Chapter 1

Clinical approach

History taking in patients with haematological disease

Approach to patient with suspected haematological disease

An accurate history combined with a careful physical examination are fundamental parts of clinical assessment. Although the likely haematological diagnosis may be apparent from tests carried out before the patient has been referred, it is nevertheless essential to assess the clinical background fully—this may influence the eventual plan of management, especially in older patients.

It is important to find out early on in the consultation what the patient may already have been told prior to referral, or what he/she thinks the diagnosis may be. There is often fear and anxiety about diagnoses such as leukaemia, haemophilia, or HIV infection.

Presenting symptoms and their duration

A full medical history needs to be taken to which is added direct questioning on relevant features associated with presenting symptoms:

- *Non-specific symptoms* such as fatigue, fevers, weight loss.
- *Symptoms relating to anaemia* e.g. reduced exercise capacity, recent onset of breathlessness and nature of its onset, or worsening of angina, presence of ankle oedema.
- *Symptoms relating to neutropenia* e.g. recurrent oral ulceration, skin infections, oral sepsis.
- *Evidence of compromised immunity* e.g. recurrent oropharyngeal infection.
- *Details of potential haemostatic problems* e.g. easy bruising, bleeding episodes, rashes.
- *Anatomical symptoms* e.g. abdominal discomfort (splenic enlargement or pressure from enlarged lymph nodes), CNS symptoms (from spinal compression).
- *Past medical history* i.e. detail on past illnesses, information on previous surgical procedures which may suggest previous haematological problems (e.g. may suggest an underlying bleeding diathesis) or be associated with haematological or other sequelae e.g. splenectomy.
- *Drug history*: ask about prescribed and non-prescribed medications.
- *Allergies*: since some haematological disorders may relate to chemicals or other environmental hazards specific questions should be asked about occupational factors and hobbies.
- *Transfusion history*: ask about whether the patient has been a blood donor and how much he/she has donated. May occasionally be a factor in iron (Fe) deficiency anaemia. History of previous transfusion(s) and their timing is also critical in some cases e.g. post-transfusion purpura.
- *Tobacco and alcohol consumption* is essential; both may produce significant haematological morbidity.
- *Travel*: clearly important in the case of suspected malaria but also relevant in considering other causes of haematological abnormality, including HIV infection.

- *Family history* is also important, especially in the context of inherited haematological disorders.

A complete history for a patient with a haematological disorder should provide all the relevant medical information to aid diagnosis and clinical assessment, as well as helping the haematologist to have a working assessment of the patient's social situation. A well taken history also provides a basis for good communication which will often prove very important once it comes to discussion of the diagnosis.

Physical examination

This forms part of the clinical assessment of the haematology patient. Pay specific attention to:

General examination—e.g. evidence of weight loss, pyrexia, pallor (the latter is not a reliable clinical measure of anaemia), jaundice, cyanosis or abnormal pigmentation or skin rashes.

The mouth—ulceration, purpura, gum bleeding, or infiltration, and the state of the patient's teeth. Hands and nails may show features associated with haematological abnormalities e.g. koilonychia in chronic Fe deficiency (rarely seen today).

Record—weight, height, T°, pulse, and blood pressure; height and weight give important baseline data against which sequential measurements can subsequently be compared. In myelofibrosis, for example, evidence of significant weight loss in the absence of symptoms may be an indication of clinical progression.

Examination—of chest and abdomen should focus on detecting the presence of lymphadenopathy, hepatic and/or splenic enlargement. Node sizes and the extent of organ enlargement should be carefully recorded.

Lymph node enlargement—often recorded in centimetres e.g. 3cm × 3cm × 4cm; sometimes more helpful to compare the degree of enlargement with familiar objects e.g. pea. Record extent of liver or spleen enlargement as maximum distance palpable from the lower costal margin.

Erythematous margins of infected skin lesions—mark these to monitor treatment effects.

Bones and joints—recording of joint swelling and ranges of movement are standard aspects of haemophilia care. In myeloma, areas of bony tenderness and deformity are commonly present.

Optic fundi—examination is a key clinical assessment in the haematology patient. May yield the only objective evidence of hyperviscosity in paraproteinaemias (📖 Hyperviscosity, p.640) or hyperleucocytosis (📖 p.655) such as in e.g. CML. Regular examination for haemorrhages should form part of routine observations in the severely myelosuppressed patient; rarely changes of opportunistic infection such as candidiasis can be seen in the optic fundi.

Neurological examination—fluctuations of conscious level and confusion are clinical presentations of hyperviscosity. Isolated nerve palsies in a patient with acute leukaemia are highly suspicious of neurological involvement or disease relapse. Peripheral neuropathy and long tract signs are well recognized complications of B_{12} deficiency.

Splenomegaly

Many causes. Clinical approach depends on whether splenic enlargement is present as an isolated finding or with other clinical abnormalities e.g. jaundice or lymphadenopathy. Mild-to-moderate splenomegaly has a much greater number of causes than massive splenomegaly.

Table 1.1 Causes of splenomegaly

Infection	Viral	EBV, CMV, hepatitis
	Bacterial	SBE, miliary tuberculosis, *Salmonella, Brucella*
	Protozoal	Malaria, toxoplasmosis, leishmaniasis
Haemolytic	Congenital	Hereditary spherocytosis, hereditary elliptocytosis, sickle cell disease (infants), thalassaemia, pyruvate kinase deficiency, G6PD deficiency
	Acquired	AIHA (idiopathic or 2°)
Myeloproliferative and leukaemic		Myelofibrosis, CML, polycythaemia rubra vera, essential thrombocythaemia, acute leukaemias
Lymphoproliferative		CLL, hairy cell leukaemia, Waldenström's, SLVL, other NHL, Hodgkin lymphoma, ALL and lymphoblastic NHL
Autoimmune disorders and storage disorders		Rheumatoid arthritis, SLE, hepatic cirrhosis, Gaucher's disease, histiocytosis X, Niemann–Pick disease
Miscellaneous		Metastatic cancer, cysts, amyloid, portal hypertension, portal vein thrombosis, tropical splenomegaly

Clinical approach essentially involves a working knowledge of the possible causes of splenic enlargement and determining the more likely causes in the given clinical circumstances by appropriate further investigation. There are fewer causes of massive splenic enlargement, i.e. the spleen tip palpable below the level of the umbilicus.

Massive splenomegaly

- Myelofibrosis.
- CML.
- Lymphoproliferative disease—CLL and variants including SLVL, HCL, and marginal zone lymphoma.
- Tropical splenomegaly.
- Leishmaniasis.
- Gaucher's disease.
- Thalassaemia major.

Lymphadenopathy

Occurs in a range of infective or neoplastic conditions; less frequently enlargement occurs in active collagen disorders. May be isolated, affecting a single node, localized, involving several nodes in an anatomical lymph node grouping, or generalized, where nodes are enlarged at different sites. As well as enlargement in the easily palpable areas (cervical, axillary, and iliac) node enlargement may be hilar or retroperitoneal and identifiable only by imaging. Isolated/localized lymphadenopathy usually results from local infection or neoplasm. Generalized lymphadenopathy may result from systemic causes, especially when symmetrical, as well as infection or neoplasm. Rarely drug-associated (e.g. phenytoin).

Table 1.2 Causes of lymphadenopathy

Infective	Bacterial	Tonsillitis, cellulitis, tuberculous infections, and 1° syphilis usually produce isolated or localized node enlargement
	Viral	EBV, CMV, rubella, HIV, HBV, HCV
	Other	Toxoplasma, histoplasmosis, chlamydia, cat-scratch
Neoplastic		Hodgkin lymphoma (typically isolated or localized lymphadenopathy), NHL isolated, generalized or localized, CLL, metastatic carcinoma, acute leukaemia (ALL especially, but occasionally AML)
Collagen and other systemic disorders		E.g. rheumatoid arthritis, SLE, sarcoidosis

History and examination—points to elicit

- Age.
- Onset of symptoms, whether progressing or not.
- Systemic symptoms, weight loss (>10% body weight loss in <6 months).
- Night sweats.
- Risk factors for HIV infection.
- Local or systemic evidence of infection.
- Evidence of systemic disorder such as rheumatoid arthritis.
- Evidence of malignancy; if splenic enlargement present then lymphoreticular neoplasm is more likely.
- Specific disease-related features e.g. pruritus and alcohol-induced lymph node pain associated with Hodgkin's disease.
- Determine the duration of enlargement ± associated symptoms, whether nodes are continuing to enlarge, and whether tender or not. Distribution of node enlargement should be recorded as well as size of node.

Investigations

- FBC and peripheral blood film examination.
- ESR or plasma viscosity.
- Screening test for infectious mononucleosis and serological testing for other viruses.

- Imaging—e.g. chest radiography; chest abdominal ± pelvic CT scanning may also be helpful to define hilar, retroperitoneal, and para-aortic nodes.
- Microbiology—e.g. blood cultures, indirect testing for TB, and culture of biopsied or aspirated lymph node material.
- Lymph node biopsy for definitive diagnosis especially if a neoplastic cause suspected. Aspiration of enlarged lymph nodes is generally unsatisfactory in providing effective diagnostic material. Avoid biopsy of groin nodes since these often show only non-specific features.
- BM examination should be reserved for staging in confirmed lymphoma or leukaemia cases—it is not commonly a useful 1° investigation of lymphadenopathy.

Unexplained anaemia

Evaluate with the combined information from clinical history, physical examination, and results of investigations.

History—focus on

- Duration of symptoms of anaemia—short duration of dyspnoea and fatigue etc. suggests recent bleeding or haemolysis. Gradual anaemia of longer duration often associated with adaptation and fewer symptoms.
- Specific questioning on blood loss—include system-related questions e.g. GIT and gynaecological sources, ask about blood donation.
- Family history—e.g. in relation to hereditary problems such as HS or ethnic Hb disorders such as thalassaemia or HbSS.
- Past history—e.g. association of gastrectomy with later occurrence of Fe and/or B_{12} deficiency.
- Drug history—including prescribed and non-prescribed medication.
- Dietary factors—mainly relates to folate and Fe deficiency, rarely B_{12} in vegans. Fe deficiency always occurs because Fe losses exceed intake (*it is extremely rare in developed countries for diet to be the sole cause of Fe deficiency*).

Examination

- May identify indirectly helpful signs e.g. koilonychia in chronic Fe deficiency (rare), jaundice in haemolytic disorders.
- Lymphadenopathy suggesting lymphoreticular disease or viral infection.
- Hepatosplenomegaly in lymphoproliferative or myeloproliferative disorders.

Full blood count

📖 Laboratory investigation of anaemia is discussed fully in Chapter 2. Anaemia in adult ♂ if Hb <13.0g/dL and in adult ♀ if Hb <11.5g/dL.

Table 1.3 MCV useful for initial anaemia evaluation

↓ MCV (<76fL)	Fe deficiency
	α & β thalassaemia, HbE, HbC
	Anaemia of chronic disorders
Normal MCV (78–98fL)	Recent bleeding
	Anaemia of chronic disorders
	Most non-haematinic deficiency causes
	Combined Fe + B_{12}/folate deficiency
↑ MCV (>100fL)	Folate or B_{12} deficiency
	Haemolytic anaemia
	Liver disease
	Marrow dysplasia and failure syndromes including aplastic anaemia
	2° to antimetabolite drug therapy e.g. hydroxyurea (now called hydroxcarbamide)

The need for film examination, reticulocyte counting, and additional tests on the FBC sample such as checking for Heinz bodies is based on the initial clinical and FBC findings. The findings from the initial FBC examination have a major influence in determining the nature and urgency of further clinical investigation.

Serum ferritin level will identify Fe deficiency and focus on the need for detailed investigation for blood loss which, for adult males and postmenopausal females, will frequently require large bowel examination with colonoscopy or barium enema, and gastroscopy. BM examination may occasionally be required.

Anaemia is not a diagnosis—it is an abnormal clinical finding requiring an explanation for its cause. There is no place for empirical use of Fe therapy for management and treatment of 'anaemia' in modern medical practice.

Patient with elevated haemoglobin

Finding a raised Hb concentration requires a systematic clinical approach for differential diagnosis and further investigation. Initially it is essential to check whether the result ties in with the known clinical findings—if unexpected the FBC should be re-checked to exclude a mix-up over samples or a sampling artefact. Dehydration and diuretic therapy may ↑ the Hct and these should be excluded in the initial phase of assessment.

Having determined that the ↑ Hb concentration is genuine the issue is whether there is a genuine ↑ in red cell mass or not, and the explanation for the elevated Hb.

Anoxia is a major stimulus to RBC production and will result in an increase in erythropoietin with consequent erythrocytosis.

History and examination should assess:

- Recent travel and residence at high altitude (>3000m).
- COAD, other hypoxic respiratory conditions, cyanotic congenital heart disease, other cardiac problems causing hypoxia.
- Smoking—heavy cigarette smoking causes ↑ carboxyHb levels leading to ↑ RBC mass to compensate for loss of O_2 carrying capacity.
- Ventilatory impairment 2° to gross obesity, alveolar hypoventilation (Pickwickian syndrome).
- Possibility of high-affinity Hb abnormalities arises if there is a FH of polycythaemia, otherwise requires assessment through Hb analysis.
- If obvious secondary causes excluded possibilities include:
  - ***Spurious polycythaemia***—pseudopolycythaemia or Gaisbock's syndrome, associated features can include cigarette smoking, obesity, hypertension, and excess alcohol consumption; sometimes described as 'stress polycythaemia'.
  - ***Primary proliferative polycythaemia (polycythaemia rubra vera)***—plethoric facies, history of pruritus after bathing or on change of environmental temperature, and presence of splenomegaly are helpful clinical findings to suggest this diagnosis.
  - ***Inappropriate erythropoietin excess***—occurs in a variety of benign and malignant renal disorders. Rare complication of some tumours including hepatoma, uterine fibroids, and cerebellar haemangioblastoma.

Part of clinical assessment must also include an evaluation of thrombotic risk; previous thrombosis or a family history of such problems ↑ the urgency of investigation and appropriate treatment (📖 see also Chapter 7, pp.260–274).

1. McMullin, M.F., *et al.* (2005) Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol*, **130**, 174–95.

Anaemia and hypoxia are detected by the renal sensors. This leads to ↑ production of Epo which drives the marrow (through BFU-E and CFU-E) to produce RBCs. Other factors may also drive red cell production, including androgens and growth hormone as shown in Fig. 1.1.

Erythropoietin

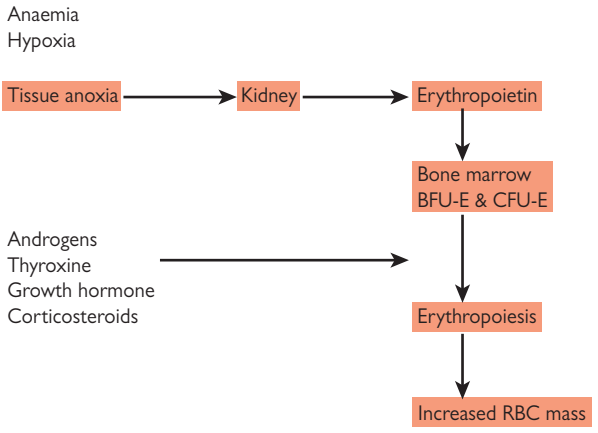

Fig. 1.1

Elevated WBC

Leucocytosis is defined as elevation of the WCC >2 SD above the mean. The detection of leucocytosis should prompt immediate scrutiny of the automated WBC differential (generally accurate except in leukaemia) and the other FBC parameters. Blood film should be examined and a manual differential count performed. Important to evaluate leucocytosis in terms of the age-related absolute normal ranges for neutrophils, lymphocytes, monocytes, eosinophils, and basophils (📖 Normal ranges (adult), p.808; Paediatric normal ranges, p.810) and the presence of abnormal cells: immature granulocytes, blasts, nucleated red cells, and 'atypical cells'.

Leukaemoid reaction—leucocytosis >50 × 10^9/L defines a neutrophilia with marked 'left shift' (band forms, metamyelocytes, myelocytes, and occasionally promyelocytes and myeloblasts in the blood film). Differential diagnosis is CGL and in children, juvenile CML. Primitive granulocyte precursors are also frequently seen in the blood film of the infected or stressed neonate, and any seriously ill patient e.g. on ITU.

Leucoerythroblastic blood film—contains myelocytes, other primitive granulocytes, nucleated red cells, and often tear drop red cells, is due to BM invasion by tumour, fibrosis, or granuloma formation and is an indication for a BM biopsy. Other causes include anorexia and haemolysis.

Leucocytosis due to blasts—suggests diagnosis of acute leukaemia and is an indication for cell typing studies and BM examination.

FBC, blood film, white cell differential count, and the clinical context in which the leucocytosis is detected will usually indicate whether this is due to a 1° haematological abnormality or reflects a 2° response.

► It is clearly important to seek a history of symptoms of infection and examine the patient for signs of infection or an underlying haematological disorder.

Neutrophilia

- 2° to acute infection is most common cause of leucocytosis.
- Usually modest (uncommonly >30 × 10^9/L), associated with a left shift and occasionally toxic granulation or vacuolation of neutrophils.
- Chronic inflammation causes less marked neutrophilia often associated with monocytosis.
- Moderate neutrophilia may occur following steroid therapy, heatstroke, and in patients with solid tumours.
- Mild neutrophilia may be induced by stress (e.g. immediate postoperative period) and exercise.
- May be seen following a myocardial infarction or major seizure.
- Frequently found in states of chronic BM stimulation (e.g. chronic haemolysis, ITP) and asplenia.
- Primary haematological causes of neutrophilia are less common. CML is often the cause of extremely high leucocyte counts (>200 × 10^9/L), predominantly neutrophils with marked left shift, basophilia and occasional myeloblasts. A low LAP score (seldom used now) and the presence of the Ph chromosome on karyotype analysis are usually helpful to differentiate CGL from a leukaemoid reaction.

- Less common are juvenile CML, transient leukaemoid reaction in Down syndrome, hereditary neutrophilia, and chronic idiopathic neutrophilia.

BM examination is rarely necessary in the investigation of a patient with isolated neutrophilia. Investigation of a leukaemoid reaction, leucoerythroblastic blood film, and possible CGL or juvenile CML are firm indications for a BM aspirate and trephine biopsy. BM culture, including culture for atypical mycobacteria and fungi, may be useful in patients with persistent pyrexia or leucocytosis.

Lymphocytosis

- Lymphocytosis >4.0 $\times$ 10^9/L.
- Normal infants and young children <5 years have a higher proportion and concentration of lymphocytes than adults.
- Rare in acute bacterial infection except in pertussis (may be >50 $\times$ 10^9/L).
- Acute infectious lymphocytosis also seen in children, usually associated with transient lymphocytosis and a mild constitutional reaction.
- Characteristic of infectious mononucleosis but these lymphocytes are often large and atypical and the diagnosis may be confirmed with a heterophil agglutination test (Monospot®; Paul–Bunnell).
- Similar atypical cells may be seen in patients with CMV and hepatitis A infection.
- Chronic infection with brucellosis, tuberculosis, 2° syphilis, and congenital syphilis may cause lymphocytosis.
- Lymphocytosis is characteristic of CLL, ALL, and occasionally NHL.

Where a 1° haematological cause is suspected, immunophenotypic analysis of the peripheral blood lymphocytes will often confirm or exclude a neoplastic diagnosis. BM examination is indicated if neoplasia is strongly suspected and in any patient with concomitant neutropenia, anaemia, or thrombocytopenia, or if there are constitutional symptoms e.g. sweats, weight loss.

Reduced WBC

It is uncommon for absolute leucopenia (WBC <4.0 × 10^9/L) to be due to isolated deficiency of any cell other than the neutrophil though in marked leucopenia several cell lines are often affected.

► Neutropenia

Defined as a neutrophil count <2.0 × 10^9/L. The risk of infective complications is closely related to the absolute neutrophil count. More severe when neutropenia is due to impaired production from chemotherapy or marrow failure rather than to peripheral destruction or maturation arrest where there is often a cellular marrow with early neutrophil precursors and normal monocyte counts. Type of infection determined by the degree and duration of neutropenia. Ongoing chemotherapy further ↑ the risk of serious bacterial and fungal opportunistic infection and the presence of an indwelling IV catheter ↑ the incidence of infection with coagulase-negative staphylococci and other skin commensals. Patients with chronic immune neutropenia may develop recurrent stomatitis, gingivitis, oral ulceration, sinusitis, and peri-anal infection.

Table 1.4 Clinical significance of neutropenia

Neutrophil count	Risk of infection
1.0–1.5 x 10^9/L	No significant ↑ risk of infection
0.5–1.0 x 10^9/L	Some ↑ in risk; some fevers can be treated as an outpatient
<0.5 x 10^9/L	Major ↑ in risk; treat all fevers with broad spectrum IV antibiotics as an inpatient

History and physical examination provide a guide to the subsequent management of a patient with neutropenia. Simple observation is appropriate initially for an asymptomatic patient with isolated mild neutropenia who has an unremarkable history and examination. If there has been a recent viral illness or the patient can discontinue a drug which may be the cause, follow-up over a few weeks may see resolution of the abnormality.

Investigations

BM examination—if there is concomitant anaemia or thrombocytopenia, history of significant infection, or if lymphadenopathy or organomegaly on examination. Usually unhelpful in patients with an isolated neutropenia >0.5 × 10^9/L. However, if neutropenia persists, perform BM aspiration, biopsy and cytogenetics, and check serology for collagen diseases, anti-neutrophil antibodies, HIV, and immunoglobulins.

Differential diagnoses

Isolated neutropenia may be the presenting feature of myelodysplasia, aplastic anaemia, Fanconi anaemia, or acute leukaemia but these conditions will usually be associated with other haematological abnormalities.

Post-infectious (most usually post-viral) neutropenia may last several weeks and may be followed by prolonged immune neutropenia.

Severe sepsis—particularly at the extremes of life.

Drugs—cytotoxic agents and many others, e.g. phenothiazines, many antibiotics, NSAIDs, anti-thyroid agents, and psychotropic drugs. Neutrophil recovery starts ~a few days of stopping offending drug.

Autoimmune neutropenia due to anti-neutrophil antibodies may occur in isolation or in association with haemolytic anaemia, ITP, or SLE.

Felty's syndrome neutropenia is accompanied by seropositive rheumatoid arthritis and splenomegaly.

Chronic benign neutropenia of infancy and childhood is associated with fever and infection; resolves by age 4 years, probably has immune basis.

Benign familial or racial neutropenia is a feature of rare families and of certain racial groups, notably negroes, is associated with mild neutropenia but no propensity to infection.

Chronic idiopathic neutropenia is a diagnosis of exclusion, associated with severe neutropenia but often a benign course.

Cyclical neutropenia is a condition usually of childhood onset and dominant inheritance characterized by severe neutropenia, fever, stomatitis, and other infections occurring at 4-week intervals.

Hereditary causes (less common) include Kostmann syndrome (📖 p.593), Shwachman–Diamond–Oski syndrome (📖 p.593), Chediak–Higashi syndrome (📖 p.599), reticular dysgenesis, and dyskeratosis congenita.

Management

Febrile episodes should be managed according to the severity of the neutropenia (Table 1.4) and the underlying cause (BM failure is associated with more life-threatening infections). Broad spectrum IV antibiotics may be required and empirical systemic antifungal therapy may be required in those who fail to respond to antibiotics. Prophylactic antibiotic and antifungal therapy may be helpful in some patients with chronic neutropenia as may G-CSF. Antiseptic mouthwash is of value and regular dental care is important.

► Lymphopenia

Lymphopenia ($<1.5 \times 10^9$/L) may be seen in acute infections, cardiac failure, pancreatitis, tuberculosis, uraemia, lymphoma, carcinoma, SLE and other collagen diseases and after corticosteroid therapy, radiation, chemotherapy, and anti-lymphocyte globulin therapy. Most common cause of chronic severe lymphopenia in recent years is HIV infection (📖 HIV infection and AIDS, p.548).

Chronic severe lymphopenia ($<0.5 \times 10^9$/L) is associated both with opportunistic infections notably *Candida species*, *Pneumocystis jerovicii*, CMV, Herpes zoster, *Mycoplasma* spp., *Cryptosporidium,* and toxoplasmosis and with an ↑ incidence of neoplasia particularly NHL, Kaposi's sarcoma and skin and gastric carcinoma.

1. Palmblad, J.E., *et al.* (2002) Idiopathic, immune, infectious, and idiosyncratic neutropenias. *Semin Hematol*, **39**, 113–20.

Elevated platelet count

Thrombocytosis is defined as a platelet count >400 × 10^9/L. May be due to a *primary* myeloproliferative neoplasm (MPN) or a *secondary* reactive feature. If the platelet count is markedly elevated a patient with a MPN has a risk of haemorrhage (due to the production of dysfunctional platelets), or thrombosis, or both. The patient's history may reveal features of the condition to which the elevated platelet count is secondary. Clinical examination may provide similar clues or reveal splenomegaly which suggests a MPN. FBC may provide useful information: marked leucocytosis with left shift (in the absence of a history of infection), basophilia, or an elevated haematocrit and red cell count are highly suggestive of a MPN when associated with thrombocytosis. Unusual for reactive thrombocytosis to cause a platelet count >1000 × 10^9/L. *Note*: platelet counts below this may occur in MPNs.

Differential diagnosis

Table 1.5 Differetial Diagnosis of Thrombocytosis

Myeloproliferative neoplasms	Disorders associated with ↑ platelets
1° thrombocythaemia	Haemorrhage
Polycythaemia vera	Trauma
Chronic granulocytic leukaemia	Surgery
Idiopathic myelofibrosis	Fe deficiency anaemia
	Malignancy (Ca lung, Ca breast, Hodgkin's disease)
	Acute and chronic infection
	Inflammatory disease e.g. rheumatoid arthritis, UC
	Post-splenectomy

Investigation

- BM aspirate may show megakaryocyte abnormalities in MPN.
- BM trephine biopsy may show marked myeloid hyperplasia, clusters of abnormal megakaryocytes, and ↑ reticulin or fibrosis in MPN.

Management

- In reactive thrombocytosis treat the underlying condition.
- Unusual to require treatment to ↓ the platelet count in a patient with reactive thrombocytosis.
- Consider low dose aspirin (or if contraindicated, dipyridamole).
- Reactive thrombocytosis is generally transient.
- If secondary to Fe deficiency—review FBC after Fe therapy: the platelet count normalizes if thrombocytosis was due to Fe deficiency.
- Fe deficiency may have masked PRV—this will be revealed by Fe therapy.
- If impossible to define the cause of thrombocytosis then a watch-and-wait policy should be followed in an asymptomatic patient.
- If MPN is suspected—📖 see Essential thrombocythaemia, p.276.

Reduced platelet count

Thrombocytopenia is defined as a platelet count $<150 \times 10^9$/L. Although there is no precise platelet count at which a patient will or will not bleed, most patients with a count $>30 \times 10^9$/L are asymptomatic. The risk of spontaneous haemorrhage ↑ significantly $<10 \times 10^9$/L. Purpura is the most common presenting symptom usually found on the lower limbs and areas subject to pressure. May be followed by bleeding gums, epistaxis, or more serious life-threatening haemorrhage. A patient with newly diagnosed severe thrombocytopenia with or without purpura is a medical emergency and may require admission for further investigation and treatment.

Confirm low platelet count by examination of the blood sample for clots (artefactual low platelets) and the blood film for platelet aggregates (causing pseudothrombocytopenia). History and examination will determine the clinical severity of the thrombocytopenia and should also reveal the duration of symptoms, presence of any prodromal illness, causative medication, or underlying disease.

Determine whether the cause of thrombocytopenia is failure of production or ↑ consumption. FBC may be helpful as the MPV is often elevated in the latter group (large platelets may also be seen on the blood film). May also reveal additional haematological abnormalities (normocytic anaemia or neutropenia) suggestive of a BM disorder. A coagulation screen should also be performed. Examination of the BM is the definitive investigation in all patients with moderate or severe thrombocytopenia—may reveal normal megakaryocytes or compensatory hyperplasia in peripheral destruction syndromes or marrow hypoplasia or infiltration. Tests for platelet antibodies are unreliable but an autoimmune screen may be helpful to exclude lupus.

Management

Treat underlying condition. Most patients with a platelet count $>30 \times 10^9$/L require no specific therapy. Avoid aspirin. In the event of life-threatening haemorrhage platelet transfusion should be administered to thrombocytopenic patients *with the exception of those with HITT and TTP.*

1. Spencer, F.A. (2000). Heparin-induced thrombocytopenia: patient profiles and clinical manifestations. *J Thromb Thrombolysis*, **10**, Suppl **1**, 21–5.

Table 1.6 Differential diagnosis of thrombocytopenia

Failure of production	Increased consumption
Drugs and chemicals (📖 p.484)	ITP (📖 p.486)
Viral infection	Drugs (📖 p.484)
Radiation	DIC (📖 p.488)
Aplastic anaemia (📖 p.98)	Infection
Leukaemia	Massive haemorrhage and transfusion (📖 p.502)
Marrow infiltration (📖 pp.484)	SLE
Megaloblastic anaemia (📖 pp.46)	CLL and lymphoma (📖 pp.150, 484)
HIV (📖 p.548)	Heparin (📖 p.508)
	TTP (📖 p.534)
	Hypersplenism (📖 p.486)
	Post-transfusion purpura (📖 p.486)
	HIV (📖 p.548)

Easy bruising

Evaluation of a patient who complains of easy bruising involves a detailed history, physical examination with particular attention to any current haemorrhagic lesions, and the performance of basic haemostatic investigations. More common in ♀ and often difficult to evaluate. Also a frequent complaint in the elderly.

History

Careful attention to the history is essential to the diagnosis of all the haemorrhagic disorders and one must attempt to define the nature of the bruising in a patient with this complaint. *Note*: many normal healthy people believe that they have excessive bleeding or bruising. Conversely some people with haemorrhagic disorders and abnormal bleeding histories will not volunteer the information unless asked directly or indeed may consider their bleeding to be normal. Remember that excessive bruising may be a manifestation of a blood vessel disorder rather than a coagulopathy or platelet disorder.

Ask about

Presenting complaint—how long and how frequently has easy bruising occurred? Is it ecchymoses or purpura? How extensive are bruises? Are they located in areas subject to trauma (e.g. limbs) or pressure (e.g. waist band)? Do petechiae occur? Are bruises painful? How long to resolution? How many currently?

Associated symptoms

Has there been gum bleeding? Has the patient experienced prolonged bleeding after skin trauma, dental extraction, childbirth, or surgery? Has there been any other form of haemorrhage e.g. epistaxis, menorrhagia, joint or soft tissue haematoma, haematemesis, melaena, haemoptysis, or haematuria? Is there a history of poor wound healing?

Family history

Has any other family member a history of excessive bleeding or bruising?

Drug history

Is the patient on any medication (remember self-medication of vitamins and food supplements), most notably aspirin, anticoagulant therapy?

Systematic enquiry

Is there evidence of a disorder associated with a haemorrhagic tendency e.g. hepatic or renal failure, malabsorption, leukaemia, connective tissue disorder, or amyloid?

Physical examination

Haemorrhagic skin lesions are likely to be present in a patient with a serious problem and their distribution will often indicate the extent to which they are likely to be related to trauma. Senile purpura is almost invariably on the hands and forearms. True purpura is easily differentiated from erythema and telangiectasis by pressure. Petechiae are highly suggestive of a platelet or vascular disorder whilst palpable purpura is associated with anaphylactoid purpura. In addition there may be other physical findings which may indicate an underlying disorder e.g. splenomegaly or

lymphadenopathy in leukaemia, signs of hepatic failure, telangiectasia in Osler–Rendu–Weber syndrome or hyperextensible joints and paper-thin scars in Ehlers–Danlos syndrome.

Basic haemostatic investigations

All patients should be investigated except those in whom history and examination has given strong grounds for believing that they are normal and in whom there is a history of a normal response to a haemostatic challenge e.g. surgery or dental extraction.

Screening tests

- FBC and blood film.
- APTT.
- PT.
- Thrombin clotting time and/or fibrinogen.
- Bleeding time (a largely obsolete investigation, of dubious value).

If these investigations are normal there is no indication for further haemostatic investigations unless the history provides strong grounds for believing that there is indeed a haemostatic disorder. The appropriate further investigation of the haemostatic mechanism is discussed in Chapter 10 (📖 Haemostasis and thrombosis, p.448).

Differential diagnoses

- Common diagnoses:
  - Simple easy bruising (purpura simplex).
  - Trauma (including non-accidental injury in children).
  - Senile purpura.
- Haemostatic defects:
  - Thrombocytopenia.
  - Platelet function defects.
  - Coagulation abnormalities (rarely).
- Vascular defects:
  - Corticosteroid excess.
  - Collagen diseases.
  - Uraemia.
  - Dysproteinaemias.
  - Anaphylactoid purpura.
  - Ehlers–Danlos syndrome.
  - Scurvy.
  - Vasculitis.

Recurrent thromboembolism

A hypercoagulable state should be suspected in all patients with recurrent thromboembolic disease, family history of thrombosis, thrombosis at a young age or at an unusual site (in addition to recurrent thromboembolism) associated with inherited thrombophilia. Further important aspects of the history are precipitating factors at the time of thrombosis and lifestyle considerations e.g. smoking, exercise, and obesity. Clinical examination may reveal signs suggestive of an associated underlying condition.

Table 1.7 Hypercoagulable states

Inherited	Activated protein C resistance (factor V Leiden)
	Protein C deficiency
	Protein S deficiency
	Prothrombin gene mutation
	Hyperhomocysteinaemia
	Sickle cell disease
	Antithrombin deficiency and some very rare abnormalities of fibrinogen, plasminogen, and plasminogen activator
Acquired	Immobilization
	Oral contraceptive or oestrogen therapy
	Postpartum
	Old age
	Postoperative
	Malignancy (notably Ca pancreas)
	Nephrotic syndrome
	Myeloproliferative disorders
	Hyperhomocysteinaemia
	Antiphospholipid syndrome (lupus anticoagulant)
	Hyperviscosity
	Paroxysmal nocturnal haemoglobinuria
	Thrombotic thrombocytopenic purpura
	Heparin-induced thrombocytopenia

Laboratory investigation

📖 see Thrombophilia, p.530.

1. Kyrle, P.A., *et al.* (2004.) The risk of recurrent venous thromboembolism in men and women. *N Engl J Med*, **350**, 2558–63.

Pathological fracture

Fracture in a bone compromised by the presence of a pathological process resulting in fracture following relatively minor trauma. Most commonly due to local neoplastic involvement or osteoporosis.

Haematological causes

- Local bony damage.
- Myelomatous deposits.
- Lymphoma.
- Metastatic carcinoma (± marrow infiltration); breast, prostate, and lung are commoner 1° sites.
- Gaucher's disease.
- Sickle cell anaemia.
- Homozygous thalassaemia.
- Osteoporosis from prolonged corticosteroid therapy e.g. for autoimmune disease.

Clinically

Presentation as local pain, discomfort, and restriction of mobility.

Diagnosis

Confirmed by x-ray or other imaging.

Management

- Awareness of risk/possibility and early diagnosis.
- Analgesia.
- Orthopaedic—immobilization and support as appropriate for nature and site of injury, surgical intervention including pinning or other fixation.
- Radiotherapy—local management of fracture 2° to local malignancy.
- Mobilization—physiotherapy.
- Treatment of underlying condition predisposing to fracture.

Raised ESR

The ESR remains an established, empirical test clinically useful as a method for identifying and monitoring the acute phase response. It is influenced by changes in fibrinogen, α-macroglobulins, and immunoglobulins which enhance red cell aggregation *in vitro*.

Plasma viscosity is also an effective measure of acute phase reactants and can be used as an alternative to the ESR in clinical practice; ↑ in ESR and plasma viscosity generally parallel each other.

Normal ranges

- 0–10mm/h for ♂ 18–65 years.
- 1–20mm/h for ♀ 18–65 years.
- Upper limits of normal ↑ by 5–10mm/h for patients >65 years.
- Other factors e.g. Hct influences the ESR.
- Should be regarded as semiquantitative.
- Marked elevations are clinically significant.
- Modest elevations can be more problematic to interpret.

The main advantages to the ESR are its low cost and technical simplicity allied to the absence of a more accurate, inexpensive, and technically simple alternative.

Table 1.8 Causes of raised ESR

Pregnancy	↑ in pregnancy; maximal in 3rd trimester
Infections	Acute and chronic infections, including TB *Note*:↑ ESR also occurs in HIV infection
Collagen disorders	Rheumatoid, SLE, polymyalgia rheumatica, vasculitides etc. (including temporal arteritis); ESR useful as non-specific monitor of disease activity
Other inflammatory processes	Inflammatory bowel disease, sarcoidosis, post-MI
Neoplastic conditions	Carcinomatosis, NHL, Hodgkin lymphoma and paraproteinaemias (benign and malignant)

Investigations

Given the wide range of situations in which a raised ESR can arise, further investigation depends on a carefully conducted history and examination. In the absence of likely causes from these, simple initial laboratory and radiology assessments to include urinalysis, FBC and blood film examination, urea, electrolytes, plasma protein electrophoresis, an autoimmune profile, and CXR should represent a practical and pragmatic primary diagnostic screen.

📖 See Haematological investigations, p.747.

1. Gabay, C., *et al.* (1999). Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med*, **340**, 448–54.

Serum or urine paraprotein

Differential diagnosis

Common

- Monoclonal gammopathy of undetermined significance (MGUS).
- Smouldering myeloma.
- Multiple myeloma.
- Solitary plasmacytoma.
- Lymphoproliferative disorders e.g. CLL, NHL, Waldenström's.

Less common

- Autoimmune disorders e.g. rheumatoid arthritis, SLE.
- Polymyalgia rheumatica.

Rare

- AL amyloid (1° amyloid).
- Plasma cell leukaemia.
- Heavy chain disease.

Discriminating clinical features

MGUS—no symptoms or signs of end-organ damage, normal FBC and biochemical profile, paraprotein level <30g/L and *stable*, immuneparesis (rarely present), BM plasma cells <10%, no lytic lesions.
Smouldering myeloma—as for MGUS but higher stable paraprotein level >30g/L or BM plasma cells >10% without end-organ damage.

Plasmacytoma—localized bone pain, low paraprotein level, isolated bony lesion.

Myeloma—symptoms and signs of anaemia or hyperviscosity (📖 see Hyperviscosity, p.640); bone pain or tenderness, raised Ca^{2+}, creatinine, urate; high β-2 micro-globulin and low albumin; immuneparesis; *paraprotein >30g/L of IgG or >20g/L of IgA or heavy Bence Jones proteinuria; BM >10% plasma cells; lytic bone lesions on x-ray.* Minimum diagnostic criteria are at least 2 of italicized items.

Plasma cell leukaemia—as myeloma but fulminant history. Plasma cells seen on blood film.

Heavy chain disease—rare, characterized by a single heavy chain only in serum or urine electrophoresis. Presence of any light chain excludes.

Amyloid—myriad clinical features. Diagnosis on biopsy of affected site or, if inaccessible, by BM or rectal biopsy—characteristic fibrils stain with Congo Red and show green birefringence in polarized light.

CLL and NHL—systemic symptoms e.g. fever, night sweats, weight loss. Lymphadenopathy or hepatosplenomegaly likely. Confirm on BM or node biopsy.

Waldenström's—as for CLL but with symptoms or signs of hyperviscosity (📖 Waldenström's macroglobulinaemia, p366).

Autoimmune disorders—suggested by joint pain, skin rashes, multisystem disease. Confirm on autoimmune profile including rheumatoid factor, ANA, ANCA.

📖 See Multiple myeloma, p.330.

Anaemia in pregnancy

Physiological changes in red cell and plasma volume occur during pregnancy.

- Red cell mass ↑ by ≤30%.
- Plasma volume ↑ ≤60%.
- Net effect to ↑ blood volume by ≤50% with lowering of the normal
- Hb concentration to 10.0–11.0g/dL during pregnancy. MCV ↑ during pregnancy.
- Fe deficiency is a common problem and cause of anaemia in pregnancy.

Table 1.9 Iron utilization in pregnancy

Cause of ↑ requirements	Amount of additional Fe
↑ Red cell mass	~500mg
Fetal requirements	~300mg
Placental requirements	~5mg
Basal losses over pregnancy (1.0–1.5mg/d)	~250mg

These result in a total requirement of ≤1000mg Fe requiring an average daily intake of 3.5–4.0mg/d. Average Western diet provides <4.0mg Fe/d so that balance is marginal during pregnancy. Diets with Fe mainly in non-haem form (e.g. vegetables) provide less Fe available for absorption. Thus a high risk of developing Fe deficiency anaemia which is exacerbated if preconception Fe stores are reduced.

Folate requirements are ↑ during pregnancy because of ↑ cellular demands; folate levels tend to drop during pregnancy.

Prophylaxis recommendation to give 40–60mg elemental Fe/d which will ↑ availability of dietary absorbable Fe and protect against chronic Fe deficiency; debated whether supplements required by all pregnant women or only for those in at-risk socio-economic and nutritionally deficient groups. Folate supplementation is recommended for all and also appears to reduce incidence of neural tube defects.

- Dilutional anaemia—Hb seldom <10.0g/dL (requires no therapy).
- Fe deficiency—may occur with normal MCV because of ↑ MCV associated with pregnancy; check serum ferritin and give Fe replacement; assess and treat the underlying cause.
- Blood loss—sudden ↓ in Hb may signify fetomaternal bleeding or other forms of concealed obstetric bleeding.
- Folate deficiency—macrocytic anaemia in pregnancy almost invariably will be due to folate deficiency (B_{12} deficiency is extremely rare during pregnancy).
- Microangiopathic haemolysis/DIC may be seen in eclampsia or following placental abruption or intrauterine death. HELLP syndrome (📖 p.92) is a rare but serious cause of anaemia.
- Anaemia may also arise during pregnancy from other unrelated causes and should be investigated.

Thrombocytopenia in pregnancy

A normal uncomplicated pregnancy is associated with a platelet count in the normal range though up to 10% of normal deliveries may be associated with mild thrombocytopenia (>100 $\times$ 10^9/L). Detection of thrombocytopenia in a pregnant patient requires consideration not only of the diagnoses listed in the previous section but also the conditions associated with pregnancy which cause thrombocytopenia. An additional important consideration is the possible effect on the fetus and its delivery.

If thrombocytopenia is detected late in pregnancy, most women will have a platelet count result from the booking visit (at 10–12 weeks) for comparison. Mild thrombocytopenia (100–150 $\times$ 10^9/L) detected for the first time during an uncomplicated pregnancy is not associated with any risk to the fetus nor does it require special obstetric intervention other than hospital delivery.

Non-immune thrombocytopenia

- Thrombocytopenia may develop in association with pregnancy-induced hypertension, pre-eclampsia, or eclampsia. Successful treatment of hypertension may be associated with improvement in thrombocytopenia which is believed to be due to consumption. Treatment of hypertension, pre-eclampsia, or eclampsia may necessitate delivery of the fetus who is not at risk of thrombocytopenia. HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets) may occur in pregnancy.
- A number of obstetric complications, notably retention of a dead fetus, abruptio placentae, and amniotic fluid embolism, are associated with DIC (📖 Disseminated intravascular coagulation, p.488).

Immune thrombocytopenia may occur in pregnancy and women with chronic ITP may become pregnant. Therapeutic considerations must include an assessment of the risk to the fetus of transplacental passage of antiplatelet antibody causing fetal thrombocytopenia and a risk of haemorrhage before or during delivery. There is no reliable parameter for the assessment of fetal risk which, although relatively low, is most significant in women with pre-existing chronic ITP. *Note*: the severity of the mother's ITP has no bearing on the fetal platelet count.

Women with a platelet count <20 $\times$ 10^9/L due to ITP should receive standard prednisolone therapy or IVIg (📖 Immune thrombocytopenia, p.486). If prednisolone fails or is contraindicated, IVIg should be administered and may need to be repeated at 3-week intervals. Splenectomy should be avoided (high rate of fetal loss). Enthusiasm has waned for assessing the fetal platelet count during pregnancy by cordocentesis followed by platelet transfusion. Fetal scalp sampling in early labour is unreliable and hazardous. Delivery should occur in an obstetric unit with paediatric support and the neonate's platelet count should be monitored for several days as delayed falls in the platelet count occur.

1. BCSH Guidelines (2003). Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol*, **120**, 574–96.

Prolonged bleeding after surgery

Prolonged bleeding following surgery often requires urgent haematological opinion and investigation. The cause of the bleeding is usually surgical, rather than due to any underlying systemic bleeding disorder.

History and clinical assessment

- Past history in relation to previous haemostatic challenges e.g. previous surgery, dental extractions. Ask specific questions about whether blood transfusion was required.
- Presence of specific clinical problems e.g. impaired liver or renal function.
- Recent drug history—especially aspirin or NSAIDs which can affect platelet function. Also enquire about cytotoxic drugs and anticoagulants.
- Family history of bleeding problems especially after surgery.
- Nature of the surgery and intrinsic haemorrhagic risks of procedure.
- Whether surgery was elective or emergency (in emergency surgery known risk factors are less likely to have been corrected).
- Check case record or ask surgeon/anaesthetist for information on intraoperative bleeding, technical problems etc.
- Whether surgery involves a high risk of triggering DIC e.g. pancreatic or major hepatobiliary surgery.
- Detailed physical examination is not usually practical but bruising, ecchymoses, or purpura should be assessed especially if remote from the site of surgery.
- What blood products have been used and over how long? Transfusion of several units of RBCs over a short period of time will dilute available clotting factors.
- Review preoperative investigation results and other information available in the record on past procedures and/or investigations.

Investigations

- Ensure samples not taken from heparinized line.
- FBC with platelet count and blood film examination.
- PT, APTT, and fibrinogen.

With normal platelets and coagulation screen bleeding is usually surgical and the patient should be supported with blood and urgent surgical re-exploration undertaken. Platelet function abnormalities may occur with aspirin/NSAIDs, uraemia, or extracorporeal circuits. Prolongation of both PT and APTT suggests massive bleeding and inadequate replacement, DIC, underlying liver disease, or oral anticoagulants. Disproportionate, isolated ↑ in either PT or APTR are more likely to indicate previously undiagnosed clotting factor deficiencies. A low platelet count may reflect dilution and consumption from bleeding or DIC if platelets were known to be normal preoperatively.

Treatment

- Low platelets or platelet function abnormalities: give 1–2 adult doses of platelets stat.
- DIC—give 2 adult doses of platelets and 4 units FFP (10–20 units of cryoprecipitate if fibrinogen low) and recheck PT, APTT, and FBC.

- Anticoagulant effect:
  - Heparin—reverse with protamine sulphate.
  - Warfarin—reverse with FFP or PCC.
- Empirical tranexamic acid or aprotinin may be tried if bleeding continues despite the above.

1. Michel, M., *et al.* (2003). Intravenous anti-D as a treatment for immune thrombocytopenic purpura (ITP) during pregnancy. *Br J Haematol*, **123**, 142–6.

Positive sickle test (HbS solubility test)

The ↓ solubility of deoxyHbS forms the basis of this test. Blood is added to a buffered solution of a reducing agent e.g. sodium dithionate. HbS is precipitated by the solution and produces a turbid appearance. *Note*: does not discriminate between sickle cell *trait* and *homozygous disease*.

Use

This is a quick screening test (takes ~20min), often used preoperatively to detect HbS.

Action if sickle test +ve

- Delay elective operation until established whether disease or trait.
- Ask about family history of sickle cell anaemia or symptoms of SCA.
- FBC and film (Table 1.10).
- Hb electrophoresis, or more commonly HPLC.
- Group and antibody screen serum.

False +ve results

- Low Hb.
- Severe leucocytosis.
- Hyperproteinaemia.
- Unstable Hb.

False –ve results

- Infants <6 months.
- HbS <20% (e.g. following exchange blood transfusion).

Sickle test not recommended as a screening test in pregnancy as it will not detect other Hb variants that interact with HbS e.g. β thalassaemia trait. Standard Hb electrophoresis of at-risk groups should be performed (and of all pregnant women if a high local ethnic population).

Table 1.10 FBC and film features of sickle trait vs. disease

Sickle cell trait	FBC—normal or ↓ MCV and MCH, no anaemia Film normal (may be microcytosis or target cells)
Sickle cell disease	FBC—Hb ~7–8g/dL (range ~4–11g/dL)
	Film—sickled RBCs, target cells, polychromasia, basophilic stippling, NRBC (hyposplenic features in adults)

1. Balasubramaniam, J., *et al.* (2001) Evaluation of a new screening test for sickle cell haemoglobin. *Clin Lab Haematol*, **23**, 379–83.