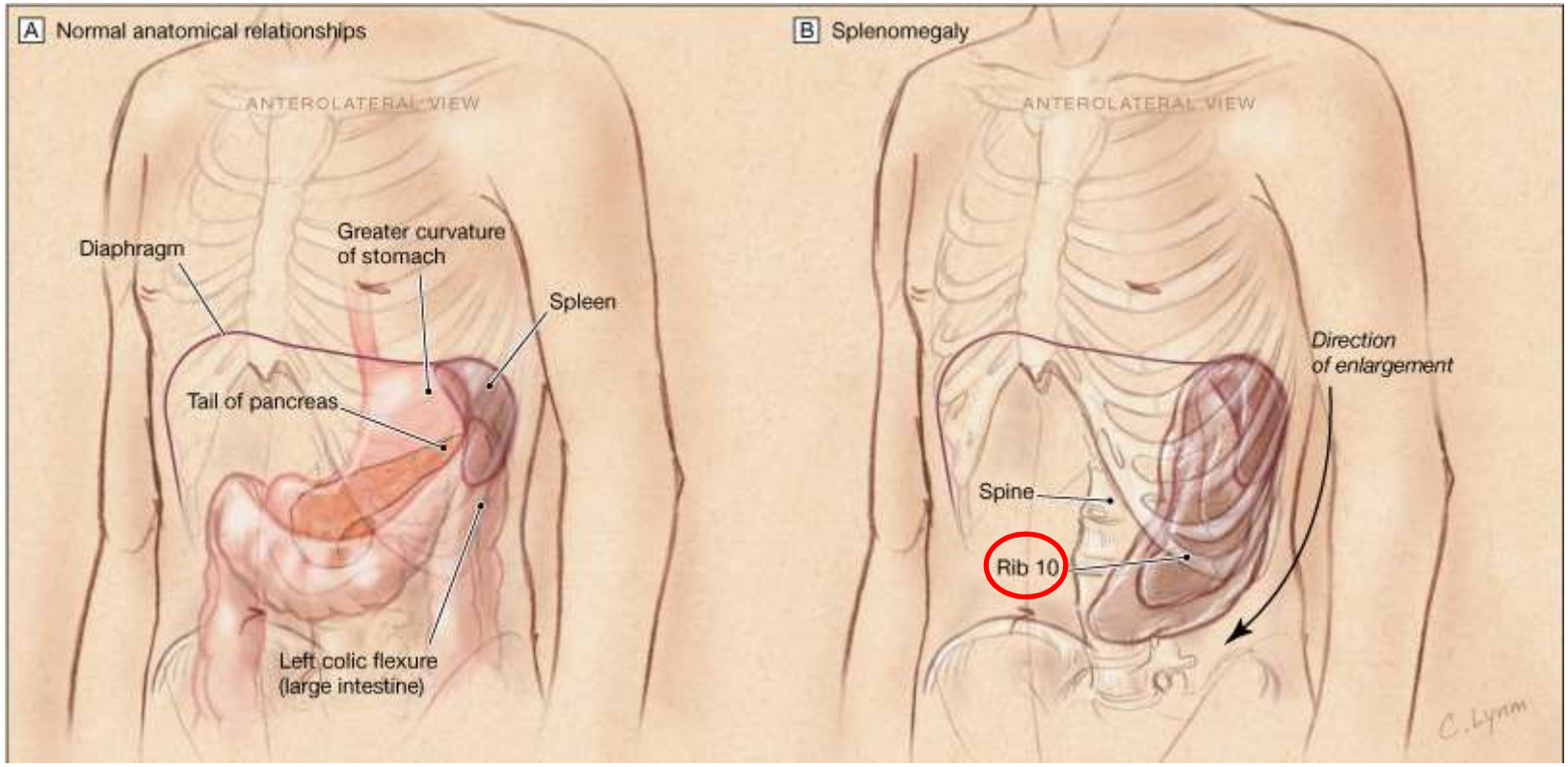
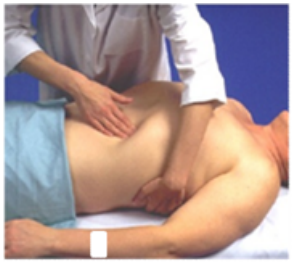


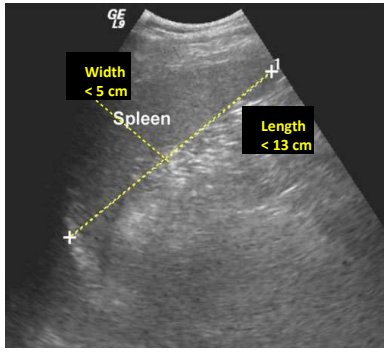
The spleen is located in the left upper quandrant of the abdomen beneath the left hemidiaphragm and lateral to the greater curvature of the stomach.

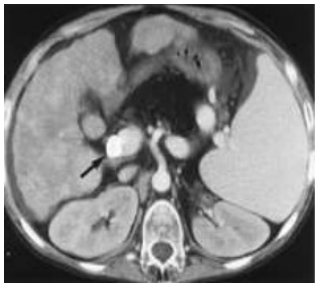


- Pull up with left hand and push in with right hand on inspiration
- Will only be able to feel if 3 times normal size

How do you differentiate the spleen from the kidney on abdominal examination?

- You can't get above the spleen (ribs overly it)
- The spleen moves towards RIF with inspiration, the kidney moves posterior only (if at all)
- The spleen is not ballotable like the kidney





Splenomegaly in a 15-year-old boy with cystic fibrosis, cirrhosis, and portal hypertension. Contrast-enhanced CT scan obtained at the level of the superior mesenteric artery shows a portosystemic shunt (arrow).

Causes of splenomegaly:

- **Congestive**
- **Infective**
- **Inflammatory**
- **Neoplastic,**
- **Infiltrative non-neoplastic**
- **Haematological hypersplenic states**

Congestive
Cirrhosis
Heart failure
Thrombosis of portal, hepatic, or splenic veins
Malignancy
Lymphoma, usually indolent variants
Acute and chronic leukemias
Polycythemia vera
Multiple myeloma and its variants
Essential thrombocythemia
Primary myelofibrosis
Primary splenic tumors
Metastatic solid tumors
Infection
Viral – hepatitis, infectious mononucleosis, cytomegalovirus
Bacterial – salmonella, brucella, tuberculosis
Parasitic – malaria, schistosomiasis, toxoplasmosis, leishmaniasis
Infective endocarditis
Fungal
Inflammation
Sarcoid
Serum sickness
Systemic lupus erythematosus
Rheumatoid arthritis (Felty syndrome)
Infiltrative, nonmalignant
Gaucher's disease
Niemann-Pick disease
Amyloid
Other lysosomal storage diseases (eg, mucopolysaccharidoses)
Langerhans cell histiocytosis
Hemophagocytic lymphohistiocytosis
Rosai-Dorfman disease
Hematologic (hypersplenic) states
Acute and chronic hemolytic anemias, all etiologies
Sickle cell disease (children)
Following use of recombinant human granulocyte colony-stimulating factor

Major causes of splenomegaly

Associations of splenomegaly:

- with fever
- with lymphadenopathy
- with purpura
- with arthritis
- with ascites
- with a murmur
- with anaemia
- with weight loss
- massive splenomegaly

Major causes of splenomegaly

Splenomegaly with fever	With lymphadenopathy	With purpura
• Infection[HS] (malaria, SBE/IE hepatitis,[HS] EBV,[HS] TB, CMV, HIV) • Sarcoid; malignancy[HS]	• Glandular fever[HS] • Leukaemias; lymphoma • Sjögren's syndrome	• Septicaemia; typhus • DIC; amyloid[HS] • Meningococcaemia
With arthritis	**With ascites**	**With a murmur**
• Sjögren's syndrome • Rheumatoid arthritis; SLE • Infection, eg Lyme (p430) • Vasculitis/Behçet's (p558)	• Carcinoma • Portal hypertension[HS]	• SBE/IE • Rheumatic fever • Amyloid[HS] (p364)
With anaemia	**With weight↓**	**Massive splenomegaly**
• Sickle-cell;[HS] thalassaemia[HS] • Leishmaniasis;[HS] leukaemia[HS] • Pernicious anaemia (p328)	• Cancer; lymphoma • TB; • Paraproteinaemia[HS]	• Malaria (hyper-reactivity after chronic exposure) • Myelofibrosis; CML[HS] • Gaucher's syndrome[HS] • Leishmaniasis

HS= causes of hepatosplenomegaly.

Hypersplenism

This can result from splenomegaly due to any cause. It is commonly seen with splenomegaly due to haematological disorders, portal hypertension, rheumatoid arthritis (Felty's syndrome) and lymphoma. Hypersplenism produces:

- pancytopenia
- haemolysis due to sequestration and destruction of red cells in the spleen
- increased plasma volume.

Treatment. This is often dependent on the underlying cause, but splenectomy is sometimes required for severe anaemia or thrombocytopenia.

Hypersplenism — Normally, about one-third of the platelet mass is sequestered in the spleen, where it is in equilibrium with circulating platelets. Splenic sequestration of platelets can be increased to 90 percent in cases of extreme splenomegaly, although total platelet mass and overall platelet survival remain relatively normal.

Splenectomy

Splenectomy is performed mainly for:

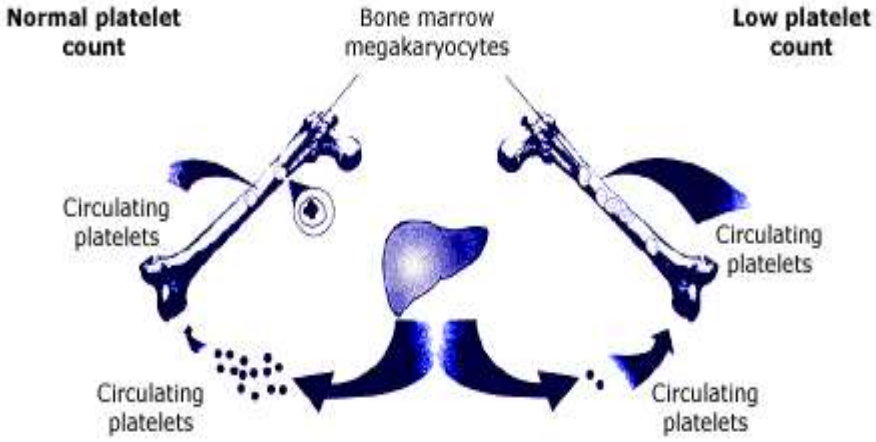
- trauma
- immune thrombocytopenic purpura
- haemolytic anaemias (see p. 386)
- hypersplenism.

Problems after splenectomy

An immediate problem is an increased platelet count (usually 600–1000$\times 10^9$/L) for 2–3 weeks. Thromboembolic phenomena may occur. In the longer term, there is an increased risk of overwhelming infections, particularly pneumococcal infections.

Prophylaxis against infection after splenectomy or splenic dysfunction

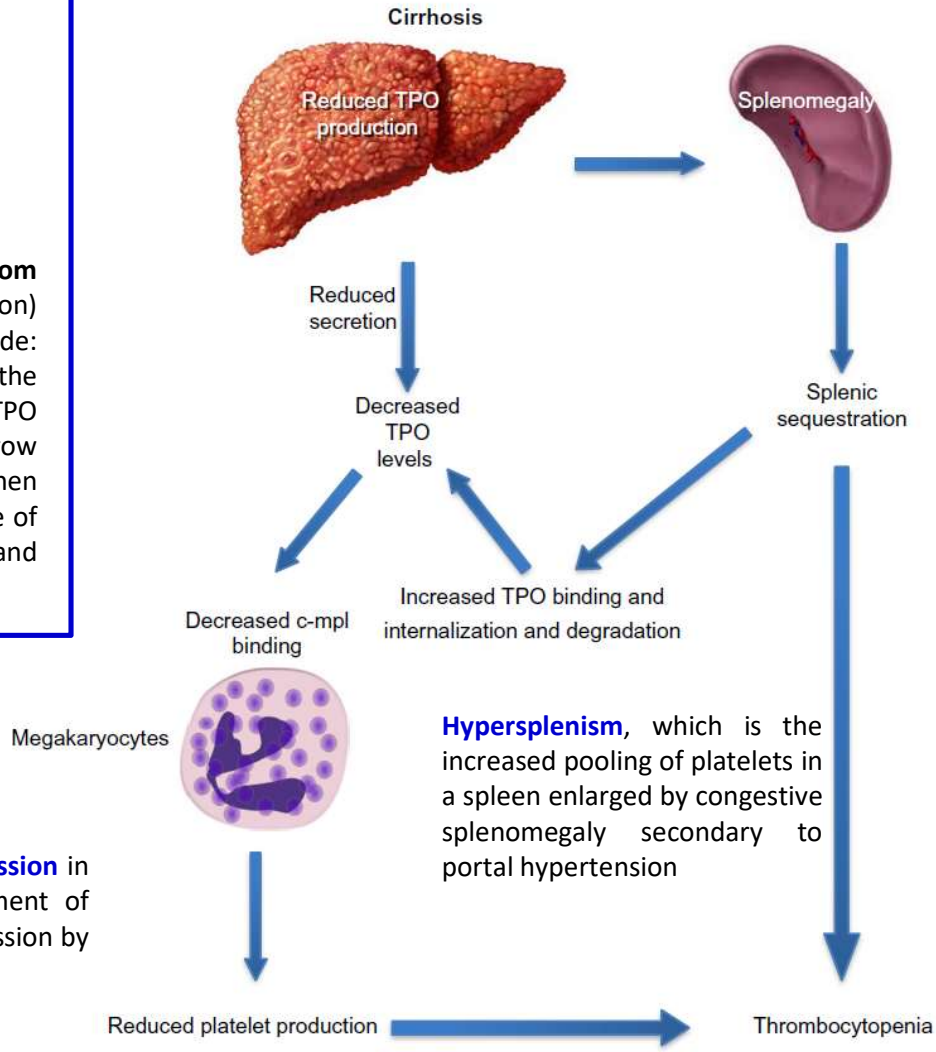
Thrombopoietin physiology



The mechanism by which **TPO regulates platelet production from megakaryocytes. TPO** (size of large arrows indicates relative concentration) is **produced constitutively by the liver** and enters the circulation. Left side: When the **platelet count is normal**, high affinity TPO receptors on the platelets clear most of the TPO and produce a normal plasma TPO concentration, thereby providing basal stimulation of bone marrow megakaryocytes and a normal rate of platelet production. Right side: When **platelet production and the platelet count are low**, the overall clearance of TPO is reduced, subsequently increasing the plasma TPO concentration and megakaryocyte and platelet production.

Thrombocytopenia in liver cirrhosis

In patients with chronic liver disease, **circulating TPO levels are decreased** due to impaired production and secretion and increased internalization and degradation by platelets sequestered in the enlarged spleen. Reduced TPO levels result in decreased megakaryocyte stimulation and platelet production.



Hypersplenism, which is the increased pooling of platelets in a spleen enlarged by congestive splenomegaly secondary to portal hypertension

Inadequate production of platelets due to **bone marrow suppression** in selected cases may also play a crucial role in the development of thrombocytopenia in cirrhosis. Possible etiologies include suppression by viruses, alcohol, iron overload, and medications.

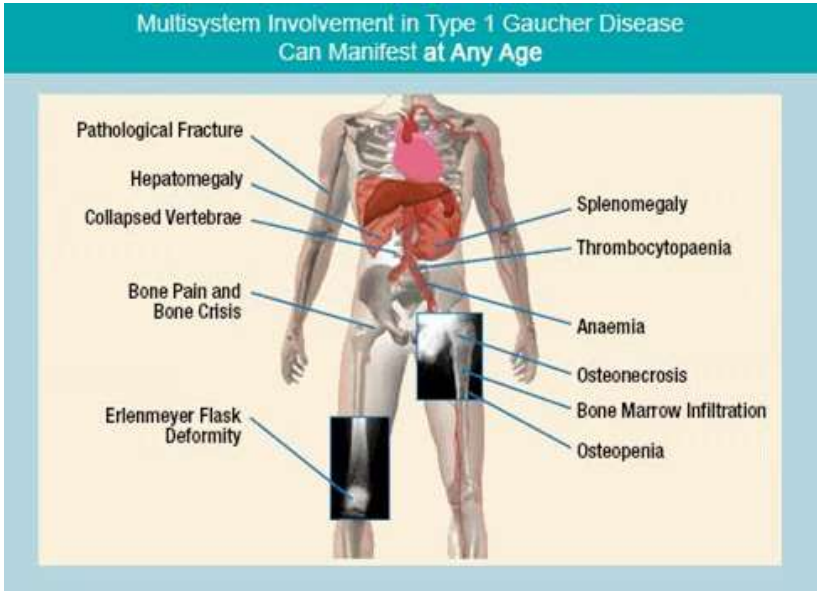
Lysosomal Storage Diseases: Gaucher's disease

This is the most prevalent lysosomal storage disease and is due to a **deficiency in glucocerebrosidase**, a specialized lysosomal acid β-glucosidase. This results in **accumulation of glucosylceramide in the lysosomes of the reticuloendothelial system**, particularly the **liver**, **bone marrow** and **spleen**.

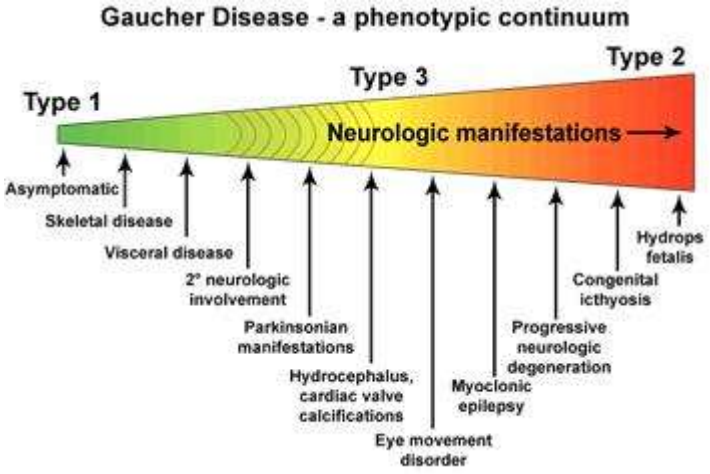
Over 200 mutations have been characterized in the glucocerebrosidase gene (1g21), the most common being a single base change (N370S) causing the substitution of arginine for serine; this is seen in 70% of Jewish patients. The **typical Gaucher cell**, a glucocerebroside-containing reticuloendothelial histiocyte, is found in the bone marrow, producing many cytokines such as CD14.

1. There are three clinical types, the most common presenting in childhood or adult life with an insidious onset of **hepatosplenomegaly** (Type 1). There is a high incidence in Ashkenazi Jews (1 in 3000 births), and patients have a characteristic pigmentation on exposed parts, particularly the forehead and hands. The clinical spectrum is variable, with patients developing **anaemia** and **thrombocytopenia**, evidence of **hypersplenism** and **pathological fractures** that are due to bone involvement. Nevertheless, many have a normal life-span. The diagnosis is made on finding **reduced glucocerebrosidase in leucocytes**. **Mutational analysis** will confirm the diagnosis. Plasma chitotriosidase (an enzyme secreted by activated macrophages) is grossly elevated in Gaucher's disease and other lysosomal disorders: it is used to monitor enzyme replacement therapy.
2. Acute Gaucher's disease (Type 2) presents in infancy with rapid onset of hepatosplenomegaly, with **neurological involvement** owing to the presence of Gaucher cells in the brain. The outlook is very poor.
3. Type 3 presents in childhood or adolescence with a variable progression of hepatosplenomegaly, **neurodegeneration** and bone disease. Again, the outlook is poor.

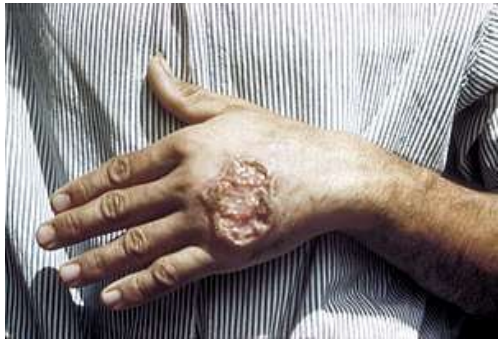
Some patients with non-neuropathic (Type 1) Gaucher's disease show considerable improvement with **infusion of human recombinant glucocerebrosidase** (imiglucerase – a human recombinant enzyme). Velaglucerase alfa is also used. Oral miglustat (an inhibitor of glucosylceramide synthase) is used for mild to moderate type 1 Gaucher's disease.



	TYPE 1	TYPE 2	TYPE 3
Frequency	General population: 1 in 40,000-60,000 Askenazi Jews: 1 in 850	<1 in 100,000	<1 in 100,000
Neurological effect	None	Severe	Moderate to severe
Symptom onset	Any age	First year of life	Childhood
Disease course	Progressive	Rapidly progressive	Progressive



Leishmaniasis



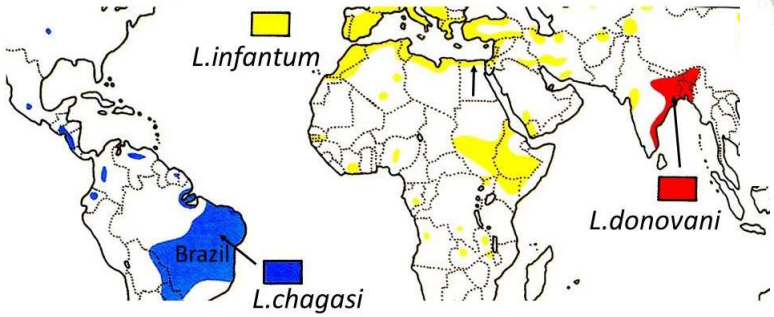
Leishmania are protozoa that cause granulomata. They are spread by sandflies in Africa, India, Latin America, southern USA, Middle East/Mediterranean. Clinical effects reflect: the ability of each species to induce or suppress the immune response, to metastasize, and to invade cartilage.

Cutaneous leishmaniasis (oriental sore) affects >300,000 people, eg in Africa, India and S. America. Lesions develop at the bite site, beginning as an itchy papule; crusts fall off to leave an ulcer (Chiclero's ulcer). Most heal in ~2 (Old World disease) to 15 months, with scarring (disfi guring if extensive). Diagnosis: microscopy and culture of aspiration from the base of the ulcer. Therapy: topical paromomycin, or IM drugs if unhealed by 6 months or lesion >5cm across (or multiple).

Mucocutaneous leishmaniasis occurs in S America. Primary skin lesions may spread to the mucosa of the nose, pharynx, palate, larynx, and upper lip and cause severe scarring.

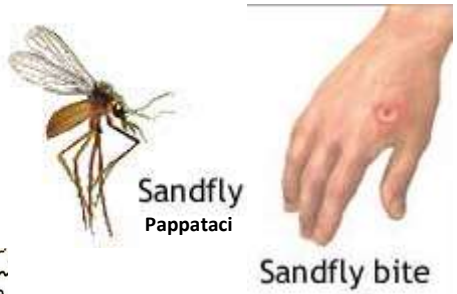
Visceral leishmaniasis (VL) (kala-azar, means black sickness) is the **2nd most deadly parasitic disease in the world after malaria** (50,000 deaths/year). It occurs in Asia, Africa, S America and Mediterranean areas. Incubation: months to years. **Protozoa spread via lymphatics from minor skin lesions and multiply in macrophages of the reticuloendothelial system**. There are 30 subclinical cases for every overt case. It can be HIV-associated. **Signs:** Dry, warty, hyperpigmented skin lesions; increased T°; sweats; burning feet; arthralgia; cough; epistaxis; abdo pain; splenomegaly (96%); hepatomegaly (63%); lymphadenopathy; emaciation; pancytopenia; hypergammaglobulinaemia. **Diagnosis: microscopic exam of lymph nodes, bone marrow or spleen are confirmatory. Ab-detection**: Indirect fluorescence antibody (IFA), ELISA, western blot, direct agglutination test (DAT) and RK39-based immunochromatographic test (ICT). Serology limitations: 1 Ab levels are detectable for years after cure, so cannot diagnose VL relapse. 2 Tests are +ve in many with no history of VL. Serology may be –ve if HIV +ve. **Ag-detection**: detects heat-stable Ag by latex agglutination. **Therapy:** Liposomal amphoterin B (1st-line in Europe/USA), or miltefosine (1st eff ective oral drug for VL; 0.75–1.2mg/kg/12h PO for 28d).

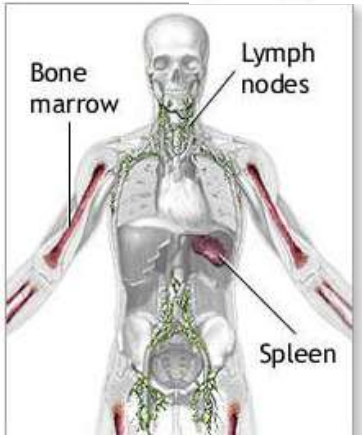
Post kala-azar dermal leishmaniasis: Years after successful therapy, lesions resemble leprosy.



Status of endemicity of visceral leishmaniasis, worldwide,

Da un quadro generale sud-europeo, l'Italia ha presentato negli anni il maggior numero assoluto di casi (~80-215/anno).
L. Gradoni, Istituto Superiore di Sanità, Roma, Italia



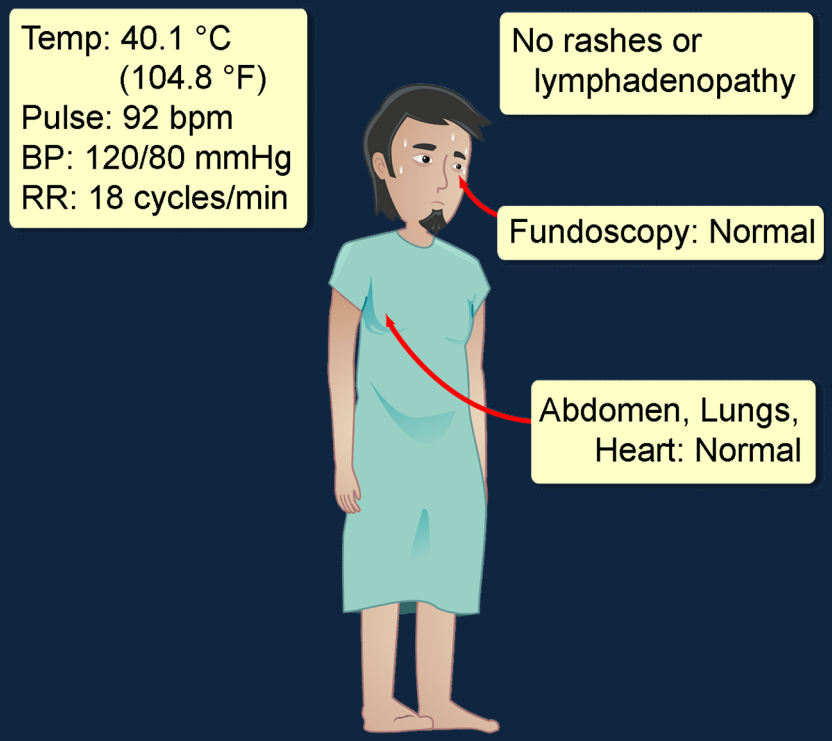


Tropical (Malaria)

A 22 year old man presents with fever for 10 days, in association with chills and sweating. One month ago, he returned from a trip to Ecuador, where he consumed the local food and water, traveled in the jungle, swam in a local lake, and received many insect bites. He had been vaccinated against hepatitis B and yellow fever before the trip. His medical history is unremarkable. He has a single stable sexual partner and denies using recreational drugs.

Select Relevant Investigations

- **Full Blood Count** Hb: 11.9 g/dL (12-18.5) Hct: 43.2 WBC: 5,000/mm3 (5,000-10,500) N: 84%, L: 10% Platelets 92,000/mm3 (150,000-500,000)
- **Liver Profile** Bilirubin 1.3 mg/dL (0.1-1.0) Albumin 4.4 g/dL (3.5-5.0) Total Protein 6.8 g/dL AST 82 U/L (8-48) ALT 97 U/L (7-55) GGT 52 U/L (9-48)
- **Antigen-detecting malaria rapid diagnostic tests (RDT):** positive
- **Blood for Malaria Parasites** Both thin and thick smears of peripheral blood show malarial parasites with a red nucleus and blue cytoplasm, within enlarged red cells.



Screen Contacts

(+) Chloroquine

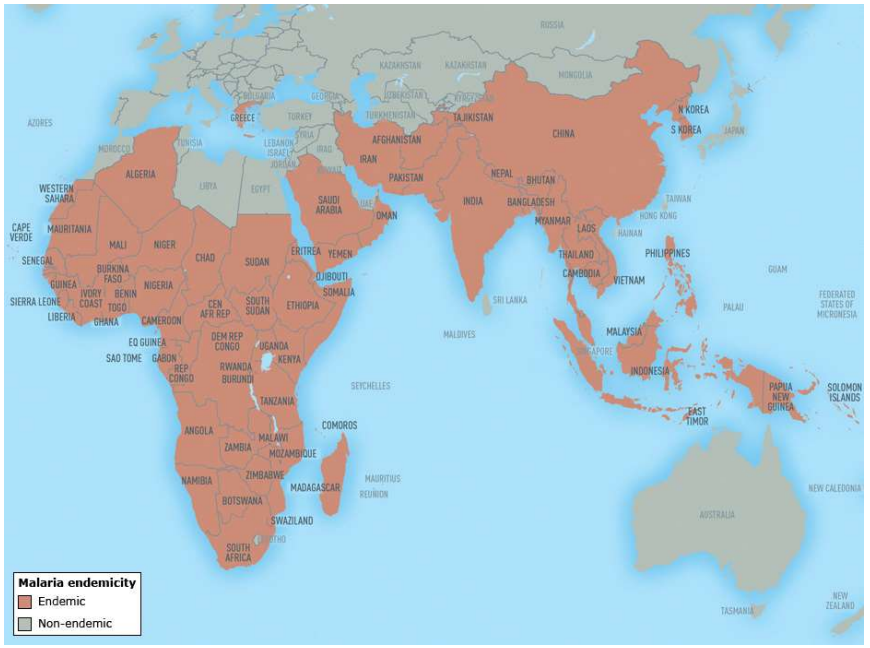
(+) Primaquine

Clindamycin

Diagnosis and reasoning

The febrile patient with a recent history of travel to a developing nation presents a unique diagnostic challenge for physicians in developed countries, as they may need to consider diseases which they are not necessarily familiar with. This problem is exacerbated by the fact that many of these patients present with vague and non-specific symptoms, which could potentially be caused by any one of a myriad of different infectious diseases. However, a careful and detailed history is often capable of making sense out of chaos, and pointing one towards a probable diagnosis. First and foremost, it should be appreciated that each geographic location has its own set of local infections; the "Travelers' Health" section of the Centers for Disease Control and Prevention (CDC) website **(https://wwwnc.cdc.gov/travel)** is an excellent resource in this regard. This reveals the presence of a broad range of bacterial, viral, protozoal and helminthic diseases endemic to **Equador**; these include **Hepatitis A and B, Malaria, Yellow Fever, Trypanosomiasis, Dengue, Bartonellosis, and Amoebiasis.** Note that the above infections are transmitted via several different modes: **ingestion**, **vector** transmission and **direct contact**. Thus, analysis of the type of travel engaged in may provide some additional clues. Unfortunately, adventure travellers (such as this patient) have ample opportunity to be exposed to all of the above pathogens. The next most important point in the history is the date of departure from the foreign country, as this gives an idea about the incubation period of the disease. In this patient, the long duration before manifestation of symptoms indicates a condition with a prolonged **incubation period**; this narrows down the list of possibilities significantly. Other important points in the history of this patient include the lack of progression of symptoms and presence of an **intermittent fever**. Note that the absence of localizing symptoms or physical findings makes a focal process (such as an abscess) clinically less likely. However, an intra-abdominal abscess (such as an amoebic liver abscess) may yet present in this manner. The next steps in the evaluation should be hematological and biochemical investigations. A full **blood count** is essential; this reveals a mild anemia, thrombocytopenia and a slightly elevated white cell count. The **liver profile** reveals mild elevation of all liver enzymes and serum bilirubin. Considering all of the above, we are left with a handful of possible differential diagnoses. **Amoebiasis** is a possibility. The white cell count and elevated liver functions are in favor of this, but the absence of abdominal tenderness and presence of thrombocytopenia make this unlikely. **Bartonellosis** (which is acquired via the bite of the sandfly in certain South American regions) is another possibility; while in most patients, the infection tends to take a fulminant course with fever, malaise, jaundice, hepatomegaly and generalized lymphadenopathy, atypical presentations are possible. Given the geographical location, prolonged incubation period and nonspecific symptoms, **Malaria** is not only a possible diagnosis but also a probable one. It is important to remember that the "classical" 48 to 72 hour fever cycles are seen only in patients with established disease, and may be absent altogether if the patient has been taking antipyretics. The diagnosis of Malaria is relatively straight forward. **Inspection of thick and thin peripheral blood smears** under direct microscopy can confirm the diagnosis and identify the species of Plasmodium causing the disease. In this case, the smear showed parasites within enlarged red cells, a characteristic feature of **P. vivax** but not P. falciparum. Once the diagnosis of malaria is established, and the type of Plasmodium identified, treatment should be started immediately. Uncomplicated cases of malaria such as this one can be treated with oral medication alone. The WHO recommends use of **Chloroquine** in treatment of P. vivax Malaria contracted in South America, combined with **Primaquine** to eliminate the liver forms of the parasite. Clindamycin is recommended by the WHO in the treatment of Malaria during pregnancy, and is not indicated in this patient. Contact screening is unnecessary, as Malaria is a vector-borne infection and is not spread by direct person to person contact.

Malaria-endemic countries



Although rare in the United States, malaria is extremely common in other countries, especially in sub-Saharan Africa, tropical South America, India, and southeast Asia. Travelers to these areas should take antimalarial prophylaxis.

WHO region (percent)	Population* (1000s)	Cases (1000s)	Decrease since 2000 (percent)	Proportion due to *P.vivax* (percent)	Deaths	Decrease since 2000 (percent)
Africa	989,173	**188,000**	-12	<1	**395,000**	-48
Southeast Asia	1,928,174	20,000	-39	50	32,000	-37
Eastern Mediterranean	643,784	3900	-57	40	7000	-57
Western Pacific	1,847,250	1500	-59	16	3200	-60
Americas	986,705	660	-74	71	500	-69
Europe	910,053	0	-100¶	0	0	-¶
World total	7,305,139	214,000	-18	6Δ	438,000	-48

¶ There were 36,000 cases and 0 deaths due to malaria in 2000. Δ 51 percent outside sub-Saharan Africa.

Four species of the genus Plasmodium classically cause human malaria. **Plasmodium falciparum** is responsible for nearly all severe disease. It is endemic in most malarious areas and is by far the predominant species in **Africa**. **Plasmodium vivax** is as common as P falciparum, except in Africa. P vivax uncommonly causes severe disease. **Plasmodium ovale** and **Plasmodium malariae** are much less common causes of disease, and generally do not cause severe illness.

MALARIA

In general, malaria should be suspected in the setting of **fever** (temperature ≥37.5°C) and **relevant epidemiologic exposure** (residence in or travel to an area where malaria is endemic)

Four species of the genus Plasmodium classically cause human malaria. **Plasmodium falciparum** (incubation 7–10 days, symptoms recur 36–48hrly) is responsible for nearly all severe disease. It is endemic in most malarious areas and is by far the predominant species in Africa. **Plasmodium vivax** (incubation 10–17d, 'benign tertian malaria', fever spikes every 48h) is as common as P falciparum, except in Africa. P vivax uncommonly causes severe disease, although this outcome may be more common than previously appreciated. Plasmodium ovale and Plasmodium malariae are much less common causes of disease, and generally do not cause severe illness.

Malaria is transmitted by the bite of infected female ***anopheline mosquitoes*****.** During feeding, mosquitoes inject **sporozoites**, which circulate to the ***liver***, and rapidly infect hepatocytes, causing asymptomatic liver infection. **Merozoites** are subsequently released from the liver, and they rapidly infect ~~***erythrocytes***~~ to begin the asexual erythrocytic stage of infection that is responsible for human disease. Multiple rounds of erythrocytic development, with production of **merozoites** that invade additional erythrocytes, lead to large numbers of circulating parasites and clinical illness. Some erythrocytic parasites also develop into sexual **gametocytes**, which are infectious to ***mosquitoes***, allowing completion of the life cycle and infection of others.

Spread: **plasmodium protozoa injected by female Anopheles mosquitoes multiply in RBCS causing haemolysis, RBC sequestration and cytokine release. Fever paroxysms reflect synchronous release of flocks merozoites from mature schizonts**. **3 phases**: 1) **Shivering** (about 1h): "I feel so cold." 2) **Hot stage** (2–6h): T ≈ 41°C, flushed, dry skin; nausea/vomiting; headache. 3) **Sweats** (~3h) as T° falls.

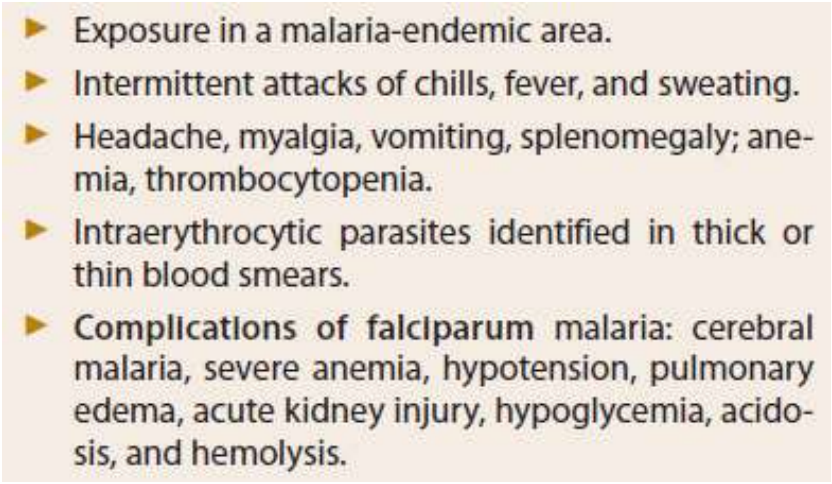
Protective factors: G6PD lack; sickle-cell trait; some HLA B53 alleles enable T cells to kill parasite-infected hepatocytes in non-Europeans.

Falciparum malaria: Mortality: eg 20%; higher if <3yrs old or pregnant. 90% present within 1 month of the mosquito event, with prodromal headache, malaise, myalgia ± anorexia before the 1st fever paroxysm (± faints). There may be no pattern to fever spikes (esp . initially); don't rely on periodicity to rule out any type of malaria!

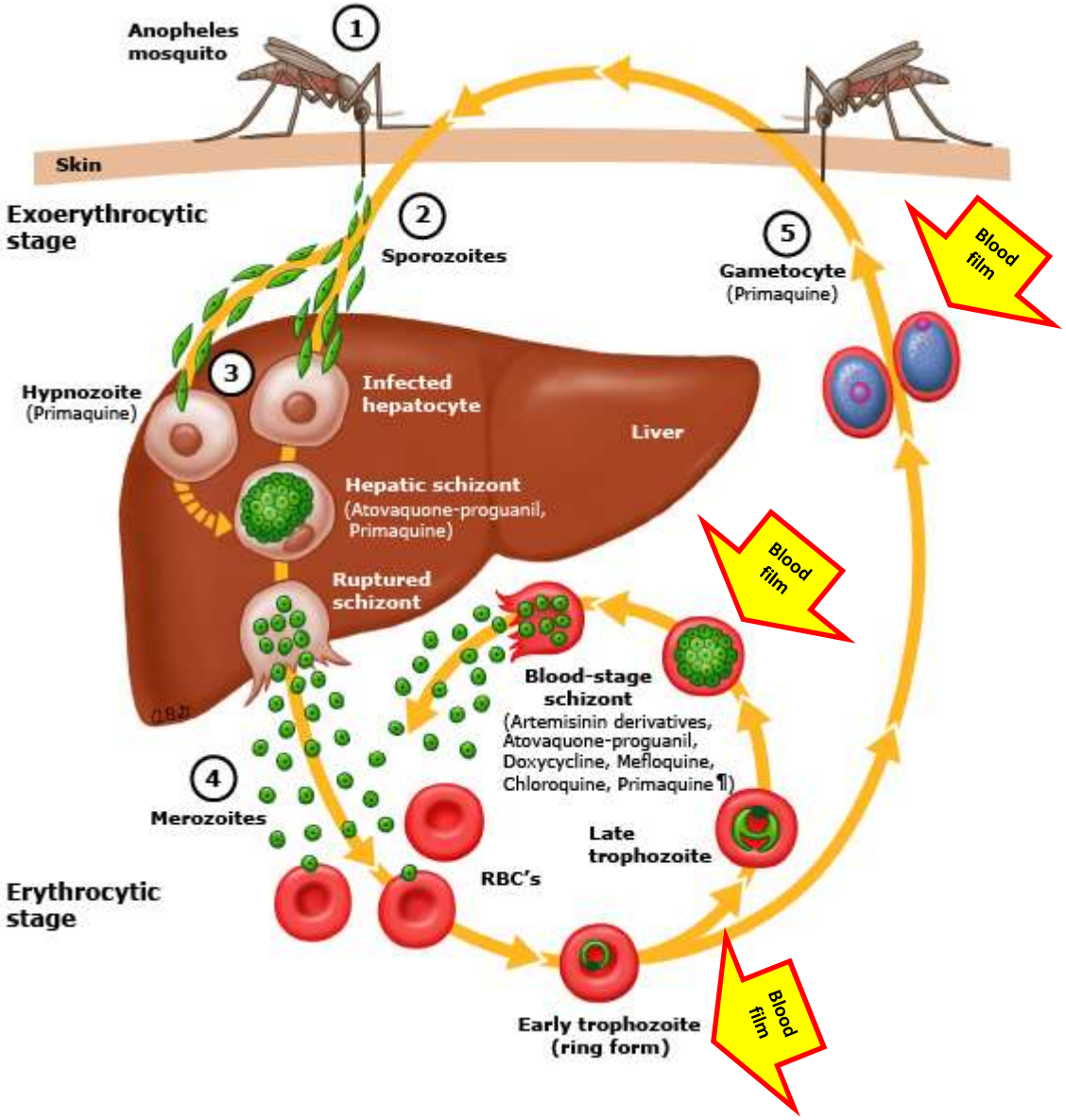
- Signs: **Anaemia**, **jaundice**, and **hepatosplenomegaly**. No rash or lymphadenopathy.
- Complications: Anaemia is common, eg from haemolysis of parasitized RBCS (often serious in children). **Thrombocytopenia**.
- 5 grim signs: 1) reduced consciousness/coma (cerebral malaria) 2) Convulsions 3) Coexisting chronic illness 4) Acidosis (eg esp bad if HCO3– <15mmol/L) 5) **Renal failure** (eg from acute tubular necrosis). **Mimic sepsis**
- **Cerebral malaria** — Cerebral malaria is an encephalopathy that presents with impaired consciousness, delirium, and/or seizures; focal neurologic signs are unusual. The onset may be gradual or sudden following a convulsion. The severity depends on a combination of factors including parasite virulence, host immune response, and time between onset of symptoms and initiation of therapy.
- Pregnancy: use chemoprophylaxis when pregnant in endemic areas.

Diagnosis

- **Serial thin & thick blood films** (needs much skill, don't always believe –ve reports, or reports based on thin film examination alone); if P. falciparum, you must know the level of parasitaemia.
- **Antigen-detecting malaria rapid diagnostic tests (RDT**) : rapid stick tests are available if microscopy cannot be performed. Serology is not useful. Nucleic acid tests (eg, PCR) are typically used as a gold standard in efficacy studies for antimalarial drugs, vaccines, and evaluation of other diagnostic agents.
- Other tests: FBC (anaemia, thrombocytopenia), clotting (DIC), glucose (hypoglycaemia), ABG/lactate (lactic acidosis), U&E (renal failure), urinalysis (haemoglobinuria, proteinuria, casts), blood culture to rule out septicaemia



Life cycle of *Plasmodium**

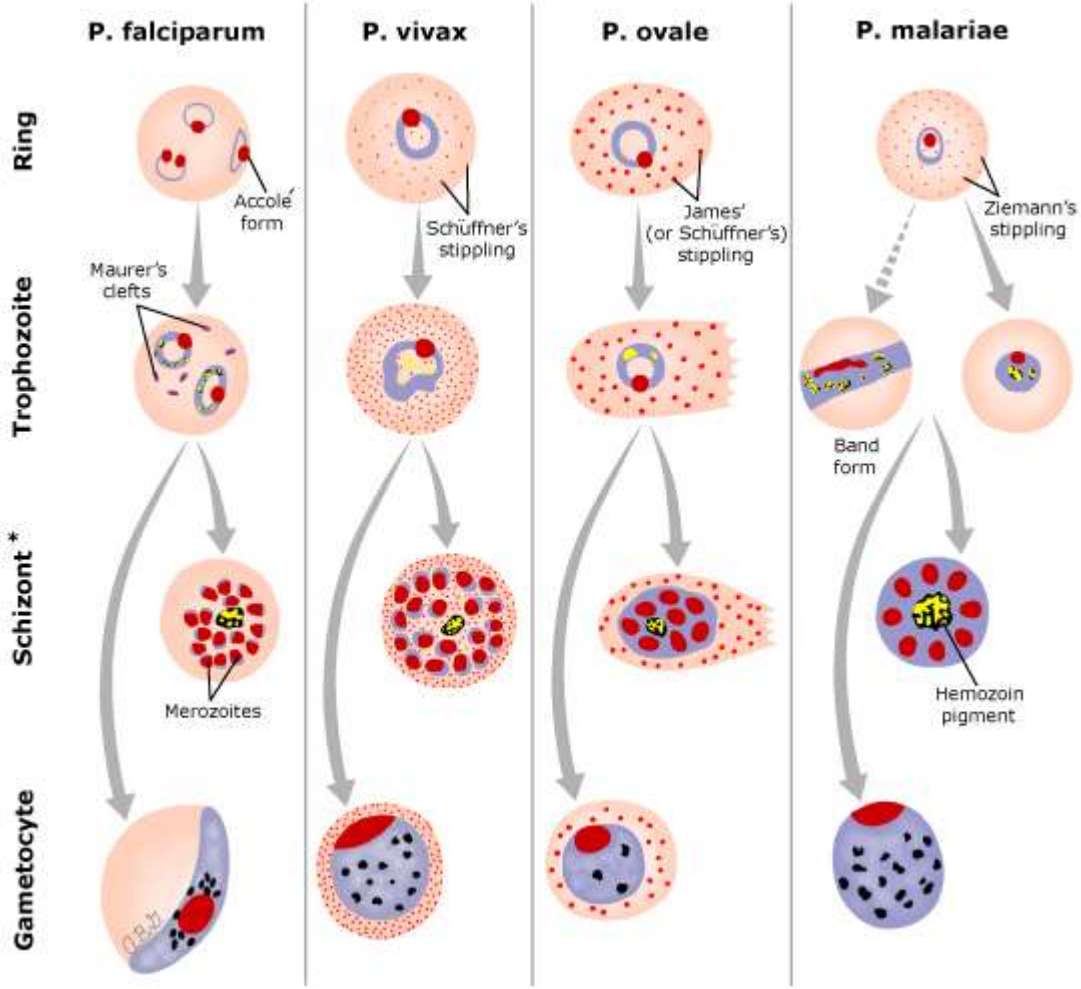


(1) *Plasmodium*-infected *Anopheles* mosquito bites a human and transmits **sporozoites** into the bloodstream.
(2) Sporozoites migrate through the blood to the liver where they invade hepatocytes and divide to form **multinucleated schizonts** (pre-erythrocytic stage). *Atovaquone-proguanil and primaquine have activity against hepatic-stage schizonts*.
(3) Hypnozoites are a quiescent stage in the liver that exist only in the setting of *P. vivax* and *P. ovale* infection. This liver stage does not cause clinical symptoms, but with reactivation and release into the circulation, late-onset or relapsed disease can occur up to many months after initial infection. *Primaquine is active against the quiescent hypnozoites of P. vivax and P. ovale.*
(4) The schizonts rupture and release **merozoites** into the circulation where they invade red blood cells. Within red cells, merozoites mature from **ring forms** to **trophozoites** and to **multinucleated schizonts** (erythrocytic stage). *Blood-stage schizonticides such as artemisinins, atovaquone-proguanil, doxycycline, mefloquine, and chloroquine interrupt schizogony within red cells.*
(5) Some merozoites differentiate into male or female **gametocytes**. These cells are ingested by the *Anopheles* mosquito and mature in the midgut, where sporozoites develop and migrate to the salivary glands of the mosquito. The mosquito completes the cycle of transmission by biting another host.

* There is strong evidence that drugs listed in parentheses are active against designated stage of parasitic life cycle

¶ Primaquine is a blood-stage schizonticide with activity against schizonts of *P. vivax* but not those of *P. falciparum*.

Red blood cell morphology in various forms of *Plasmodium* infections



* Identification of a schizont with >12 merozoites in the peripheral circulation is an important diagnostic clue for P. vivax. In general, schizonts of P. falciparum are very rarely seen in blood films; they are generally absent from the peripheral circulation except in cases of severe infection with overwhelming parasitemia

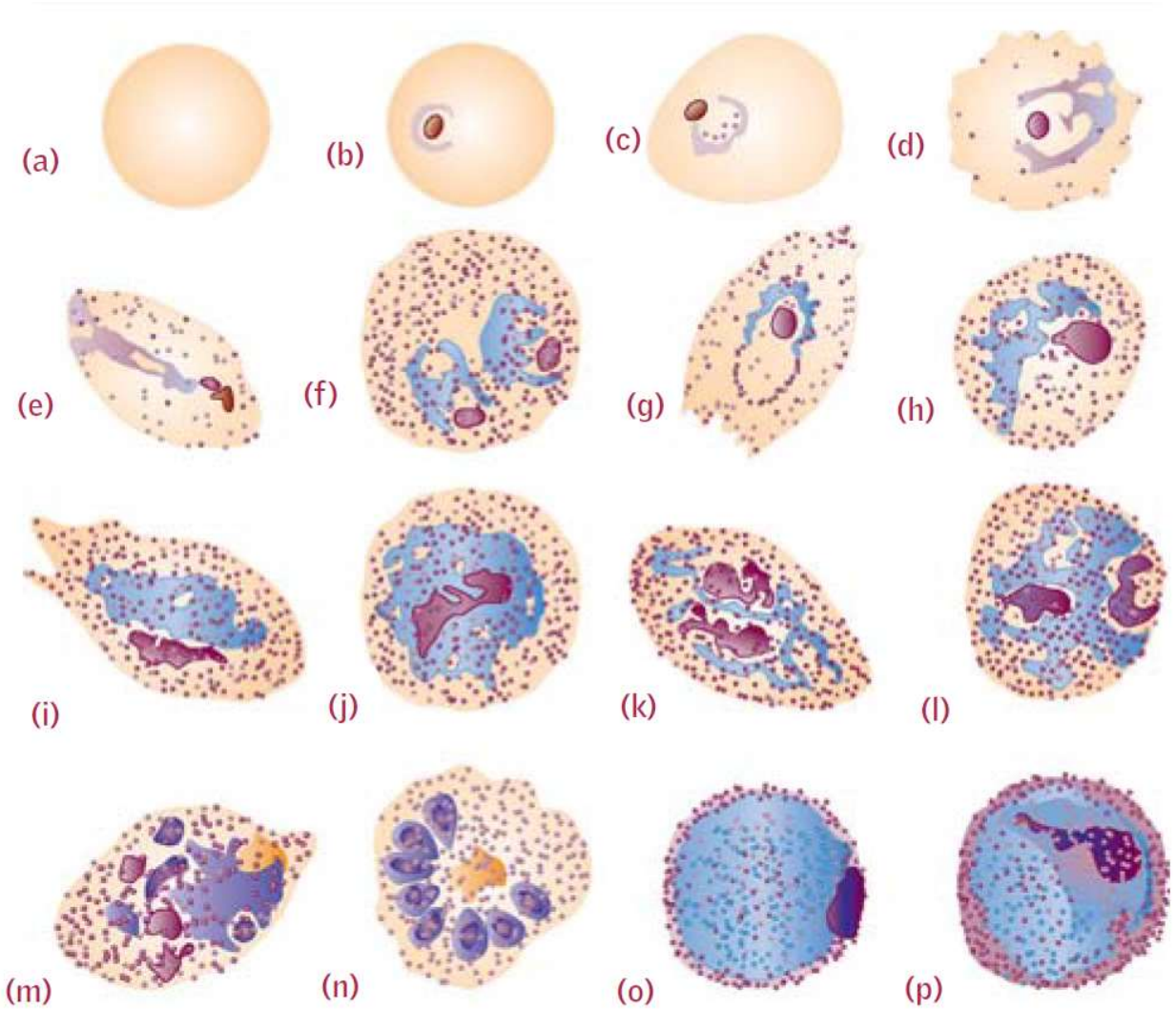
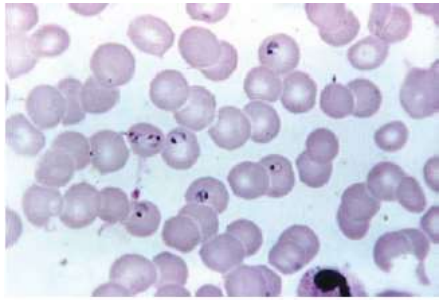


Fig 2. *P. ovale*. Plasmodia live in red cells: what a fantastic niche!—full of food and protected from prowling immunocytes. **a** is void—an unclaimed bag of food; **b-i** show trophozoites; **g**'s RBC is fimbriated and oval, giving the species its name; **k-n** are schizonts containing segmenting merozoites; **o** and **p** are ♀ and ♂ gametocytes. Having this marvellous knack of sexual reproduction (in the mosquito's gut) ensures the almost infinite variety of plasmodia, and their co-evolution with man.[101] With this in mind, it is interesting to note that the development of haemoglobin AS, CC, and AC genotypes and homozygous and heterozygous α-thalassaemia give significant protection only from *severe* malaria.[102]

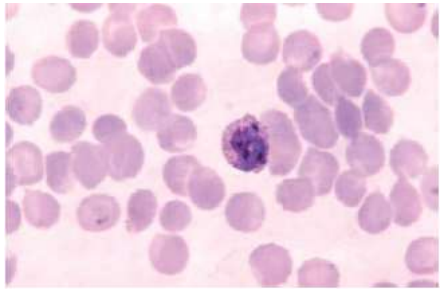
Giemsa-stained blood smears remain the mainstay of diagnosis to demonstrate parasites. **Thick smears** provide efficient evaluation of large volumes of blood, but **thin smears** are simpler for inexperienced personnel and better for discrimination of parasite species. Single smears are usually positive in infected individuals, although parasitemias may be very low in nonimmune individuals. If illness is suspected, repeating smears in 8- to 24-hour intervals is appropriate.

A second means of diagnosis is **rapid diagnostic tests to identify circulating plasmodial antigens** with a simple **"dipstick"** format. These tests are not well standardized but are widely available. **Serologic tests indicate history of disease but are not useful for diagnosis of acute infection.**

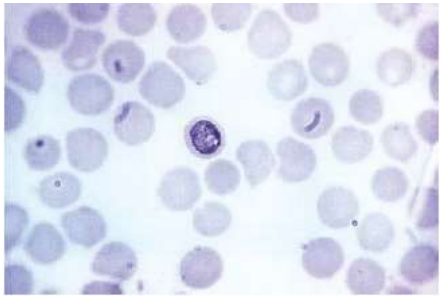
Thin film Giemsa-stained micrographs



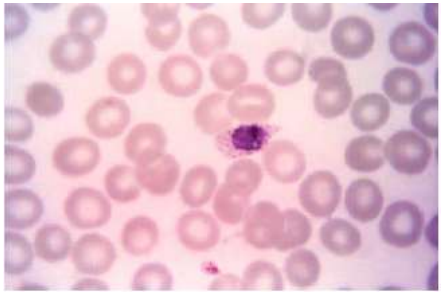
P. falciparum ring forms



P. vivax schizont



P. malariae trophozoite



P. ovale trophozoite

Treatment of malaria

Clinical Setting	Drug Therapy[1]	Alternative Drugs
Chloroquine-sensitive *Plasmodium falciparum* and *Plasmodium malariae* infections	Chloroquine phosphate, 1 g, followed by 500 mg at 6, 24, and 48 hours –or– Chloroquine phosphate, 1 g at 0 and 24 hours, then 0.5 g at 48 hours	
Plasmodium vivax and *Plasmodium ovale* infections	Chloroquine (as above), then (if G6PD normal) primaquine, 30 mg base daily for 14 days	For infections from Indonesia, Papua New Guinea, and other areas with suspected resistance: therapies listed for uncomplicated chloroquine-resistant *P falciparum* plus primaquine
Uncomplicated infections with chloroquine-resistant *P falciparum*	Coartem (artemether 20 mg, lumefantrine 120 mg), four tablets twice daily for 3 days –or– Malarone, four tablets (total of 1 g atovaquone, 400 mg proguanil) daily for 3 days –or– Quinine sulfate, 650 mg three times daily for 3–7 days Plus one of the following (when quinine given for < 7 days) Doxycycline, 100 mg twice daily for 7 days –or– Clindamycin, 600 mg twice daily for 7 days	Mefloquine, 15 mg/kg once or 750 mg, then 500 mg in 6–8 hours –or– Dihydroartemisinin-piperaquine[2] (dihydroartemisinin 40 mg, piperaquine 320 mg), 4 tablets daily for 3 days –or– ASAQ[2] (artesunate 100 mg, amodiaquine 270 mg), two tablets daily for 3 days
Severe or complicated infections with *P falciparum*	Artesunate 2.4 mg/kg intravenously every 12 hours for 1 day, then daily[3,6]	Quinidine gluconate,[4–6] 10 mg/kg intravenously over 1–2 hours, then 0.02 mg/kg intravenously/min –or– Quinidine gluconate,[4–6] 15 mg/kg intravenously over 4 hours, then 7.5 mg/kg intravenously over 4 hours every 8 hours –or– Quinine dihydrochloride,[2,4–6] 20 mg/kg intravenously over 4 hours, then 10 mg/kg intravenously every 8 hours –or– Artemether,[2,6] 3.2 mg/kg intramuscularly, then 1.6 mg/kg/d intramuscularly

Treatment ▶ If the patient has taken prophylaxis, don't use the same drug for treatment. If species unknown or mixed infection, treat as *P. falciparum*. Nearly all *P. falciparum* is resistant to chloroquine and in many areas also to Fansidar® (*pyrimethamine + sulfadoxine*). If in doubt, consider as resistant. *Chloroquine*[103] is 1st choice for benign malarias in most parts of the world, but chloroquine-resistant *P. vivax* occurs in Papua New Guinea, Indonesia, parts of Brazil, Colombia and Guyana.[104] Never rely on chloroquine if used alone as prophylaxis. See HPA (www.hpa.ork.uk).

Treating uncomplicated P.ovale, P. vivax, & P. malariae: Chloroquine base:[1] 10mg/kg (max 620mg), then 5mg/kg (max 310mg) at 6h, 24h and 48h. In resistant cases, try Malarone®, quinine, or Riamet®. Primaquine dose in *P. vivax:* 500µg/kg (max. 30mg) daily for 14d; *P. ovale:* 250µg/kg (max. 15mg) daily for 14d—given after chloroquine to treat liver stage and prevent relapse. Screen for G6PD deficiency first. CI: pregnancy. *P. malariae* does not need primaquine.

Treating uncomplicated Falciparum malaria (or if species is uncertain): As multidrug resistance (to chloroquine, amodiaquine, etc) is common, combination therapy, preferably containing artemisinin derivatives, is recommended by WHO.[105] • Artemether-lumefantrine (Riamet®[2])—if >35kg: 4 tabs stat, then 4 tablets at 8, 24, 36, 48 and 60h.[105] • Artesunate-amodiaquine (Coarsucam®); if a fixed combination pill is available (AS 100mg + AQ 270mg), the dose is 2 pills/d for 3d. If aged 7–13yrs, it is 1 pill/d for 3d.[106] • Dihydroartemisinin-naphthoquine[107] • Dihydroartemisinin-piperaquine.[108] • Atovaquone-proguanil (Malarone®; 4 'standard' tablets once daily for 3 days) may also work. These are better than quinine regimens (eg 600mg quinine salt/8h PO for 7d, + doxycycline 200mg/24h or clindamycin 450mg/8h for 7d).[109] Artemisinins are OK in children and pregnancy (from 13 weeks; use quinine + clindamycin in 1st trimester).[110] The oral route is OK if able to swallow and no severe signs.

Treating severe[3] Falciparum malaria: IV ℞ is needed. Take to ITU. ▶▶ See BOX.

Other treatments: Tepid sponging + paracetamol if necessary for fever. Transfuse if severe anaemia. Consider exchange transfusion if patient severely ill. Treat 'algid' malaria as malaria + bacterial shock (p778). Monitor TPR, BP, urine output, and blood glucose frequently. Daily parasite count, platelets, U&E, LFT.

Prophylaxis for travellers ► *Prophylaxis does not give full protection*. Risks vary; get local advice. Avoid mosquitos: wear long-sleeves between dusk and dawn, use repellents (diethyltoluamide/DEET), long-lasting insecticidal bed-nets (US$5; last ~5yrs).

Except for Malarone® & mefloquine (below), take drugs from 1wk before travel (to reveal any SE) and continue for 4wks after return. None is required if just visiting cities of East Asia. There is no good protection for parts of SE Asia.[111]

If little/no chloroquine resistance: Proguanil 200mg/24h+chloroquine base 300mg/wk.

If chloroquine-resistant P. falciparum: Mefloquine 250mg/wk (18d before to 4wks after trip) or doxycycline 100mg/d (1d before to 4wks after) or atovaquone[250mg]+proguanil[100mg] (Malarone®) 1 tab/d (1d before travel to 7d after).[112] If poor medical care and not pregnant, carry standby treatment (eg Riamet®, Malarone®).

Antimalarial SE *Chloroquine:* headache, psychosis, retinopathy (in chronic use). *Fansidar®:* Stevens-Johnson syndrome, erythema multiforme, LFT↑, blood dyscrasias. *Primaquine:* Epigastric pain, haemolysis if G6PD-deficient, methaemoglobinaemia. *Malarone®:* Abdominal pain, nausea, headache, dizziness. *Mefloquine:* Nausea, dizziness, dysphoria, insomnia, neuropsychiatric signs, long t½. Avoid mefloquine if: • Low risk of chloroquine-resistant malaria • Past or family history of epilepsy, psychosis • Need for delicate work (pilots[etc]) • Risk of pregnancy within 3 months of last dose. *Interactions:* Quinidine, halofantrine.

[1]Recommendations may change, as resistance to all available drugs is increasing. See text for additional information on toxicities and cautions. For additional details and pediatric dosing, see Centers for Disease Control and Prevention's guidelines (phone: 800-CDC-INFO; http://wwwnc.cdc.gov/travel/). Travelers to remote areas should consider carrying effective therapy (see text) for use if a febrile illness develops, and they cannot reach medical attention quickly.

[2]Areas without known chloroquine-resistant *P falciparum* are Central America west of the Panama Canal, Haiti, Dominican Republic, Egypt, and most malarious countries of the Middle East. Malarone or mefloquine is currently recommended for other malarious areas except for border areas of Thailand, where doxycycline is recommended.

[3]For drugs other than primaquine, begin 1–2 weeks before departure (except 2 days before for doxycycline and Malarone) and continue for 4 weeks after leaving the endemic area (except 1 week for Malarone). All dosages refer to salts unless otherwise indicated.

[4]Screen for glucose-6-phosphate dehydrogenase deficiency before using primaquine.

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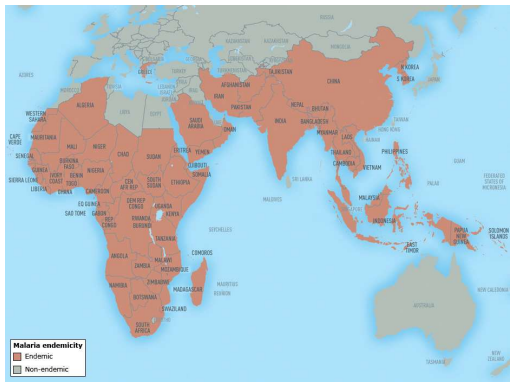


- **Chloroquine-resistant P. falciparum** is widespread in endemic areas of Africa, Asia, and Oceania.
- **Chloroquine-sensitive P. falciparum** exists in the Caribbean, Central America west and north of the Panama Canal, and parts of North Africa, the Middle East, and China.
- **P. falciparum strains resistant to chloroquine, mefloquine, and sulfonamides** are rare but are prevalent in the regions of Thailand bordering Burma (Myanmar) and Cambodia (eg, eastern provinces of Myanmar and western provinces of Cambodia) and in parts of China, Laos, and Vietnam.
- **Chloroquine-resistant P. vivax** is widespread in Indonesian Papua and Papua New Guinea

Drug	Use[2]	Adult Dosage (all oral)[3]
Chloroquine	Areas without resistant *Plasmodium falciparum*	500 mg weekly
Malarone	Areas with multidrug-resistant *P falciparum*	1 tablet (250 mg atovaquone/100 mg proguanil) daily
Mefloquine	Areas with chloroquine-resistant *P falciparum*	250 mg weekly
Doxycycline	Areas with multidrug-resistant *P falciparum*	100 mg daily
Primaquine[4]	Terminal prophylaxis of *Plasmodium vivax* and *Plasmodium ovale* infections; alternative for *P falciparum* prophylaxis	30 mg base daily for 14 days after travel

Severe *P. falciparum* malaria

Falciparum malaria is one of the great killers (mortality is ~100% in untreated severe malaria, 15–20% with treatment), so get expert help in anyone who could have travelled abroad particularly in the last few months, who is feverish with ↓consciousness. But fever is not *always* a feature of malaria, and signs may be unusual if prophylaxis has been given, and is partly effective. The central event in severe falciparum malaria is sequestration of parasitized erythrocytes in the microvasculature of vital organs. Death rate: ~1 million deaths/yr, worldwide.[113]

Key questions What is the parasite count, the plasma bicarbonate and the creatinine? Are there complications: shock (algid malaria), metabolic acidosis, hypoglycaemia, renal failure, or acute respiratory distress syndrome (ARDS, p178)?

℞: (on ITU) *Always* take advice. The main goal is to prevent death. Check FBC, daily parasite count, platelets, U&E, LFT, plasma glucose. Degree of acidosis is an important determinant of outcome. Assess fluid balance meticulously. ▶▶*Start antimalarials in full dose as soon as possible*. Meta-analyses unequivocally favour parenteral artesunate over quinine for the treatment of severe malaria in adults and children and in different regions[114] of the world—so, give **artesunate** (if *immediately* available[1]) or **quinine** (dihydrochloride) 20mg salt/kg IVI (max 1.4g) over 4h, then after 8h give 10mg/kg (max 700mg) over 4h every 8h.[2] Give IV until the patient can swallow; complete the course orally (see 'c' below). Monitor for hypoglycaemia. Alternative: **artemether** (3.2mg/kg followed by 1.6mg/kg daily); in the UK, artemether is not always available: get local advice. Don't wait for an ideal drug if a good alternative is to hand: delay is fatal![115]

If swallowing OK and no complications (shock, ARDS, renal failure) give either:

a) **Artemether-lumefantrine** Riamet®, see p396.
b) **Malarone®** (atovaquone + proguanil; 4 tabs once daily for 3d with food).
c) **Quinine** (600mg salt/8h PO for 7d), with either **doxycyline** 200mg daily or **clindamycin** 450mg/8h for 7d PO.

ITU monitoring in cerebral malaria

- ▶▶Fluid requirements vary widely; careful fluid management is critical. Haemofilter early if renal failure. Ventilate early if pulmonary oedema.
- ▶▶Consider exchange transfusion in very seriously ill patients if feasible.
- ▶▶Monitor blood lactate (or bicarbonate) and glucose: quinine may cause hypoglycaemia. Do LFT + clotting studies; crossmatch blood if haematocrit <20%.
- ▶▶Repeated U&E (and arterial blood gases if ARDS).
- ▶▶Arrange repeated skilled microscopy to monitor parasite counts.[116]

Expect at least a 75% decrease in the parasite count by 48h of treatment.

Pitfalls

- Failure to take a full travel history (+stop-overs) and failure to check if the patient has already received treatment (can make the blood smear 'negative').
- Thinking that malaria in returning travellers is too rare (1000–2000/yr UK) or too exotic for today's work-a-day ward round or clinic, where "it's probably just flu".
- Delay in treatment while seeking lab confirmation.
- Failure to examine enough blood films before excluding the diagnosis.
- Belief that preventive drugs will work, when the parasite is often one step ahead.
- Not asking local experts about emerging patterns of drug resistance.
- Ignoring the possibility of counterfeit drugs (38% in one study from SE Asia).[117]
- No IV artesunate/quinine available *immediately*. (Quinidine is an alternative.[2])
- Not observing falciparum patients closely for the first few days.
- Forgetting that malaria is a big cause of coma, jaundice, anaemia & renal failure.

Fever and frequent infections in a patient with bleeding gums

A 24-year-old woman presents with ***bleeding gums*** and ***easy bruising*****.** She is found to have a hematocrit of 29%, a white blood cell count of 4800/µL with 5% peripheral promyelocytes**,** and a platelet count of 38,000/µL. A **bone marrow study shows morphologic and molecular evidence of acute promyelocytic leukemia**. She is begun on ATRA and daunorubicin. Infection prophylaxis includes a quinolone and Bactrim. Six days after starting therapy, the patient presents with ***fever*** and increasing ***shortness of breath*** that has developed over several days. Her white **blood cell count** has risen to 15,000/µL with 20% **promyelocytes** and **metamyelocytes**. A chest radiograph shows diffuse **pulmonary infiltrates**.

A 66-year-old man presents with ***fatigue*** and is found to have **pancytopenia** with a hematocrit of 31%, a white blood cell count of 2300/µL with peripheral blasts, and a platelet count of 9000/µL. A **bone marrow** study shows 60% **myeloblasts** consistent with M1 **acute myeloid leukemia**. The patient had previously been in outstanding health. The choice is made to attempt induction therapy with daunorubicin and cytarabine.

A 44-year-old woman presents with increasing ***bone pain*** and ***pallor*** and is found to have a hematocrit of 24%, a white blood cell count of 32,000/µL with circulating myeloblasts, and a platelet count of 45,000/µL. A **bone marrow study shows acute myeloid leukemia.** with t(4;11). Three years earlier, she had been diagnosed with ***breast cancer*** and had been treated with surgery, **radiation,** and adjuvant chemotherapy including cyclophosphamide and doxorubicin. She is treated for her AML with daunorubicin and cytarabine and after one cycle achieves a complete remission.

A 74 year-old woman presents with ***increasing peripheral edema*** and is found to have a hematocrit of 26%, a white blood cell count of 38,000/µL with circulating lymphoblasts, and a platelet count of 110,000/µL. A bone marrow shows **Ph+ acute lymphoblastic leukemia.**

A **7-year-old boy** presented with malaise and ***lethargy*** of 6 months' duration. He had become inattentive at school, anorexic and had ***lost 3kg in weight***. On examination he was thin, anxious and clinically **anaemic**. There was mild, bilateral, cervical ***lymphadenopathy*** and moderate **splenomegaly.** On investigation, his haemoglobin (8 g/dl) and platelet count (66000/mm^3) were low, but the white-cell count was high (25000/mm^3). The blood film showed that **most leucocytes were blasts**; the red cells were normochromic and normocytic. **Bone marrow** examination showed an overgrowth of **primitive white cells** with **diminished numbers of normal erythroid and myeloid precursors**. **Acute lymphoblastic leukaemia** was diagnosed.

Clinical Presentation of Leukemias

Gum and lung infiltration (AML derived from monocytes M4 and M5)

Leukemic meningitis, signs of involvement of the central nervous system, cranial nerve abnormalities, headache (ALL)

Fever, weight loss (CML)

Symptoms related to anemia: Fatigue, pallor, dyspnea (AML, ALL, CML)

Lymphadenopathy (ALL, CLL)

Abdominal discomfort and early satiety

Splenomegaly (CML, ALL, CLL)

Peripheral blood examination:

AML: High WBC counts, predominating blasts. Neutropenia or thrombocytopenia

ALL: Pancytopenia, WBC count may be elevated or low. Monoclonality is indicative of acute leukemia (specific T- and B-cell surface markers identify the subset of leukemia)

CML: High WBC count with mature neutrophils with early occasional myeloid forms and an occasional blast. Low leukocyte alkaline phosphatase score. Elevated platelet count, with dysmorphism and large size. Elevated basophils count and blasts is seen in accelerated phase of this disorder

CLL: Elevated WBC count. Mature lymphocytes with "smudge" or broken cells are prevalent

Hepatomegaly (CML)

Bone marrow examination:

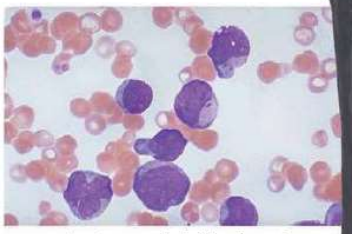
AML: Hypercellularity with blast count greater than 30%

ALL: Monoclonality is indicative of acute leukemia (Specific T- and B-cell surface markers identify the subset of leukemia). Presence of Philadelphia chromosome (Ph) in a subset of ALL confers a poor prognosis

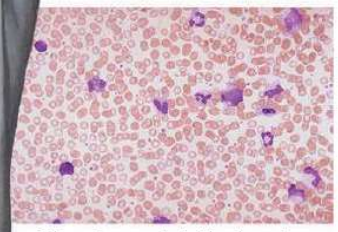
CML: Presence of Ph. More than 30% blasts count characterizes blast crisis

CLL: Diffuse infiltration with mature lymphocytes

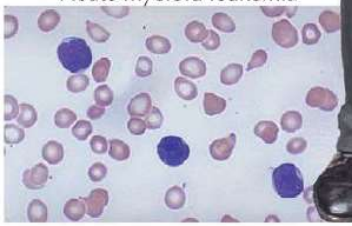
Signs of bleeding, petechiae, purpura (AML, ALL)



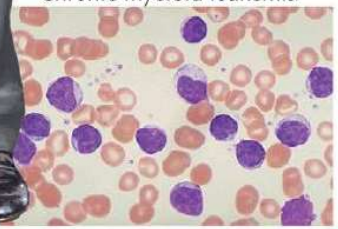
Acute myeloid leukemia



Chronic myeloid leukemia



Acute lymphoblastic leukemia



Chronic lymphocytic leukemia

- AML, acute myeloid leukemia;
- ALL, acute lymphoblastic leukemia;
- CML, chronic myelogenous leukemia;
- CLL, chronic lymphocytic leukemia.

Leukemia

A. **Malignant transformation** of myeloid or lymphoid cells involving bloodstream and bone marrow.

B. **Acute** leukemia tends to involve immature cells, whereas **chronic** leukemia involves more mature cells..

C. **Bone marrow involvement** can cause pancytopenia.

D. **Constitutional Symptoms** (fever, weight loss, fatigue, night sweats)

E. **Organ infiltration** (skin, gastrointestinal tract, lung, gum, meninges, liver, spleen, lymphonodes, etc.).

Leukemia

A. Malignant transformation of myeloid or lymphoid cells involving bloodstream and bone marrow. B. Acute leukemia tends to involve immature cells, whereas chronic leukemia involves more mature cells..C. Bone marrow involvement can cause pancytopenia.

1. Acute lymphocytic leukemia (ALL)

a. Most common in children (2 to 5 years of age); whites>blacks. **b**. Proliferation of **lymphoid cells**. **c**. H/P: bone pain, frequent infections, fatigue, dyspnea on exertion, easy bruising; fever, pallor, purpura, hepatosplenomegaly, lymphadenopathy. d. Labs: decreased Hgb, decreased Hct, decreased platelets, decreased WBCs, increased uric acid, increased LDH; bone marrow biopsy shows abundant blasts; Philadelphia chromosome (i.e., translocation of chromosomes 9 and 22 in BCR-ABL genes) found in 15% adult cases. e. Blood smear: numerous blasts. **f.** Treatment: hemotherapy (induction followed by maintenance dosing), bone marrow transplant. **g**. Complications: although:-year survival rates are good (85%) in children, adults have worse prognosis; presence of Philadelphia chromosome carries poor Prognosis

2. Acute myelogenous leukemia (AML)

a. Proliferation of **myeloid cells**; both children and adults affected. b. H/P: fatigue, easy bruising, dyspnea on exertion, frequent infections, arthralgias; fever, pallor, hepatosplenomegaly, mucosal bleeding, ocular hemorrhages . **c**. Labs: decreased Hgb, decreased Hct, decreased platelets, decreased WBCs; bone marrow biopsy shows blasts of myeloid origin and staining with myeloperoxidase. **d.** Blood smear: large myeloblasts with notched nuclei and Auer rods **e.** Treatment: chemotherapy (regimen guided by cytogenetic analysis), bone marrow transplant. **f.** Complications: relapse common, DIC; long-term survival is poor despite frequently successful remissions

3. Chronic lymphocytic leukemia (CLL)

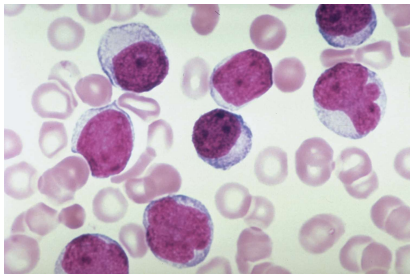
a. Proliferation of **mature B cells** in patients .65 years of age. **b.** H/P: fatigue, frequent infection (secondary to no plasma cells), night sweats; fevers, lymphadenopathy, hepatosplenomegaly. **c.** Labs: increased WBCs (may be .100,000/mL); bone marrow shows lymphocyte infiltration. d. Blood smear: numerous small lymphocytes, smudge cells. **e.** Treatment: upportive therapy, chemotherapy, radiation for bulky lymphoid masses, splenectomy for splenomegaly. **f.** Complications: malignant B cells may form autoantibodies, leading to severe hemolytic anemia; course of disease tends to be either indolent (.10-year survival) or aggressive with high mortality within 4 years

4. Chronic myelogenous leukemia (CML)

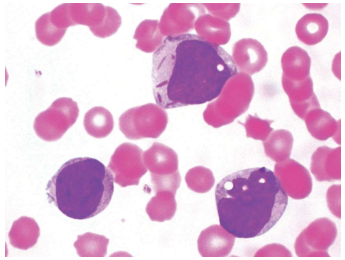
a. Proliferation of **mature myeloid cells** seen in middle-aged adults; can be associated with radiation exposure. b. Follows stable course for several years before progressing into blast crisis (i.e., rapid worsening of neoplasm) that is usually fatal **c.** H/P: possibly asymptomatic before progression; fatigue, weight loss, night sweats; fever, splenomegaly; blast crisis presents with worsening symptoms and bone pain. **d.** Labs: increased WBCs (.100,000/ml) with high proportion of neutrophils,
decreased leukocyte alkaline phosphatase; bone marrow shows granulocyte hyperplasia; cytogenetic analysis demonstrates Philadelphia chromosome (t[9;22]) or BCR-ABL fusion gene. e. Treatment: chemotherapy (imatinib is promising agent), bone marrow transplant in younger patients. f. Complications: blast crisis signals rapid progression and is usually fatal.

5. Hairy cell leukemia

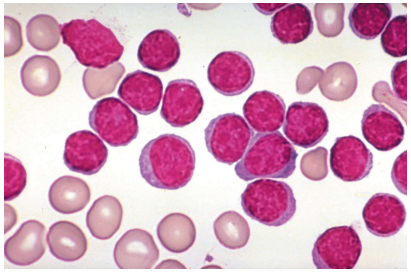
a. Proliferation of **B cells** most frequently in middle-aged men. **b.** Similar in appearance to CLL (but better prognosis); now considered an indolent type of non-Hodgkin lymphoma. **c.** H/P: fatigue, frequent infections, abdominal fullness, no night sweats; no fever, massive splenomegaly, no lymphadenopathy .**d.** Labs: decreased Hgb, Hct, platelets, and WBCs (rarely, WBCs increased); bone marrow biopsy shows lymphocyte infiltration. **e.** Blood smear: numerous lymphocytes with “hairy” projections (irregular cytoplasmic projections). **f.** Treatment: chemotherapy once patients develop symptomatic cytopenia



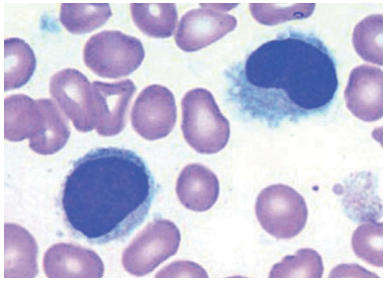
Acute lymphocytic leukemia. Note lymphoblasts with irregular nuclei and prominent nucleoli.



Acute promyelocytic leukemia (a subtype of AML). Prominent Auer rods are seen (arrow)

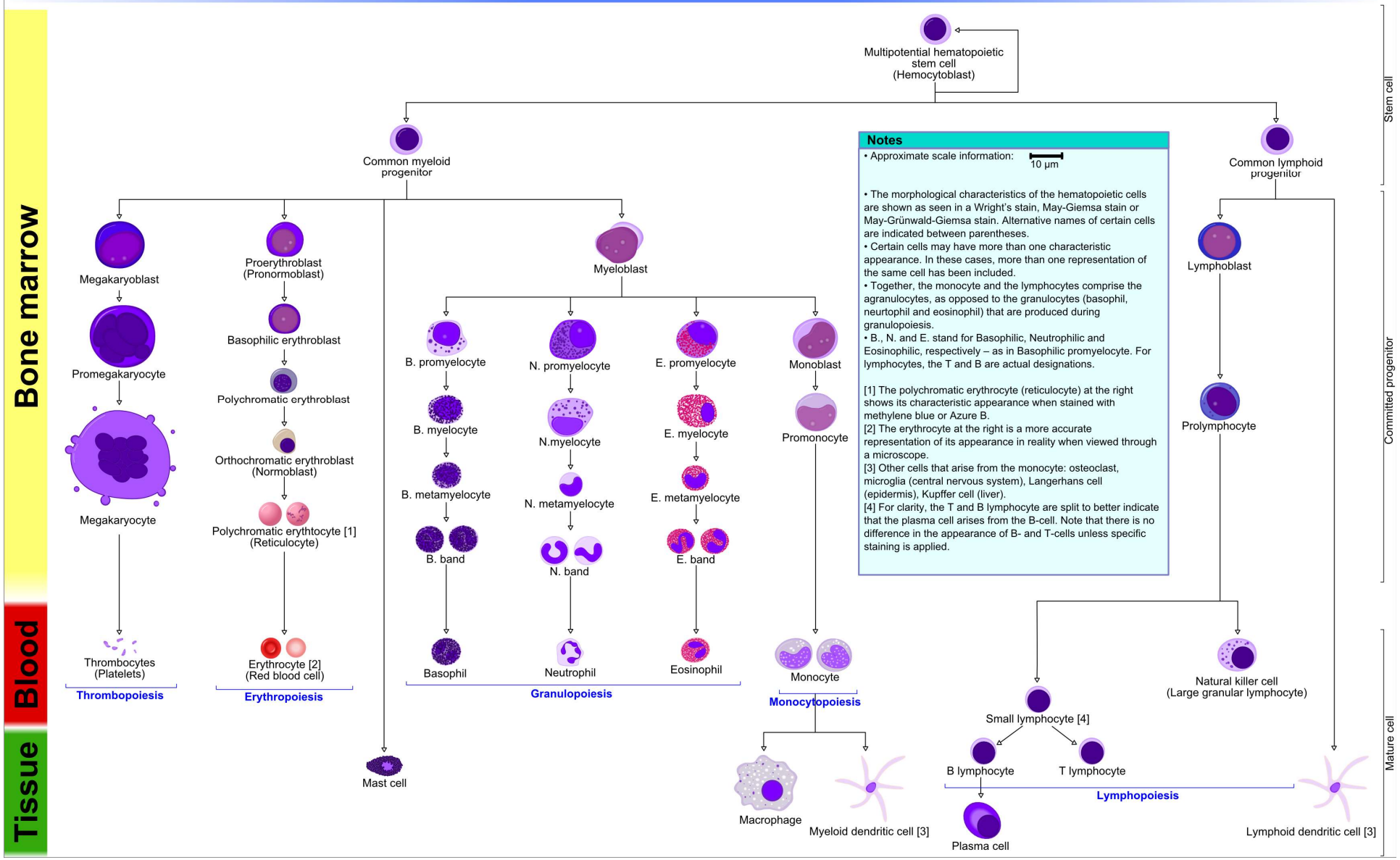


Chronic lymphocytic leukemia. Note small lymphocytes of comparable size to nearby red blood cells (RBCs) and presence of smudge cells (fragile lymphocytes disrupted during smear preparation) in upper portion of image.



Hairy cells typical of **hairy cell leukemia.** Note the numerous cytoplasmic projections giving the cell its name.

Hematopoiesis in humans



Leukaemia

Leukaemia divides into 4 main types depending on the cell line involved:

	Lymphoid	Myeloid
Acute	Acute lymphoblastic leukaemia (ALL)	Acute myeloid leukaemia (AML)
Chronic	Chronic lymphocytic leukaemia (CLL)	Chronic myeloid leukaemia (CML)

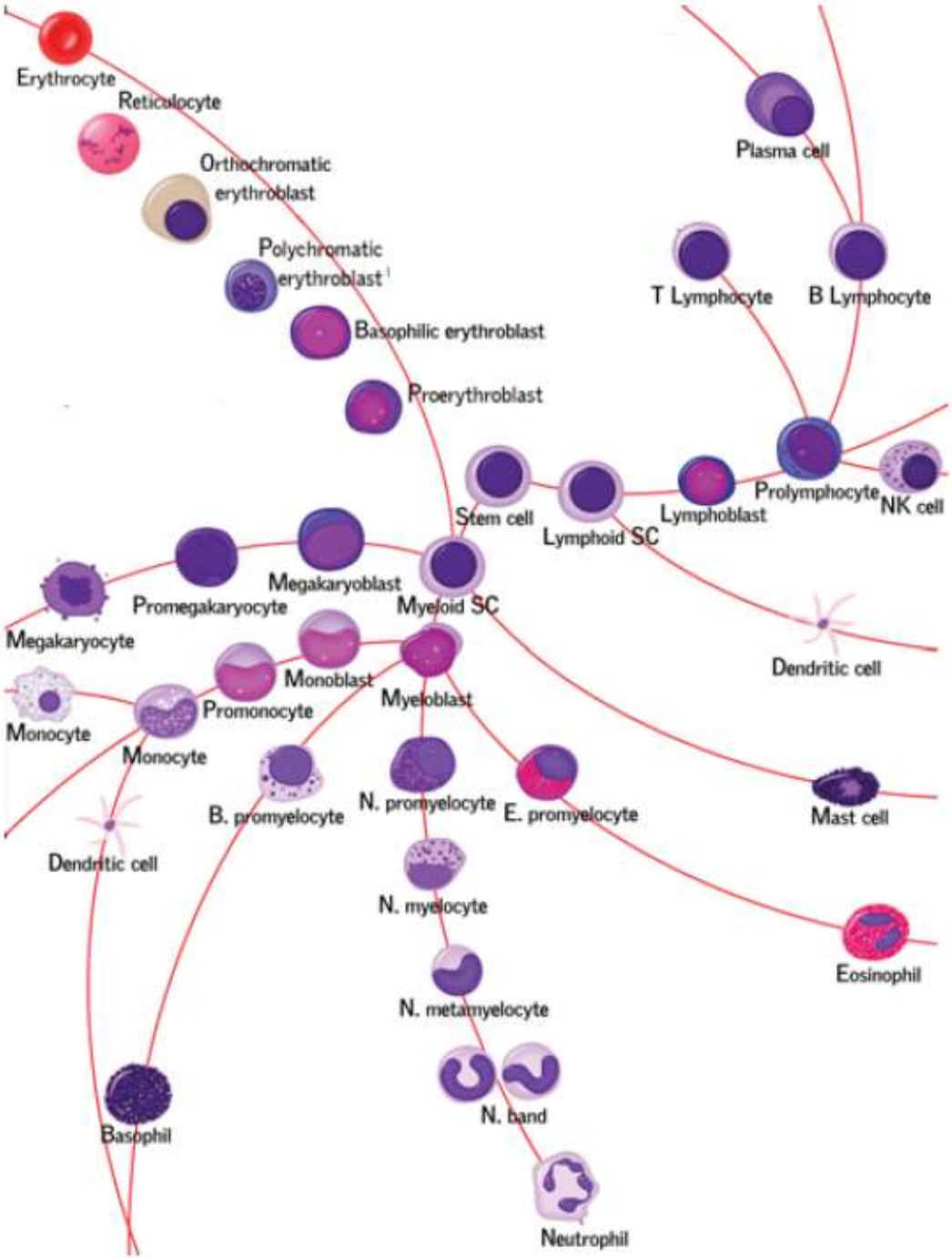
These patients (esp. AML) fall ill suddenly and deteriorate fast, eg with: ▸▸Infection ▸▸Bleeding (℞: platelets ± FFP) and ▸▸Hyperviscosity (p366). Take

neutropenia ▸ neutrophil count ≤0.5 × 10^9/L

Anemia

Other dangers • *Tumour lysis syndrome:* Caused by a massive destruction of cells leading to K^+↑, urate↑ and renal injury. *Risk*↑ if: LDH↑, creatinine↑, urate↑, wcc >25×10^9/L.[65] *Prevention:* high fluid intake + allopurinol pre-cytotoxics. For those at high risk of cell lysis, recombinant uricase (rasburicase) may be given. Seek advice.

- *Hyperviscosity:* (p366). If WCC is >100×10^9/L WBC thrombi may form in brain, lung, and heart (leukostasis). Avoid transfusing before lowering WCC, eg with hydroxycarbamide or leukopheresis, as viscosity rises (risk of leukostasis ↑).
- *DIC:* Widespread activation of coagulation, from release of procoagulants into the circulation with consumption of clotting factors and platelets, with ↑risk of bleeding. Fibrin strands fill small vessels, haemolysing passing RBCs, and fibrinolysis is also activated. *Causes:* Malignancy, sepsis, trauma, obstetric events: *OHCS* p88. *Signs:* (fig 1) Bruising, bleeding anywhere (eg venepuncture sites), renal failure. *Tests:* Platelets↓; PT↑; APTT↑; fibrinogen↓ (correlates with severity); fibrin degradation products (D-dimers) ↑↑. Film: broken RBCs (schistocytes). *℞:* Treat the cause. Replace platelets if <50×10^9/L, cryoprecipitate to replace fibrinogen, FFP to replace coagulation factors. Heparin is controversial. Activated protein C reduces mortality in DIC with severe sepsis or multi-organ failure.[66] The use of all-transretinoic acid (ATRA) has significantly reduced the risk of DIC in acute promyelocytic leukaemia (the commonest leukaemia associated with DIC).


Erythrocyte
Reticulocyte
Orthiochromatic erythroblast
Polychromatic erythroblast
Basophilic erythroblast
Proerythroblast
Plasma cell
T Lymphocyte
B Lymphocyte
Prolymphocyte
NK cell
Lymphoblast
Stem cell
Lymphoid SC
Megakaryoblast
Promegakaryocyte
Myeloid SC
Megakaryocyte
Dendritic cell
Monoblast
Myeloblast
Promonocyte
Monocyte
Monocyte
B. promyelocyte
N. promyelocyte
E. promyelocyte
Mast cell
Dendritic cell
N. myelocyte
Eosinophil
N. metamyelocyte
N. band
Basophil
Neutrophil

ACUTE LEUKEMIA

Acute leukemia is a **malignancy of the hematopoietic progenitor cell.** These cells proliferate in an uncontrolled fashion and replace normal bone marrow elements

Most of the clinical findings in acute leukemia are due to (*) **replacement of normal bone marrow elements by the malignant cells**. Less common manifestations result from (*) **organ infiltration (skin, gastrointestinal tract, meninges)**. Acute leukemia is potentially curable with combination chemotherapy..

- Short duration of symptoms, including fatigue, fever, and bleeding.
- Cytopenias or pancytopenia.
- More than 20% blasts in the bone marrow.
- Blasts in peripheral blood in 90% of patients.

A. Acute Lymphoblastic Leukemia (ALL)

B. Acute Myeloid Leukemia (AML)

C. Acute Promyelocytic Leukemia (APL)

Acute lymphoblastic leukaemia (ALL)

This is a malignancy of lymphoid cells, affecting B or T lymphocyte cell lines, arresting maturation and promoting uncontrolled proliferation of immature blast cells, with marrow failure and tissue infiltration. It is thought to develop from a combination of genetic susceptibility (eg with translocations, and gains and losses of whole chromosomes[1]) + an environmental trigger. Ionizing radiation, eg X-rays, during pregnancy, and Down's syndrome are important associations.[70] It is the commonest cancer of childhood, and is rare in adults. CNS involvement is common.

Classification is based on 3 systems:

1 *Morphological* The FAB system (French, American, British) divides ALL into 3 types (L1, L2, L3) by microscopic appearance. Provides limited information (figs 1–4).

2 *Immunological* Surface markers are used to classify ALL into:
- Precursor B-cell ALL • T-cell ALL • B-cell ALL.

3 *Cytogenetic* Chromosomal analysis. Abnormalities are detected in up to 85%, which are often translocations. Useful for predicting prognosis, eg poor with Philadelphia (Ph) chromosome (below), and for detecting disease recurrence.

Signs and symptoms (fig 5) are due to:
- Marrow failure: Anaemia (↓Hb), infection (↓WCC), and bleeding (↓platelets).
- Infiltration: Hepato- and splenomegaly, lymphadenopathy—superficial or mediastinal, orchidomegaly, CNS involvement—eg cranial nerve palsies, meningism.

Common infections: Especially chest, mouth, perianal and skin. Bacterial septicaemia, zoster, CMV, measles, candidiasis, *Pneumocystis* pneumonia (p410).

Tests • Characteristic blast cells on blood film and bone marrow. WCC usually high.
- CXR and CT scan to look for mediastinal and abdominal lymphadenopathy.
- Lumbar puncture should be performed to look for CNS involvement.

Treatment Educate and motivate: without this, many may shy away from the responsibilities of self-care, to their detriment.[71] Interactive video games help.[72]

- *Support:* Blood/platelet transfusion, IV fluids, allopurinol (prevents tumour lysis syndrome). Insert a subcutaneous port system/Hickman line for IV access.[73]
- *Infections:* These are dangerous, due to neutropenia caused by the disease and treatment. Immediate IV antibiotics for infection. Start the neutropenic regimen (p346): prophylactic antivirals, antifungals and antibiotics, eg co-trimoxazole to prevent *Pneumocystis* pneumonia (p346), but beware: can worsen neutropenia.
- *Chemotherapy:* Patients are entered into national trials. A typical programme is:
  Remission induction: eg vincristine, prednisolone, L-asparaginase + daunorubicin.
  Consolidation: High-medium-dose therapy in 'blocks' over several weeks.
  CNS prophylaxis: Intrathecal (or high-dose IV) methotrexate ± CNS irradiation.
  Maintenance: Prolonged chemotherapy, eg mercaptopurine (daily), methotrexate (weekly), and vincristine + prednisolone (monthly) for 2yrs. Relapse is common in blood, CNS, or testis (examine these sites at follow-up). More details: *OHCS* p194.
- *Matched related allogeneic marrow transplantations* once in 1st remission is the best option in standard-risk younger adults (?too many SE if older).[74, 75]

Haematological remission means no evidence of leukaemia in the blood, a normal or recovering blood count, and <5% blasts in a normal regenerating marrow.

Prognosis Cure rates for children are 70–90%; for adults only 40% (higher when imatinib/rituximab, p353, are used). Poor prognosis if: adult, male, Philadelphia chromosome (p352): BCR-ABL gene fusion due to translocation of chromosomes 9 and 22, presentation with CNS signs, Hb↓[76] or WCC >100×10^9/L or B-cell ALL. PCR is used to detect minimal residual disease, undetectable by standard means. Prognosis is poor if seen in high amounts at presentation or during remission. Prognosis in relapsed Ph-negative ALL is poor (improvable by marrow transplant).[77]

Personalized treatment ►*One size does not fit all!*[78] Aim to tailor therapy to the exact gene defect, and according to individual metabolism. Monoclonal antibodies, gene-targeted retinoids, cytokines, vaccines, and T-cell infusions are relevant here.[79] Biomarkers, eg thiopurine methyltransferase, can predict toxicity from thiopurines.

Acute myeloid leukaemia (AML)

This neoplastic proliferation of blast cells is derived from marrow myeloid elements. It progresses rapidly (death in ~2 months if untreated; ~20% 3yr survival after Rx).

Incidence The commonest acute leukaemia of adults (1/10,000/yr; increases with age). AML can be a long-term complication of chemotherapy, eg for lymphoma. Also associated with myelodysplastic states (BOX), radiation, and syndromes, eg Down's.

Morphological classification There is much heterogeneity.[1] Now based on WHO histological classification, which is complex and requires specialist interpretation. It recognizes the important prognostic information from cytogenetics and molecular genetics.[1] 5 types:

1. AML with recurrent genetic abnormalities.
2. AML multilineage dysplasia (eg 2° to pre-existing myelodysplastic syndrome).
3. AML, therapy related.
4. AML, other.
5. Acute leukaemias of ambiguous lineage (both myeloid and lymphoid phenotype).

Symptoms • *Marrow failure:* Symptoms of anaemia, infection or bleeding. DIC occurs in acute promyelocytic leukaemia, a subtype of AML, where there is release of thromboplastin. Use of all-transretinoic acid with chemotherapy ↓risk of DIC (p346). • *Infiltration:* Hepatomegaly and splenomegaly, gum hypertrophy (fig 3), skin involvement. CNS involvement at presentation is rare in AML.

Diagnosis WCC is often ↑, but can be normal or even low. Blast cells may be few in the peripheral blood, so diagnosis depends on bone marrow biopsy. Differentiation from ALL may be by microscopy (figs 1, 2, 4; Auer rods are diagnostic of AML), but is now based on immunophenotyping and molecular methods. Cytogenetic analysis (eg type of mutation) affects treatment recommendations, and guides prognosis.[1]

Complications • Infection is the major problem, related to both the disease and during treatment. Be alert to septicaemia (p346). Infections may be bacterial, fungal or viral, and prophylaxis is given for each during therapy. *Pitfalls:* AML itself causes fever, common organisms present oddly, few antibodies are made, rare organisms—particularly fungi (esp. *Candida* or *Aspergillus*). • Chemotherapy causes ↑plasma urate levels (from tumour lysis)—so give allopurinol with chemotherapy, and keep well hydrated with IV fluids. • Leukostasis (p346) may occur if WCC ↑↑.

Treatment • *Supportive care* As for ALL. Walking exercises can relieve fatigue.[80]

- *Chemotherapy* is very intensive, resulting in long periods of marrow suppression with neutropenia + platelets↓. The main drugs used include ***daunorubicin*** and ***cytarabine***, with ~5 cycles given in 1-week blocks to get a remission (RAS mutations occur in ~20% of patients with AML and enhance sensitivity to cytarabine).[81]
- *Bone marrow transplant (BMT)* Pluripotent haematopoietic stem cells are collected from the marrow. *Allogeneic* transplants from HLA-matched siblings or matched unrelated donors (held on international databases) are indicated during 1st remission in disease with poor prognosis. The idea is to destroy leukaemic cells and the immune system by cyclophosphamide + total body irradiation, and then repopulate the marrow by transplantation from a matched donor infused IV. BMT allows the most intensive chemotherapy regimens because marrow suppression is not an issue. Ciclosporin ± methotrexate are used to reduce the effect of the new marrow attacking the patient's body (graft *vs* host disease).
  Complications: Graft *vs* host disease (may help explain the curative effect of BMT); opportunistic infections; relapse of leukaemia; infertility.
  Prognosis: Lower relapse rates ~60% long-term survivors, but significant mortality of ~10%. Autologous BMT where stem cells are taken from the patient themselves, is used in intermediate prognosis disease, although some studies suggest better survival rates with intensive chemotherapy regimens.
  Autologous mobilized peripheral blood stem cell transplantation may offer faster haemopoietic recovery and less morbidity.[82]
- Supportive care, or lower-dose chemotherapy for disease control, may be more appropriate in elderly patients, where intensive therapies have poorer outcomes.

- Low leukocyte alkaline phosphatase (LAP) and presence of basophilia are seen in CML, and help distinguish it from leukemoid reaction (high LAP).
- The BCR-ABL fusion gene found in the Philadelphia chromosome t(9;22) produces a deregulated tyrosine kinase that is implicated in the pathogenesis of CML, and is the target of therapy.
- Acute leukemias present with symptoms due to symptomatic anemia, bleeding due to thrombocytopenia, infection due to neutropenia, or with hyperleukocytosis and symptoms of CNS or pulmonary microvascular ischemia.
- CLL/SLL is an indolent disease characterized by the monoclonal proliferation of mature B-lymphocytes expressing the CD5 antigen, and typically presents as asymptomatic lymphocytosis or painless lymphadenopathy.
- Complications of CLL include autoimmune hemolytic anemia or thrombocytopenia, recurrent infections due to immune dysfunction, or transformation to a more aggressive large cell lymphoma.

Shaking chills in a patient with acute lymphoblastic leukemia

A 24-year-old man presents to the emergency room complaining of **24 hours of fevers with shaking chills**. He is currently being **treated for acute lymphoblastic leukemia** (ALL). His most recent **chemotherapy** with hyperfractionated CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) was **7 days ago**. He denies any cough or dyspnea, headache, abdominal pain, or diarrhea. He has had no sick contacts or recent travel. On physical examination, he is febrile to **39.4°C**, with heart rate **122 bpm**, blood pressure 118/65 mm Hg, and respiratory rate **22 breaths per minute**. He is ill appearing; his skin is warm and moist but without any rashes. He has no oral lesions, his chest is clear to auscultation, his heart rate is tachycardic but regular with a soft systolic murmur at the left sternal border, and his abdominal examination is benign. The perirectal area is normal, and digital rectal examination is deferred, but his stool is negative for occult blood. He has a **tunneled vascular catheter at the right internal jugular vein** without erythema overlying the subcutaneous tract and no purulent discharge at the catheter exit site. Of note, he reports an onset of **shaking chills 30 minutes after the catheter was flushed**. Laboratory studies reveal a **total white blood cell count** of **1100 cells/mm^3**, with a differential of **10% neutrophils**, 16% band forms, 70% lymphocytes, and 4% monocytes (**absolute neutrophil count 286/mm^3**). Chest radiograph and urinalysis are normal.

What is the most likely diagnosis?

What are your next therapeutic steps?

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What is the most likely diagnosis? Neutropenic fever and possible infected vascular catheter.

What are your next therapeutic steps? **After drawing blood cultures**, the patient should undergo **broad-spectrum intravenous antibiotic** administration, including coverage for gram-positive organisms such as Staphylococcus spp. The **vascular catheter should be removed.**

NEUTROPENIA

- Neutrophils less than 1800/mcL (1.8×10^9/L).
- Severe neutropenia if neutrophils below 500/mcL (0.5×10^9/L).

Bone marrow disorders
- Congenital
  - Dyskeratosis congenita
  - Fanconi anemia
- Cyclic neutropenia
- Large granular lymphoproliferative disorder
- Hairy cell leukemia
- Myelodysplasia

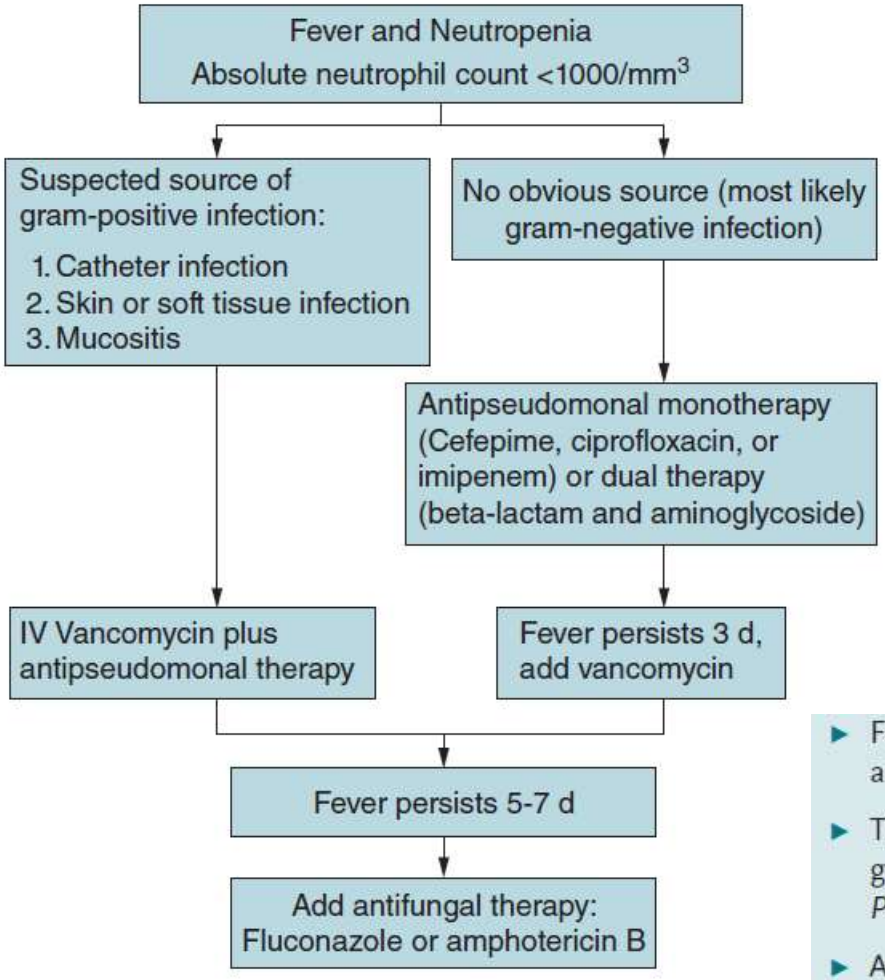
Non-bone marrow disorders
- Drugs: sulfonamides, chlorpromazine, procainamide, penicillin, cephalosporins, cimetidine, methimazole, phenytoin, chlorpropamide, antiretroviral medications, rituximab
- Aplastic anemia
- Myelosuppressive cytotoxic chemotherapy
- Benign chronic neutropenia
- Pure white cell aplasia
- Hypersplenism
- Sepsis
- Other immune
  - Autoimmune (idiopathic)
  - Felty syndrome
  - Systemic lupus erythematosus
  - HIV infection

Neutropenia results in stomatitis and in infections due to gram-positive or gram-negative aerobic bacteria or to fungi such as *Candida* or *Aspergillus*. The most common infections are septicemia, cellulitis, pneumonia, and neutropenic fever of unknown origin. Fever in neutropenic patients should always be initially assumed to be of infectious origin until proven otherwise (Chapter 30).

Treatment of neutropenia depends on its cause. Potential causative drugs should be discontinued. Myeloid growth factors (filgrastim or sargramostim) help facilitate neutrophil recovery after offending drugs are stopped. Chronic

Use of antibiotics in neutropenia ► Treat any known infection promptly.

- If T° >38°C or T° >37.5°C on 2 occasions, >1h apart, or the patient is toxic, assume septicaemia and start blind combination therapy—eg piperacillin-tazobactam—p378 (+ vancomycin, p381, if Gram +ve organisms suspected or isolated, eg Hickman line sepsis). Check local preferences. Continue until afebrile for 72h or 5d course, and until neutrophils >0.5×10^9/L. If fever persists despite antibiotics, think of CMV, fungi (eg *Candida*; *Aspergillus*, p440) and central line infection.
- Consider treatment for *Pneumocystis* (p411, eg co-trimoxazole, ie trimethoprim 20mg/kg + sulfamethoxazole 100mg/kg/day PO/IV in 2 daily doses). Remember TB.



- Fever in a neutropenic patient should be considered a medical emergency and is associated with a high mortality rate.
- The usual sources of bacterial infection in neutropenic patients are gram-positive skin or oral flora or gram-negative enteric flora, including *Pseudomonas*.
- Antifungal therapy should be started in neutropenic patients who have persistent fever despite broad-spectrum antibiotic therapy and who have no obvious source of infection.
- Vascular catheters with evidence of infection along a subcutaneous tract or purulent discharge at the exit site should be removed; replacement over a guidewire is insufficient.
- If a catheter is deemed necessary but it is infected with coagulase-negative staphylococci, antibiotic treatment may sterilize the catheter, allowing it to remain in place. For *S aureus*, gram-negative rods, or fungal catheter infections, the catheter usually requires removal.

27.1 Which of the following infectious agents is the most likely etiology associated with an infected central venous catheter?

A. *Streptococcus pyogenes*
B. *Pseudomonas aeruginosa*
C. Coagulase-negative *Staphylococcus*
D. *Klebsiella pneumoniae*
E. *Candida albicans*

27.2 A 32-year-old man with acute myelogenous leukemia is undergoing chemotherapy. He was hospitalized 7 days ago for fever to 102°F with an absolute neutrophil count of 100 cells/mm^3, and he has been placed on intravenous imipenem and vancomycin. He continues to have fever to 103°F without an obvious source. Which of the following is the best next step?

A. Perform lumbar puncture to assess cerebrospinal fluid.
B. Continue present therapy.
C. Stop all antibiotics because he likely has drug fever.
D. Add an aminoglycoside antibiotic.
E. Add an antifungal agent.

27.3 A 68-year-old woman is diagnosed with acute leukemia and is undergoing induction of chemotherapy. Last cycle, she developed neutropenia with an absolute neutrophil count of 350 cells/mm^3, which has now resolved. Which of the following is appropriate therapy?

A. Immunization against varicella
B. Immunization against mumps
C. Use of recombinant erythropoietin before the next cycle of chemotherapy
D. Use of G-CSF after the next cycle of chemotherapy

27.1 **C.** Coagulase-negative staphylococci, such as *S epidermidis*, along with *S aureus*, are the most common etiology of catheter-related infections.

27.2 **E.** Antifungal therapy should be added when the fever is persistent despite broad-spectrum antibacterial agents.

27.3 **D.** Granulocyte colony-stimulating factor given after chemotherapy can decrease the duration and severity of neutropenia and the subsequent risk of sepsis. Live vaccines, such as varicella and mumps, are contraindicated. Erythropoietin is not indicated because the patient is not anemic.

INFECTIONS IN THE IMMUNOCOMPROMISED PATIENT

ESSENTIALS OF DIAGNOSIS

- Fever and other symptoms may be blunted because of immunosuppression.
- A contaminating organism in an immunocompetent individual may be a pathogen in an immunocompromised one.
- The interval since transplantation and the degree of immunosuppression can narrow the differential diagnosis.
- Empiric broad-spectrum antibiotics may be appropriate in high-risk patients whether or not symptoms are localized.

- Immunocompromised patients have defects in their natural defense mechanisms resulting in an increased risk for infection.
- infection is often severe, rapidly progressive, and life threatening.
- Organisms that are not usually problematic in the immunocompetent person may be important pathogens in the compromised patient (eg, *Staphylococcus epidermidis, Corynebacterium jeikeium, Propionibacterium acnes, Bacillus species).*
- *Therefore, culture* results must be interpreted with caution, and isolates should not be disregarded as merely contaminants.

A. Impaired Humoral Immunity (hypogammaglobulinemia)

- Congenital
- Acquired (multiple myeloma, chronic lymphocytic leukemia, splenectomy).

Patients with ineffective humoral immunity lack opsonizing antibodies and are at particular risk for infection with encapsulated organisms, such as *Haemophilus influenzae, Neisseria meningitides,* and *Streptococcus pneumoniae. Although rituximab is normally* thought of as being linked to impaired cellular immunity, it has been associated with the development of *Pneumocystis jirovecii infection as well as with hepatitis B* reactivation.

B. Granulocytopenia (Neutropenia)

hematopoietic cell transplantation, myelosuppressive chemotherapy, acute leukemias.

Infection risk→ granulocyte <1000/mcL, (great risk<100/mcL)

The granulocytopenic patient is particularly susceptible to infections with gram-negative enteric organisms, *Pseudomonas*, *gram-positive cocci* (particularly *Staphylococcus aureus, S epidermidis, and viridans*streptococci), *Candida, Aspergillus, and other fungi* that have recently emerged as pathogens such as *Trichosporon, Scedosporium, Fusarium, and the mucormycoses.*

C. Impaired Cellular Immunity

HIV infection; lymphoreticular malignancies (Hodgkin disease); immunosuppressive medications (prolonged high-dose corticosteroid treatment, cyclosporine, tacrolimus, and other cytotoxic drugs as in patients receiving therapy for organ transplantation or solid tumors- Tumor necrosis factor (TNF) inhibitors (etanercept and infliximab).

Patients with cellular immune dysfunction are susceptible to infections by a large number of organisms, particularly ones that replicate intracellularly. Examples include bacteria, such as Listeria, Legionella, Salmonella, and Mycobacterium; viruses, such as herpes simplex, varicella,
and CMV; fungi, such as Cryptococcus, Coccidioides, Histoplasma, and Pneumocystis; and protozoa, such as Toxoplasma. **Patients taking TNF inhibitors have specific defects that increase risk of bacterial, mycobacterial (particularly tuberculosis), and fungal infections (primary and reactivation).**

D. Hematopoietic Cell Transplant Recipients

E. Solid Organ Transplant Recipients

F. Other Immunocompromised States

A large group of patients who are not specifically immunodeficient are at increased risk for infection due to:

debilitating injury (eg, burns or severe trauma), invasive procedures (eg, chronic central intravenous catheters, Foley catheters, dialysis catheters), central nervous system dysfunction (which predisposes patients to aspiration pneumonia and decubitus ulcers), obstructing lesions (eg, pneumonia due to an obstructed bronchus, pyelonephritis due to nephrolithiasis, cholangitis secondary to cholelithiasis), use of broadspectrum antibiotics.

Diabetes mellitus (alterations in cellular immunity, resulting in mucormycosis, emphysematous pyelonephritis, and foot infections).

▶▶Prevention

There is great interest in preventing infection with prophylactic antimicrobial regimens but no uniformity of opinion about optimal drugs or dosage regimens.

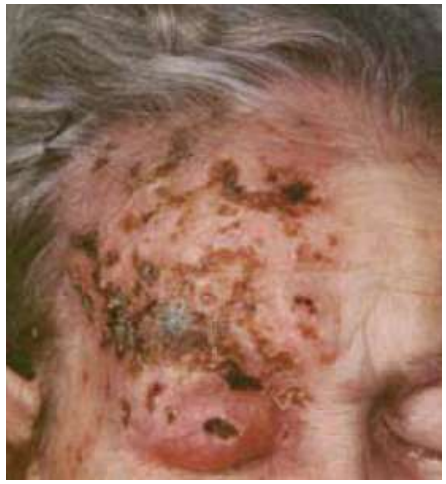
Hand washing is the simplest and most effective means of decreasing hospital associated
infections, especially in the compromised patient.

Invasive devices such as central and peripheral lines and Foley catheters are potential sources of infection.

Colony stimulating factors decrease rates of infection and episodes of febrile neutropenia, but not mortality, during chemotherapy or during stem-cell transplantation.

A 65-year-old man presents with a rash of 2 days' duration over the right forehead with **vesicles and pustules**, a few lesions on the right side and tip of the nose, and slight blurring of vision in the right eye. The rash was preceded by **tingling in the area** and is now associated with **aching pain**.

How should this patient be evaluated and treated?



The patient should receive **oral antiviral therapy**, **medication for pain** (e.g., an opioid, with the addition of gabapentin if needed), and prompt **referral to an ophthalmologist**. He should also be advised to avoid contact with persons who have not had varicella or have not received the varicella vaccine until his lesions have completely crusted. I would recommend herpes zoster **vaccination** to reduce the risk of recurrence, but in an immunocompetent patient such as this one, I would defer vaccination for approximately 3 years, since the current episode of herpes zoster should boost his cellular immune response to VZV for that period of time.

N Engl J Med 2013;369:255-63.

Varicella zoster Varicella (chickenpox; fig 1) is a contagious febrile illness with crops of blisters at various stages, eg on the back. Complications, eg purpura fulminans/DIC (get help; ▶▶may need heparin[141]), pneumonitis, and ataxia, are commoner in pregnancy and adults than in children.[142] Incubation: 11–21d. Infectivity: 4d before the rash until all lesions are scabbed (~1 week). *OHCS* p144. After infection, virus is dormant in dorsal root ganglia. Reactivation causes **shingles** (affects 20% at some time; eg if old or immunosuppressed). Pain in dermatomal distribution (p458, fig 1) precedes malaise and fever by some days. *Shingles Rx:* Treat acute zoster, eg with **aciclovir** 800mg 5 times/d PO for 7d if eGFR >25; if immunocompromised: 10mg/kg/8h slowly IVI for 10d; alternative: **famciclovir**, or **valaciclovir** (1g/8h PO for 7d; it is aciclovir's prodrug—a 2012 meta-analysis says that post-herpetic neuralgia is less).[143] MET If conjunctiva affected, use 3% aciclovir ointment 5×/day. Beware iritis; test acuity often; say to report *any* visual loss at once. SE of aciclovir: GFR↓ (do U&E & LFT), vomiting, encephalopathy, urticaria. *Post-herpetic neuralgia (PHN)* in affected dermatomes can last years; it is hard to treat and can be intolerable.[1] Try amitriptyline (start with 10mg at night), topical **lidocaine** patches, or gabapentin (p508) ± carbamazepine, phenytoin, or topical capsaicin as a counter-irritant. Last resort: ganglion ablation. Refer to a pain clinic. ▶In those ≥60yrs **HZ vaccine** prevents PHN in >60%.[1] Those 50–59yrs benefit too. CI: immunosuppression.

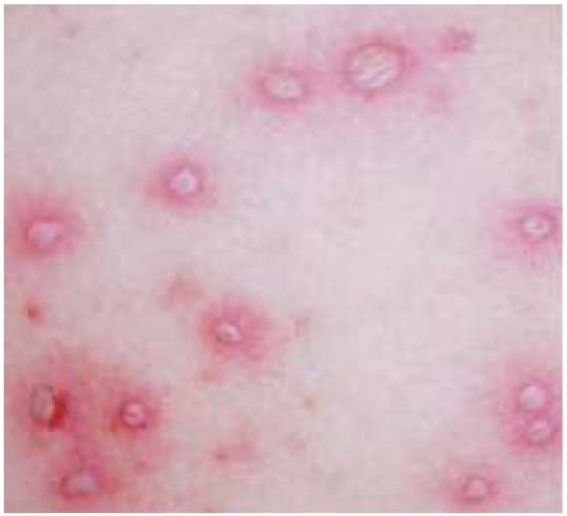
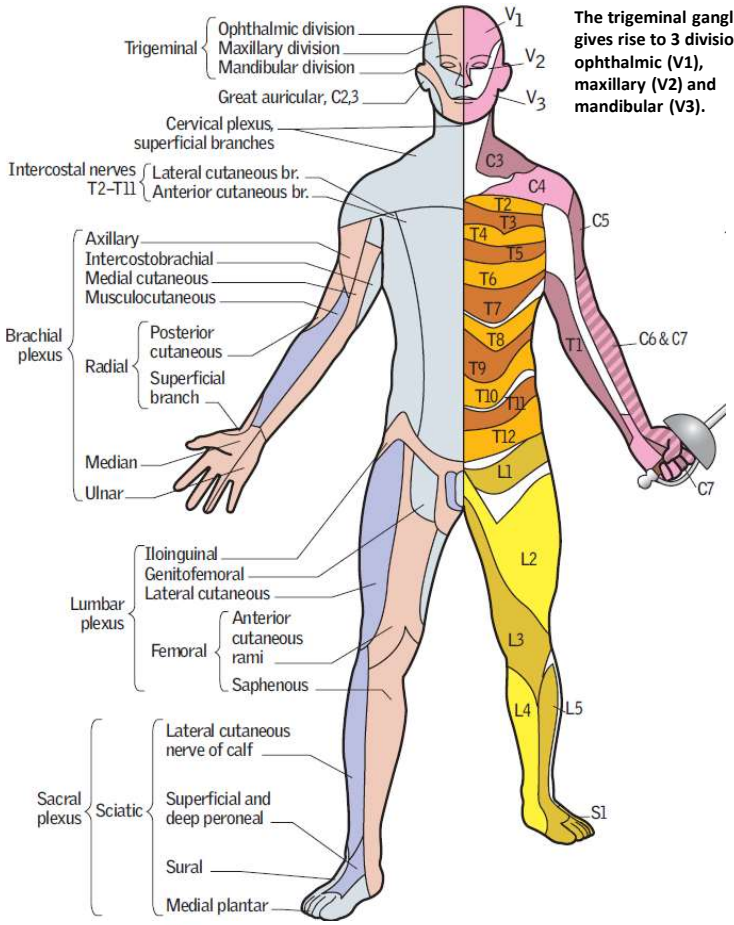


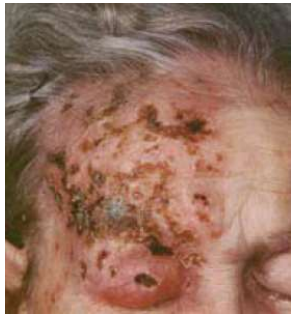
Fig 1. Chickenpox. ©Dr C Leung.

A **nucleus** is a collection of nerve cell bodies within the central nervous system. A **ganglion** refers to a collection of the nerve cell bodies outside the central nervous system.

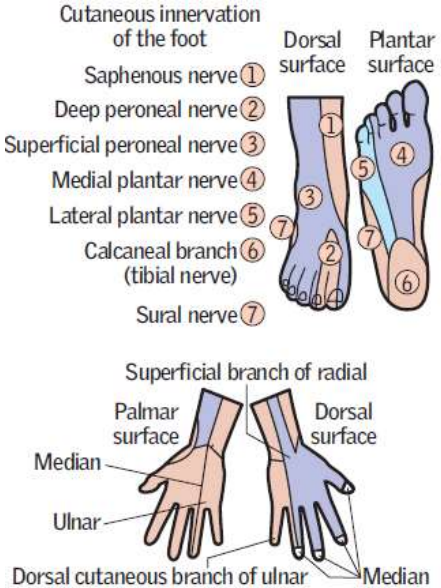
Dermatomes and peripheral nerves

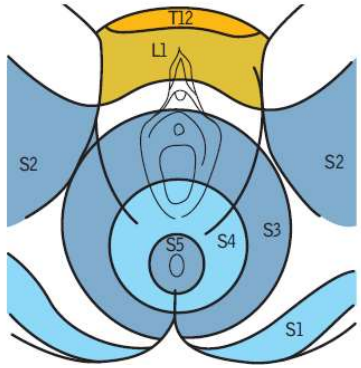


The trigeminal ganglion gives rise to 3 divisions: ophthalmic (V1), maxillary (V2) and mandibular (V3).

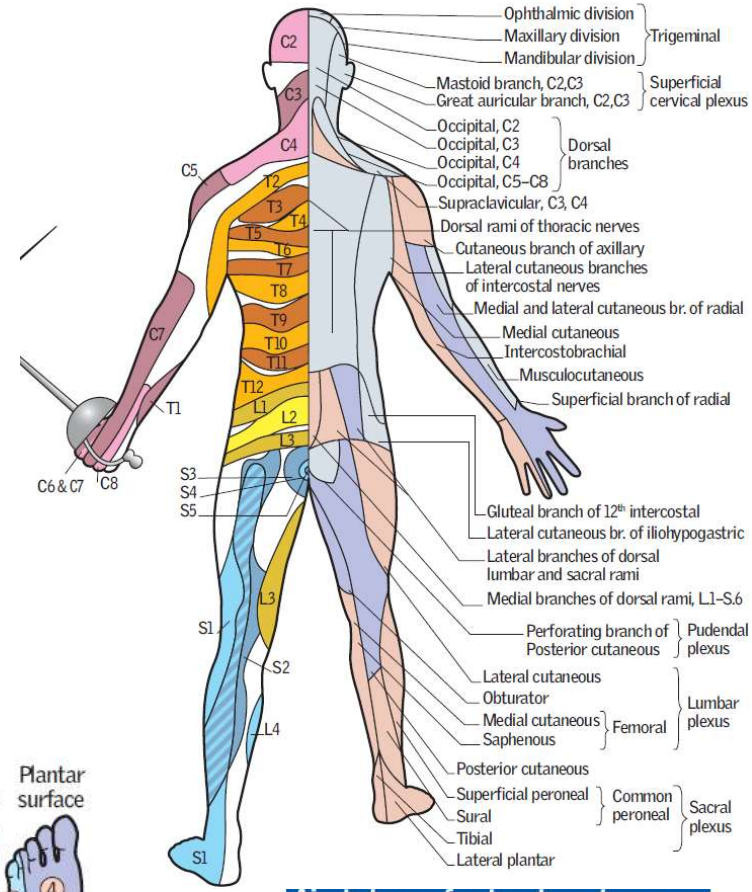


Pain in a dermatomal distribution suggests a problem with a cranial nerve or dorsal root ganglion (radiculopathy)— where the cell bodies of sensory fibres live. What is the dermatome? What is the lesion?





3 views. In 2, the anterior ⅓ of the scrotum is L1; the posterior ⅔ is S3. The penis is S2/3 (L1 at its root).



Aim to keep a few key dermatomes up your sleeve (C5-T2)	
C3–4	Clavicles
C6–7	Lateral arm/forearm
T1	Medial side of arm
C6	Thumb
C7	Middle finger
C8	Little finger
T4	Nipples
T10	Umbilicus
L1	Inguinal ligament
L2–3	Anterior and inner leg
L5	Medial side of big toe
L5, S1–2	Posterior and outer leg
S1	Lateral margin of foot and little toe
S2–4	Perineum

Rough approximations!

Selected Complications of Herpes Zoster in Nonimmunocompromised Persons.

Complication	Manifestations	Site of VZV Reactivation
Aseptic meningitis	Headache, meningismus	Cranial nerve V
Bacterial superinfection	Streptococcus, staphylococcus cellulitis	Any sensory ganglia
Bell's palsy	Unilateral facial paralysis	Cranial nerve VII
Eye involvement (herpes zoster ophthalmicus)	Keratitis, episcleritis, iritis, conjunctivitis, uveitis, acute retinal necrosis, optic neuritis, acute glaucoma	Cranial nerve II, III, or V (ophthalmic [V1] branch)
Hearing impairment	Deafness	Cranial nerve VIII
Motor neuropathy	Weakness, diaphragmatic paralysis, neurogenic bladder	Any sensory ganglia
Postherpetic neuralgia	Pain persisting after the rash has resolved	Any sensory ganglia
Ramsay Hunt syndrome	Ear pain and vesicles in the canal, numbness of anterior tongue, facial paralysis	Cranial nerve VII geniculate ganglia, with spread to cranial nerve VIII
Transverse myelitis	Paraparesis, sensory loss, sphincter impairment	Vertebral ganglia
Vasculopathy (encephalitis)	Vasculitis of cerebral arteries, confusion, seizures, TIAs, stroke	Cranial nerve V

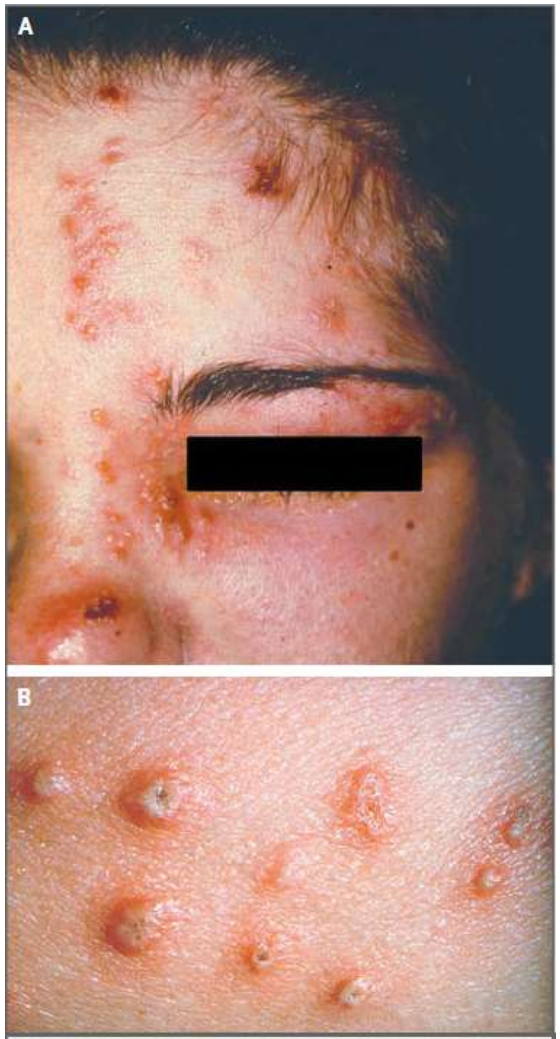


Figure 1. Clinical Features of Herpes Zoster.
Panel A shows herpes zoster in the ophthalmic (V1) branch of the trigeminal ganglia. Photograph courtesy of Michael Oxman, M.D. Panel B shows vesicles and pustules in a patient with herpes zoster. These are representative photographs and are not from the case presented.

Herpes simplex virus (HSV) Manifestations of primary infection:

1 *Genital herpes* can be a chronic, life-long infection. Majority of cases (esp. recurrent) are caused by HSV-2 (HSV-1 is taking over).[138] *Signs:* Flu-like prodrome, then grouped vesicles/papules develop around genitals, anus, or throat. These burst, forming shallow ulcers (heal in ~3wks). Also: urethral discharge ± dysuria (esp if ♀); urinary retention. *OHCS* p268. *Tests:* PCR. *℞:* Give analgesia. *Aciclovir* 400mg/8h PO, *famciclovir* 250mg/8h PO (500mg/12h for 10d if immunocompromised[139]), or *valaciclovir* 500mg/12h for 5d (for longer if healing is incomplete). If frequent (≥6/yr) or severe recurrences, continuous *aciclovir* 400mg/12h PO, *famciclovir* 250mg/12h PO or *valaciclovir* 500mg/24h.[138] *Prevention:* Condoms, even for oral sex.

2 *Gingivostomatitis:* Ulcers filled with yellow slough appear in the mouth.

3 *Herpetic whitlow:* Abrasions allow virus to enter the finger, causing a vesicle.

4 *Herpes gladiatorum:* Vesicles wherever HSV is ground into the skin by force.

5 *Eczema herpeticum:* HSV infection of eczematous skin; usually children.

6 *Herpes simplex meningitis:* This is uncommon and usually self-limiting (typically HSV-2 in women during a primary attack).

7 *Systemic infection* may be mild but life-threatening if immunocompromised. Signs: fever, sore throat, lymphadenopathy, pneumonitis, and hepatitis.

8 *Herpes simplex encephalitis:* Spreads from cranial nerve ganglia, to frontal and temporal lobes. ►*Suspect if:* fever, fits, headaches, odd behaviour, dysphasia, hemiparesis, or coma or brainstem encephalitis, meningitis, or myelitis. *Δ:* Urgent PCR on CSF (it remains +ve ~5d after initiating ℞). CT/MRI or EEG: non-specific temporal lobe changes; brain biopsy is needed[140] if MRI cannot distinguish from glioma. Seek expert help: careful fluid balance to minimize cerebral oedema, p840; ►►*prompt* aciclovir, eg 10mg/kg/8h IV for ≥10d, saves lives (p834). Mortality: 19%.

9 *HSV keratitis:* Corneal dendritic ulcers. *Avoid steroids*. See *OHCS* p416.

Tests: Rising antibody titres in 1° infection; culture; PCR for fast diagnosis.

Recurrent HSV: Dormant HSV in ganglion cells may be reactivated by illness, immunosuppression, menstruation, or sunlight. Cold sores (perioral vesicles) are one manifestation. Aciclovir cream may be disappointing.

Occasional lymphocytosis in an elderly men

A 65-year-old man with benign prostatic hypertrophy had been experiencing difficulty with urination, and so he saw his urologist to be evaluated for a transurethral resection of the prostate. As part of the routine preoperative evaluation, he had a **complete blood count**, but that was found to be **abnormal**. The procedure was cancelled and he is now referred to the internal medicine clinic for additional evaluation. Aside from his prostate symptoms, the patient is **asymptomatic**. He has not experienced any recent fevers, chills, night sweats, arthralgias, or myalgias. His appetite is good and his weight has been stable. He is moderately physically active, plays golf regularly, and has not noted any fatigue or exertional dyspnea.

On examination, he is **afebrile** and normotensive. His conjunctivae are anicteric, and his skin and oral mucosa show no pallor. His chest is clear to auscultation, and his heart is regular without any murmurs. On abdominal examination, his liver span seems normal, and there is no palpable spleen. He does not have any palpable cervical, axillary, or inguinal adenopathy. Labs show the following results: **White blood cell count is 56 000** with **90% mature lymphocytes** and 10% neutrophils, hemoglobin is 14.8 g/dL, hematocrit 45%, and platelet count 189 000. Other labs including electrolytes, creatinine, and transaminases are all within normal limits.

What is the most likely diagnosis? **Chronic lymphocytic leukemia** (CLL)

What is the most appropriate next step? **Flow cytometry of peripheral blood** to demonstrate a monoclonal B-cell population, and confirm the diagnosis

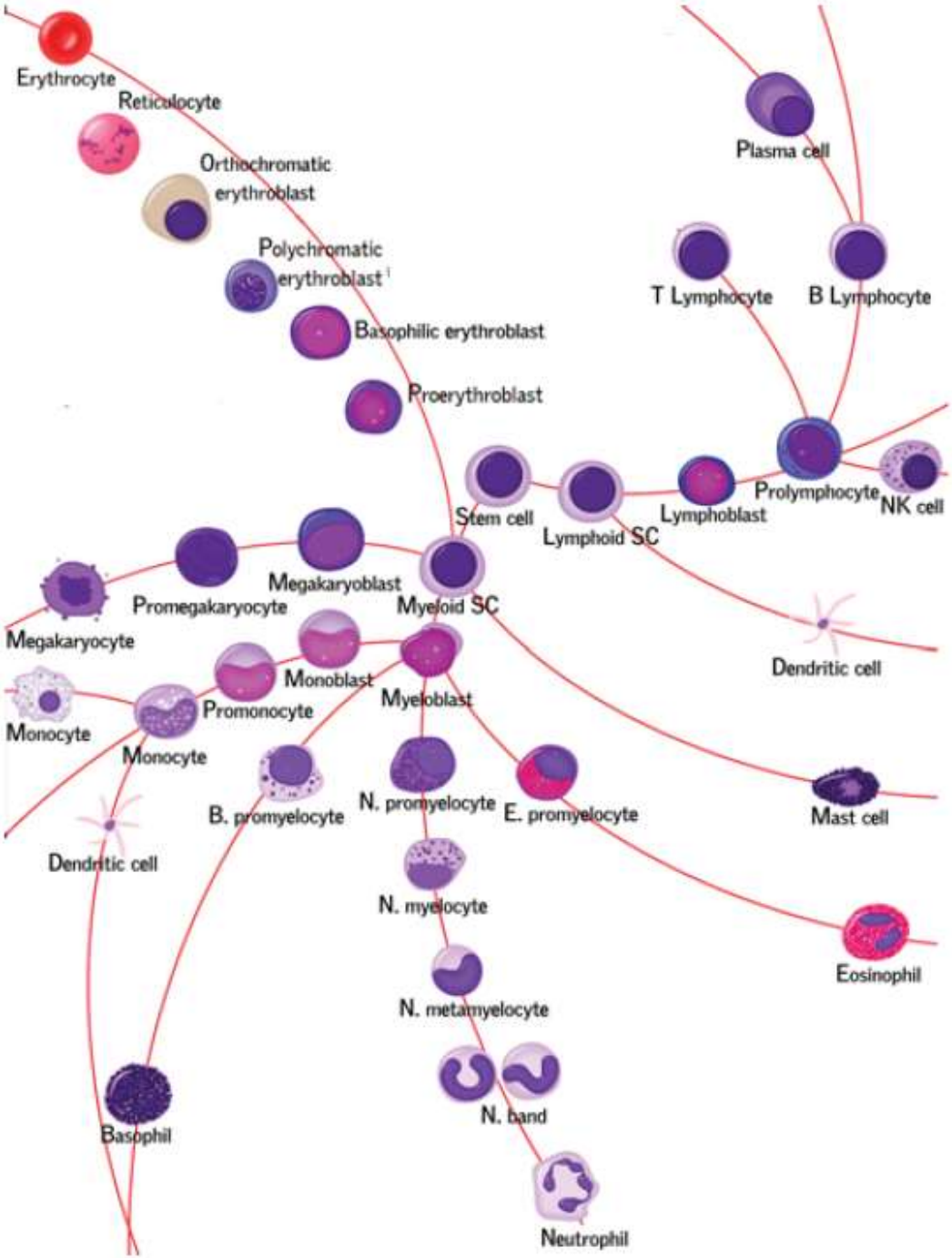
Rai stage:	0	Lymphocytosis alone	Median survival >13yrs
	I	Lymphocytosis + lymphadenopathy	8yrs
	II	Lymphocytosis + spleno- or hepatomegaly	5yrs
	III	Lymphocytosis + anaemia (Hb <110g/L)	2yrs
	IV	Lymphocytosis + platelets <100 × 10^9/L	1yr

CFIM n°59

A 62-year-old man presented with increasing **shortness of breath on exercise** and **loss of weight.** He had suffered **five chest infections during the previous winter**, despite being a non-smoker. On examination, there was moderate, **bilateral cervical lymphadenopathy** and **left inguinal lymph node enlargement**. The **spleen and liver were enlarged** 5cm below the costal margins. There was no bone tenderness and there were no lesions in the skin. On investigation, his **haemoglobin (132g/l) and platelet count (251 x 10^9/l) were normal** but his **white-cell count** was increased to **150000/mmc**; the film showed that **98% of these were small lymphocytes.**

The features on the **blood film** were suggestive of ***chronic lymphocytic leukaemia*** and immunophenotyping confirmed this diagnosis (Table C6.2). Ninety per cent of the cells were B cells; they all expressed surface immunoglobulin (mu, delta and kappa chains), major histocompatibility complex class II antigens (DR) and CD5. **The serum immunoglobulins were low:** IgG 2.2g/l (NR 7.2-19.0g/l); IgA 0.6g/l (NR 0.8-5.0g/l) and IgM 0.4g/l (NR 0.5-2.0g/l). There was no monoclonal immunoglobulin in the serum or the urine.

Rai stage:	0	Lymphocytosis alone	Median survival >13yrs
	I	Lymphocytosis + lymphadenopathy	8yrs
	II	Lymphocytosis + spleno- or hepatomegaly	5yrs
	III	Lymphocytosis + anaemia (Hb <110g/L)	2yrs
	IV	Lymphocytosis + platelets <100 × 10^9/L	1yr


Erythrocyte
Reticulocyte
Orthiochromatic erythroblast
Polychromatic erythroblast
Basophilic erythroblast
Proerythroblast
Plasma cell
T Lymphocyte
B Lymphocyte
Prolymphocyte
NK cell
Lymphoblast
Stem cell
Lymphoid SC
Megakaryoblast
Promegakaryocyte
Myeloid SC
Megakaryocyte
Dendritic cell
Monoblast
Myeloblast
Promonocyte
Monocyte
Monocyte
B. promyelocyte
N. promyelocyte
E. promyelocyte
Mast cell
Dendritic cell
N. myelocyte
Eosinophil
N. metamyelocyte
N. band
Basophil
Neutrophil

Chronic lymphocytic leukaemia (CLL)

Accumulation of mature B cells that have escaped programmed cell death and undergone cell-cycle arrest in the G0/G1 phase is the hallmark of CLL. It is the commonest leukaemia (>25%; incidence: ~4/100,000/yr). ♂:♀≈2:1. Mutations, trisomies and deletions (eg del17p13) influence risk; pneumonia may be a triggering event.[84]

Rai stage:		Median survival
0	Lymphocytosis alone	>13yrs
I	Lymphocytosis + lymphadenopathy	8yrs
II	Lymphocytosis + spleno- or hepatomegaly	5yrs
III	Lymphocytosis + anaemia (Hb <110g/L)	2yrs
IV	Lymphocytosis + platelets <100 × 10^9/L	1yr

Symptoms Often none, presenting as a surprise finding on a routine FBC (eg done pre-op). May be anaemic or infection-prone. If severe: weight↓, sweats, anorexia.

Signs Enlarged, rubbery, non-tender nodes (fig 3). Splenomegaly, hepatomegaly.

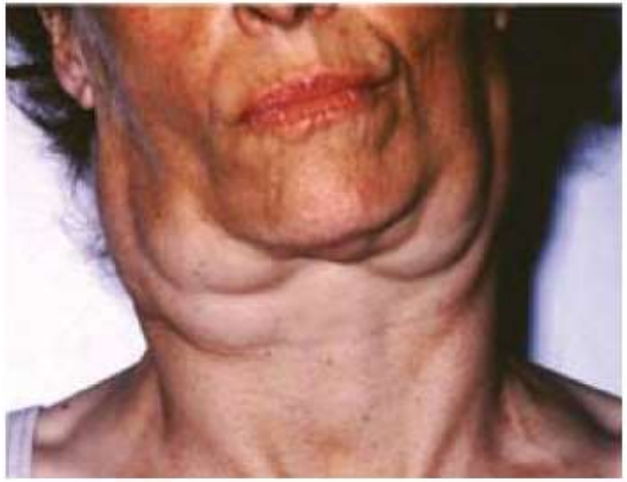
Tests ↑Lymphocytes—may be marked (fig 4). Later: autoimmune haemolysis (p332), marrow infiltration: ↓Hb, ↓neutrophils, ↓platelets.

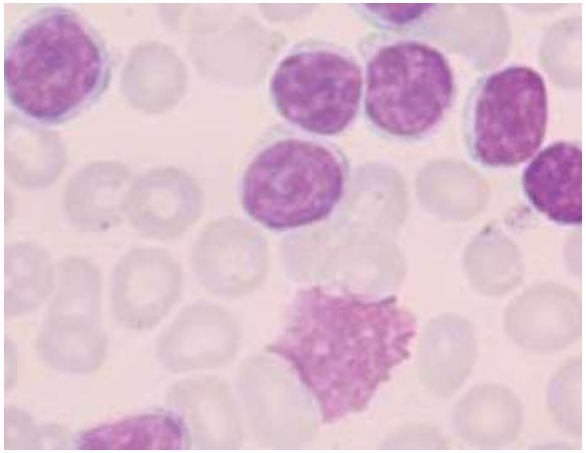
Complications 1 Autoimmune haemolysis. 2 ↑Infection due to hypogammaglobulinaemia (=↓IgG), bacterial, viral especially herpes zoster. 3 Marrow failure.

Natural history Some remain in *status quo* for years, or even regress. Usually nodes slowly enlarge (± lymphatic obstruction). Death is often due to infection (commonly pneumococcus, haemophilus, meningococcus, *Candida* or aspergillosis), or transformation to aggressive lymphoma (Richter's syndrome).

Treatment Consider drugs if: •Symptomatic •Immunoglobulin genes (IgVH) are unmutated •17p deletions (consider intensive R). *Fludarabine + cyclophosphamide + rituximab* if 1st line[85] (there is synergism).[86] *Bendamustine, alemtuzumab,* and *ofatumumab* may have a role (the latter is "not cost effective").[87,88 NICE] *Steroids* help autoimmune haemolysis. *Radiotherapy* helps treat lymphadenopathy and splenomegaly. *Supportive care:* Transfusions, IV human immunoglobulin if recurrent infection. *Relapsed disease:* One option is rituximab + dexamethasone (R-DEX). R-DEX can also be used to debulk before a *stem-cell transplant*.[89]

Prognosis ⅓ never progress, ⅓ progress slowly, and ⅓ progress actively. CD23 and β2 microglobulin correlate with bulk of disease and rates of progression.





CLL: many lymphocytes and a 'smear' cell: a fragile cell damaged in preparation.

59.1 A 25-year-old man presents with a 2-week history of low-grade fever, slight cough, malaise, and myalgias, and is noted on physical examination to have enlarged posterior cervical lymph nodes and significant splenomegaly. His CBC shows a lymphocytosis with ALC 10 000/μL, normal hemoglobin level, and normal platelet count. The peripheral smear shows large atypical lymphocytes. What is the most likely diagnosis?

A. ALL
B. CLL
C. Acute HIV infection
D. EBV infection
E. Pertussis

59.2 Which of the following statements regarding CML is true?

A. Peripheral smear shows elevated WBC count with mature and immature granulocytes, toxic granulation, and high LAP score.
B. Usually presents initially with splenomegaly, anemia, and thrombocytopenia.
C. Chromosomal translocations, most often t(9;22), are found in 90%-95% of patients.
D. Is an indolent disease, and should be monitored without treatment until patients enter accelerated or blast phase.

59.3 A 75-year-old woman, diagnosed with stage 0 CLL 1 year ago and being monitored without treatment, now complains of fatigue and dyspnea. She has no palpable adenopathy or splenomegaly, no rashes or arthritis, and her CBC shows ALC 11 000/μL, with hemoglobin 6.8 mg/dL, and platelet count 127 000/μL. What is the most appropriate diagnostic test?

A. Direct antiglobulin (Coombs) test
B. Antinuclear antibody
C. Bone marrow biopsy
D. Test for Lewis alloantibody

59.1 **D.** The clinical presentation of fever, malaise, adenopathy, and splenomegaly is consistent with infectious mononucleosis, which is most often associated with EBV, but can also be due to CMV or other viral infections. The absence of cytopenias makes ALL unlikely. The lymphocytosis in CLL and pertussis consists of mature small lymphocytes. Acute HIV infection can present similarly to mononucleosis, but does not typically cause massive splenomegaly.

59.2 **C.** Definitive diagnosis of CML is established by demonstrating the presence of the Philadelphia chromosome or the underlying t(9;22) translocation, the BCR-ABL1 fusion gene or mRNA fusion product, which is found in nearly all patients. Toxic granulation and high LAP score are features of leukemoid reaction. Splenomegaly is common in CML, but significant cytopenias are not seen. Before imatinib and other TKIs, median survival in CML was 4 years with progression to blast (acute leukemic) phase and death. Imatinib or other TKIs are indicated as initial treatment for patients in chronic phase, with the goals of achieving remission and preventing progression of disease.

59.3 **A.** The most likely diagnosis is autoimmune hemolytic anemia (AIHA), which can be confirmed by detection of antibody and/or complement components on the surface of the RBC, usually by the direct antiglobulin (Coombs) test. AIHA is a common complication of CLL. ANA to screen for systemic lupus erythematosus has a low probability in a woman of this age, without other clinical features of SLE. Bone marrow biopsy to evaluate for bone marrow failure due to CLL could be considered, but rapid progression to stage III/IV would be unlikely. Lewis alloantibodies have no clinical significance.

- Low leukocyte alkaline phosphatase (LAP) and presence of basophilia are seen in CML, and help distinguish it from leukemoid reaction (high LAP).
- The BCR-ABL fusion gene found in the Philadelphia chromosome t(9;22) produces a deregulated tyrosine kinase that is implicated in the pathogenesis of CML, and is the target of therapy.
- Acute leukemias present with symptoms due to symptomatic anemia, bleeding due to thrombocytopenia, infection due to neutropenia, or with hyperleukocytosis and symptoms of CNS or pulmonary microvascular ischemia.
- CLL/SLL is an indolent disease characterized by the monoclonal proliferation of mature B-lymphocytes expressing the CD5 antigen, and typically presents as asymptomatic lymphocytosis or painless lymphadenopathy.
- Complications of CLL include autoimmune hemolytic anemia or thrombocytopenia, recurrent infections due to immune dysfunction, or transformation to a more aggressive large cell lymphoma.

Chronic macrocytic anemia and generalized fatigue in a elderly woman

The patient is a woman aged 72 years who has developed **generalised fatigue** and **macrocytic anemia over the past year**. Gastroenterology evaluation resulted in **negative colonoscopy and EGDS**. The patient was referred to hematology for an evaluation in August 2010. Laboratory studies revealed a **WBC count of 3.3 with 1200 neutrophils**, **hemoglobin 9.4, an MCV of 108**, and a **platelet count of 44,000**. She had **normal vitamin B12 and folic acid levels**. Her **reticulocyte count was unusually low at 0.1%.** She had normal iron stores and normal iron saturation. The patient's renal and hepatic functions were confirmed to be normal.
She subsequently underwent a **bone marrow biopsy** which was consistent with **myelodysplastic syndrome**. Specifically, the marrow was described as being normocellular 40% with a relative megakaryocytic hyperplasia, including dysplasia. There were also approximately 6% to 8% immature myeloid cells present with interstitial clustering. Stainable iron was present. Flow cytometry confirmed 5% to 6% blast forms, expressing the myeloid antigens CD33, CD13, CD34, CD117, and HLA-DR. Cytogenetics revealed a deletion of 5q in 16 out of 20 examined cells. There were no additional clonal abnormalities. FISH studies also confirmed the presence of the 5q abnormality. Past medical history: Significant for hiatal hernia and hypertension. Diagnosed with breast cancer in 1975 and treated with 1 year of oral melphalan.

Many patients are asymptomatic at diagnosis, and **myelodysplastic syndrome** is found on routine laboratory tests. If symptoms develop they are usually non-specific and related to **anaemia** - weakness, fatigue, decreased exercise tolerance, light-headedness, or angina. Less common symptoms are easy bruising, bleeding, and infections. Occasionally, MDS can present with autoimmune abnormalities, such as arthritis, pericarditis, pleural effusions, skin ulcerations, uveitis, myositis, and peripheral neuropathy. Rarely, patients can present with an acute illness characterised by cutaneous vasculitis, fever, arthritis, peripheral oedema, and pulmonary infiltrates.

Myelodysplastic syndromes (MDS, myelodysplasia)

These are a heterogeneous group of disorders that manifest as marrow failure with risk of life-threatening infection and bleeding. Most are primary disorders, but they may also develop secondary to chemotherapy or radiotherapy. 30% transform to acute leukaemia. *Tests:* Pancytopenia (p358), with ↓reticulocyte count. Marrow cellularity is usually increased due to ineffective haematopoiesis. Ring sideroblasts may also be seen in the marrow (fig 5, p321). There are different subtypes, grouped according to WHO classification.

Treatment:

- Multiple transfusions of red cells or platelets as needed.
- Erythropoietin ± human granulocyte colony stimulating factor (G-CSF) may lower transfusion requirement.
- Immunosuppressives are also used, eg ciclosporin or antithymocyte globulins.
- Curative allogeneic stem cell transplantation is one option—often inappropriate owing to age-related comorbidities—most are >70yrs old.
- Thalidomide analogues such as lenalidomide have a role, eg in low-risk MDS with 5q deletions. Hypomethylating agents (eg azacytidine and decitabine) have a role in symptomatic MDS (these target epigenetic changes in MDS).

Prognosis: Median survival: from 6 months to 6 years according to disease type.

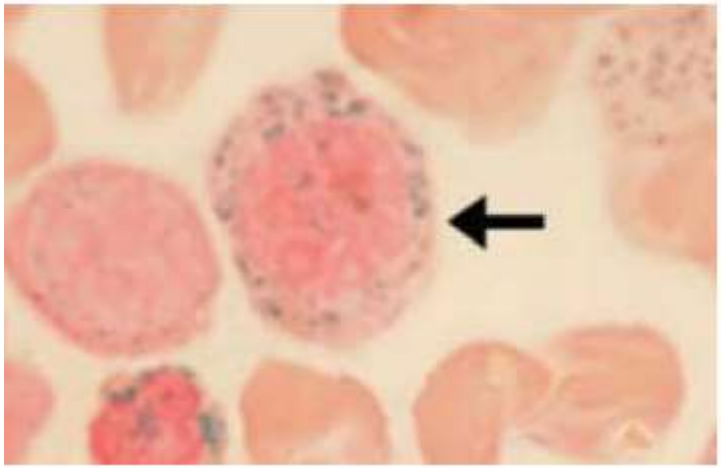


Fig 5. Ring sideroblasts in the marrow, with a perinuclear ring of iron granules, found in sideroblastic anaemia. It is characterized by ineffective erythropoiesis, leading to ↑iron absorption, iron loading in marrow ± haemosiderosis (endocrine, liver and heart damage due to iron deposition). It may be congenital (rare, x-linked) or acquired, eg idiopathic as one of the myelodysplastic/myeloproliferative diseases, but it can follow chemotherapy, anti-TB drugs, irradiation, alcohol or lead excess.

- **Myeloproliferative disorders are due to acquired clonal abnormalities of the hematopoietic stem cell.**
- Since the stem cell gives rise to **myeloid**, **erythroid**, and **platelet** cells, qualitative and quantitative changes are seen in all these cell lines.
- Classically, the myeloproliferative disorders produce characteristic syndromes with well-defined clinical and laboratory features. However, these disorders are grouped together because they may evolve from one into another and because hybrid disorders are commonly seen.
- **All of the myeloproliferative disorders may progress to myelodysplastic syndrome and acute myeloid leukemia.**
- The **Philadelphia chromosome** seen in chronic myeloid leukemia (CML) was the first recurrent cytogenetic abnormality to be described in a human malignancy. Since that time, there has been tremendous progress in elucidating the genetic nature of these disorders, with identification of mutations in *JAK2, MPL, CALR, CSF3R, and other genes*

Myeloproliferative neoplasms
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocytosis
- Chronic myeloid leukemia

Myelodysplastic syndromes

Acute myeloid leukemia

	White Count	Hematocrit	Platelet Count	Red Cell Morphology
Polycythemia vera	N or ↑	↑	N or ↑	N
Essential thrombocytosis	N or ↑	N	↑↑	N
Primary myelofibrosis	N or ↓ or ↑	↓	↓ or N or ↑	Abn
Chronic myeloid leukemia	↑↑	N	N or ↑	N

Abn, abnormal; N, normal.

POLYCYTHEMIA VERA

- *JAK2 (V617F)* mutation.
- Increased red blood cell mass.
- Splenomegaly.
- Normal arterial oxygen saturation.
- Usually elevated white blood count and platelet count.

ESSENTIAL THROMBOCYTOSIS

- Elevated platelet count in absence of other causes.
- Normal red blood cell mass.
- Absence of *bcr/abl* gene (Philadelphia chromosome).

PRIMARY MYELOFIBROSIS

- Striking splenomegaly.
- Teardrop poikilocytosis on peripheral smear.
- Leukoerythroblastic blood picture; giant abnormal platelets.
- Initially hypercellular, then hypocellular bone marrow with reticulin or collagen fibrosis.

CHRONIC MYELOID LEUKEMIA

- Elevated white blood count.
- Markedly left-shifted myeloid series but with a low percentage of promyelocytes and blasts.
- Presence of *bcr/abl* gene (Philadelphia chromosome).

Myelofibrosis

- **haemopoietic stem cell proliferation**
- **marrow fibrosis**
- **abnormal megakaryocyte precursors release fibroblast-stimulating factors**

Chronic myeloid leukaemia (CML)

CML is characterized by an uncontrolled clonal proliferation of myeloid cells (fig 1). It accounts for 15% of leukaemias. It is a myeloproliferative disorder (p360) having features in common with these diseases, eg splenomegaly. It occurs most often between 40–60yrs, with a slight male predominance, and is rare in childhood.

Philadelphia chromosome (Ph) Present in >80% of those with CML. It is a hybrid chromosome comprising reciprocal translocation between the long arm of chromosome 9 and the long arm of chromosome 22—t(9;22)—forming a fusion gene BCR/ABL on chromosome 22, which has tyrosine kinase activity. Those without Ph have a worse prognosis. Some patients have a masked translocation—cytogenetics do not show the Ph, but the rearrangement is detectable by molecular techniques.

Symptoms Mostly chronic and insidious: weight↓, tiredness, fever, sweats. There may be features of gout (due to purine breakdown), bleeding (platelet dysfunction), and abdominal discomfort (splenic enlargement). ~30% are detected by chance.

Signs Splenomegaly (>75%)—often massive. Hepatomegaly, anaemia, bruising (fig 2).

Tests WBC↑↑ (often >100×10^9/L) with whole spectrum of myeloid cells, ie ↑neutrophils, myelocytes, basophils, eosinophils. Hb↓ or normal, platelets variable. Urate↑, B_{12}↑. Neutrophil alk phos score↓ (seldom performed now). Bone marrow is hypercellular. Ph found on cytogenetic analysis of blood or bone marrow.

Natural history Variable, median survival 5–6yrs. There are 3 phases: *chronic*, lasting months or years of few, if any, symptoms → *accelerated phase*, with increasing symptoms, spleen size, and difficulty in controlling counts → *blast transformation*, with features of acute leukaemia ± death. **Treatment** See BOX.

Treating CML

CML is the first example of a cancer where knowledge of the genotype has led to a rationally designed drug—*imatinib* (Glivec®), a specific BCR-ABL tyrosine kinase inhibitor, which has transformed therapy over the last 10yrs.[90]

More potent 2nd-generation BCR-ABL inhibitors: *dasatinib*, *nilotinib*, *bosutinib* and *ponatinib*. Dasatinib and nilotinib allow more patients to achieve deeper, more rapid responses associated with improved outcomes[91] (NICE says that dasatinib is often not cost-effective).[92] Imatinib SE: usually mild: nausea, cramps, oedema, rash, headache, arthralgia. May cause myelosuppression. Dasatinib has been used in imatinib-resistant blast crises. *Hydroxycarbamide* is also used.

Those with lymphoblastic transformation may benefit from treatment as for ALL. Treatment of myeloblastic transformation with chemotherapy rarely achieves lasting remission, and allogeneic transplantation offers the best hope.

Stem cell transplantation Allogeneic transplantation from an HLA-matched sibling or unrelated donor offers the only cure, but carries significant morbidity and mortality. Guidelines suggest that this approach should be used 1st line only in young patients where mortality rates are lower. Other patients should be offered imatinib. Patients are then reviewed annually to decide whether to continue imatinib, or to offer combination therapy or stem cell transplantation.

The role of autologous transplantation, if any, in CML remains to be defined.