South Tees Hospitals NHS
NHS Foundation Trust

Haematology Handbook

Division of Specialty Medicine

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Haematology Handbook

Although this document is designed for use in General Practice, it can also be used in hospital medicine as a tool for investigating common haematological abnormalities and for guiding appropriate referral. Within hospital practice, the causes for haematological abnormalities will be skewed towards acute causes (e.g. acute illness, medications) rather than chronic conditions. Co-morbidities should also be taken into account.

Further guidance on thrombosis and anticoagulation can be found on the South Tees Intranet under 'Resources & Guidelines'

This handbook can also be accessed via the internet:
https://www.southtees.nhs.uk/services/pathology/haematology-lab/

Questions about specific patients are best directed to our Advice & Guidance page on the Choose & Book system.

The NICE Clinical Knowledge Summaries also provide a very thorough and useful summary of several of the topics in this handbook including: iron deficiency, B12/folate deficiency, bruising, referral of suspected haematological malignancy, neck lumps, suspected myeloma, sweats, sickle cell disease, erythrocytosis, abnormal platelet counts, deep vein thrombosis (including prevention in travellers), superficial thrombophlebitis, pulmonary embolism and oral anticoagulation.

Contents

Clinical Problem: Anaemia

The most common cause of anaemia will be iron deficiency presenting with a low MCV/MCH and low serum ferritin (see separate protocol). There are however many other possible causes of anaemia so co-morbidities, medication, diet, ethnicity and family history are all potentially relevant.

Initially consider the MCV as this can help narrow down the cause of anaemia:

- *Low MCV*- iron deficiency, some anaemia of chronic disease (otherwise MCV normal) or haemoglobinopathy. Rare sideroblastic anaemia or lead poisoning.
- *Normal MCV*- some anaemia of chronic disease, acute bleeding, mixed iron and B12/folate deficiency and most non-haematinic causes of anaemia.
- *High MCV* – B12/folate deficiency, liver disease, hypothyroidism, some bone marrow disorders (e.g. myelodysplastic syndrome) or increased red cell destruction. A mildly increased MCV can also be seen in pregnancy (~4fl above baseline).

Differential Diagnosis:

- *Iron deficiency*- usually low MCV/MCH. Low serum ferritin, although this can be masked by inflammation. Usually due to chronic blood loss, but consider diet and malabsorption (e.g. coeliac disease). NICE CKS on iron deficiency.
- *Acute bleeding*- may have normal MCV if not yet iron deficient. May have increased reticulocytes. Most commonly gastrointestinal if no obvious source.
- *Anaemia of chronic disease*- normal or low MCV/MCH (often normal MCV, low MCH). Normal or increased ferritin with low serum iron, transferrin & transferrin saturation. True iron deficiency should have a low ferritin and increased transferrin. Raised inflammatory markers due to underling infection, inflammation, malignancy or autoimmune disease. Treat underlying cause.
- *Megaloblastic anaemia* (B12, folate or anti-metabolite drugs) - high MCV and megaloblastic features on blood film. Low serum B12 or folate. See NICE Clinical Knowledge Summary https://cks.nice.org.uk/anaemia-b12-and-folate-deficiency
- *Increased red cell destruction*- inherited or acquired haemolytic anaemia with raised reticulocytes, bilirubin and LDH. Positive Direct Coombs test if autoimmune. Blood film may show spherocytes. Needs Haematology referral.
- *Bone marrow disorder*– blood film appearances may be suggestive. May also have low WCC and PLT. Many possibilities - needs Haematology referral.
- *Medications*- e.g. GI bleeding with NSAIDs; bone marrow suppression with chemotherapy, azathioprine or methotrexate; red cell haemolysis with dapsone or sulphasalazine. Many other possibilities.
- *Renal impairment*- often with normal MCV. Incidence increases as renal function declines, although the cause of renal impairment is also relevant (e.g. diabetic nephropathy tends to be more anaemic than expected from the eGFR alone). If suspected then refer to renal team to consider erythropoietin.

- *Liver disease*- often with high MCV, although could be normal, or low if concurrent iron deficiency, e.g. GI bleeding due to varicies.
- *Endocrine*- thyroid, parathyroid, pituitary or adrenal dysfunction.
- *Physiological* - a mild drop in haemoglobin is normal in pregnancy and with increasing age (e.g. if age 70+ then the lower end of the normal range drops to 105g/L in females and 115g/L in males).

Examination:

- Depends on suspected cause.
- Include abdominal examination and rectal exam if considering iron deficiency anaemia or occult bleeding (rectal exam if tenesmus or history of fresh bleeding).
- Include examination for lymphadenopathy, splenomegaly and hepatomegaly if considering a haematological disorder.

Baseline investigations:

- Depending on suspected cause, additional investigation may include:
    - *Low MCV*: blood film, U+E, LFT, ferritin / iron studies, CRP. Screening for a haemoglobinopathy is normally carried out automatically by the laboratory if the red cell indices and ethnic origin are suggestive.
    - *Normal MCV:* blood film, reticulocytes, U&E, LFT, ferritin, B12/folate, CRP.
    - *High MCV*: blood film, reticulocytes, U+E, LFT, TSH, B12/folate.
- Serum immunoglobulins and serum free light chains (more sensitive than urine Bence-Jones protein) if myeloma is being considered.
- Consider HIV serology in patients with any unexplained cytopenia.

Referral:

Consider Haematology referral if:

- Suspected primary haematological disorder (bone marrow disorder, haemolytic anaemia).
- Unexplained anaemia with haemoglobin <100g/L (female) / <110g/L (male), especially if progressive or symptomatic.
- We do not routinely see haemoglobinopathy carriers, however an information sheet is sent from the laboratory for all new cases.
- Other specialty referrals based on suspected cause. If anaemia of chronic disease but no obvious explanation for the inflammatory process then consider referral to General Medicine.

Clinical Problem: High haemoglobin / haematocrit

Investigation is suggested if the haematocrit is persistently (>2 months, preferably repeated without tourniquet) >0.52 (male) or >0.48 (female). This may be due to increased red cell mass (true polycythaemia) or reduced plasma volume (apparent polycythaemia). If the haematocrit is >0.6 (male) or >0.56 (female) then it can be assumed that there is a true increase in red cell mass.

Differential Diagnosis:

- Apparent polycythaemia – may be due to a variety of causes such as diuretics, heavy smoking or alcohol, dehydration, stress, oedema, hypertension, obesity.
- True polycythaemia
    - *Reactive to hypoxia*- e.g. pulmonary disease, carbon monoxide / heavy smoking, sleep apnoea or congenital cyanotic heart disease.
    - *Abnormal high erythropoietin*- e.g. secondary to various tumours (e.g. renal carcinoma or hepatoma), renal transplant or renal artery stenosis.
    - *Polycythaemia vera*- bone marrow disorder with uncontrolled red cell proliferation. Usually positive for JAK2 V617F mutation. Associated with thrombotic and haemorrhagic complications. May be associated with generalised itch (classically after hot shower or bath), splenomegaly or raised WCC / PLT.
    - *Endocrine*- Cushing's syndrome, Conn's syndrome, phaeochromocytoma or androgens (including *testosterone supplements and anabolic steroids*).
    - *Inherited* erythropoietin or haemoglobin variants (rare).

Examination:

- Features of cardiac or pulmonary disease.
- Features of hyperviscosity (fatigue, headache, slowed thought, muscosal / retinal bleeding, blurred / double vision, chest / abdominal pain, myalgia).
- Splenomegaly suggests polycythaemia vera, although this is not consistent.

Baseline investigations:

- FBC, U+E, LFT, ferritin (a high haematocrit despite low ferritin suggests polycythaemia vera. DO NOT give iron replacement).
- Review cardiovascular risk factors, although primary aspirin prophylaxis is not recommended unless PRV.
- Further tests as indicated by history, e.g. oxygen saturations, PFT, CXR.
- Approximately 98% of patients with polycythaemia vera will have a JAK2 V617F mutation or a JAK2 exon 12 mutation (testing in WebICE "Pathology > Haemat/Coag > JAK2/MPL/CALR > JAK2 PRV").

Referral:

- Review cardiovascular risk factors for all patients, regardless of cause
- Haematocrit persistently >0.52 (male) or >0.48 (female) without obvious cause or with suspicion of polycythaemia vera. URGENT referral if features of hyperviscosity.
- Other referrals as directed by suspected cause, e.g. may benefit from long-term oxygen therapy or ACE-inhibitors if chronic hypoxia.

References:

- McMullin MF, et al. A guideline for the investigation and management of polycythaemia vera. Br J Haematol 2018; doi.org/10.1111/bjh.15648
- NICE Clinical Knowledge Summary. Polycythaemia / Erythrocytosis (September 2020). https://cks.nice.org.uk/polycythaemiaerythrocytosis

Clinical Problem: Iron deficiency

Iron deficiency often shows as a hypochromic microcytic anaemia (low MCH and MCV) with a low ferritin value.

Diagnostic problems can occur in the presence of an acute or chronic inflammatory condition. This can cause a falsely elevated ferritin despite true iron deficiency. It can also cause anaemia of chronic disease with a mildly low MCV/MCH and low serum iron despite normal iron stores. This picture may become easier to interpret if the underlying disease can be controlled.

Anaemia with a markedly low MCV/MCH can also be seen with a haemoglobinopathy. Consider if the MCV/MCH is lower than expected, normal ferritin and usually non-Caucasian ethnicity. The laboratory will normally automatically add haemoglobinopathy screening in this situation.

Differential Diagnosis:

- *Blood loss*- most commonly gastrointestinal (NSAIDs or pathological lesion) or gynaecological / menstrual. Unusual causes such as hookworm after travel.
- *Malabsorption*- such as coeliac disease, gastrectomy / gastric bypass.
- *Poor intake*- unusual as a sole cause, except with extreme diets.
- *Pregnancy* – common, although serum ferritin falls in 2-3rd trimesters due to dilution and redistribution. A ferritin value <30ug/L should prompt replacement therapy.

Examination:

- Abdominal examination, including rectal exam if tenesmus or bleeding.
- Gynaecological examination as appropriate.

Baseline investigations:

- FBC, blood film (elliptocytes or pencil cells suggest iron deficiency), ferritin. Check inflammatory markers if ferritin unexpectedly normal (if concurrent inflammation, a ferritin >100ug/L normally excludes iron deficiency except in severe inflammation, while a value <50ug/L is suspicious but not diagnostic).
- Coeliac serology in all cases of iron deficiency anaemia
- Urinalysis
- Consider the possibility of atrophic gastritis (anti-parietal cell / anti-intrinsic factor antibodies) or *H. pylori* infection (faecal antigen test) as a cause of unexplained or refractory iron deficiency anaemia.
- Faecal occult blood / faecal immunochemical testing neither confirms nor excludes gastrointestinal pathology. Stool parasite testing may be suggested based on travel history.

Treatment:

- Standard treatment is ferrous sulphate 200mg OD or ferrous fumarate 210mg OD until anaemia resolves (Hb should rise by 20g/L in 3-4 weeks), then a further 3 months to build iron stores. Monitor blood count 3 monthly for 1 year.
- If intolerant of ferrous sulphate / fumarate then try alternate iron preparations (e.g. ferrous gluconate). These may be better tolerated although the iron content may be lower. Avoid slow release or enteric coated preparations.

- Iron is also better tolerated (although less well absorbed) if taken with food. Avoid taking with calcium or phosphate containing foods / drinks / supplements, cereals, eggs, tea / coffee or high fibre foods.
- A small glass of orange juice (or ascorbic acid 250mg) may improve absorption, while medications to reduce gastric acid reduce absorption.

Referral:

- The majority of patients will require referral to Gastroenterology to look for an underlying cause. 2WW if age >60yr and unexplained IDA, positive FOB/FIT test or suspicious clinical features (eg. consider urgent referral if <50yr and rectal bleeding).
- Consider Gynaecology referral based on symptoms. 2WW if age >55yr and post-menopausal bleeding
- Haematology referral if considering parenteral iron therapy- i.e. unresponsive or intolerant of oral iron. Patients will still need referral to Gastroenterology / Gynaecology to identify and treat the underlying cause.

References:

- British Society of Gastroenterology Guidelines. Snook J, Bhala N, Beales ILP, et al. Gut Epub ahead of print. doi:10.1136/ gutjnl-2021-325210
- NICE Clinical Knowledge Summary. Anaemia- iron deficiency (November 2021). https://cks.nice.org.uk/anaemia-iron-deficiency

Clinical Problem: High ferritin

In healthy subjects the serum ferritin concentration correlates with iron stores, however high levels do not necessarily reflect iron overload. Ferritin behaves as an acute phase reactant in many inflammatory diseases. Tissue damage, particularly to the liver, can also release large amounts of ferritin into the plasma.

Differential diagnosis:

- *Acute phase reaction*- infection, inflammation or malignancy.
- *Release of ferritin by tissue damage*, *especially to iron rich organs*- e.g. chronic liver disease (including alcoholic liver disease and cirrhosis) or splenic infarction.
- *True iron overload*: genetic haemochromatosis, iron overload secondary to repeated blood transfusions, massive ineffective erythropoeisis (thalassaemia, sideroblastic anaemia), porphyria cutanea tarda or rare genetic causes of iron overload.

Baseline investigations:

- FBC, LFT, CRP, iron studies (in particular **fasting** transferrin saturation). Repeat serum ferritin levels >3 months apart. If the fasting transferrin saturation is normal then this strongly suggests a falsely elevated ferritin rather than true iron overload.
- Genetic screening for haemochromatosis is indicated if positive family history OR if persistently raised ferritin with high transferrin saturation.
- If persistently raised ferritin with raised CRP and / or normal transferrin saturation then consider alternate causes.

Referral (see pathway on next page):

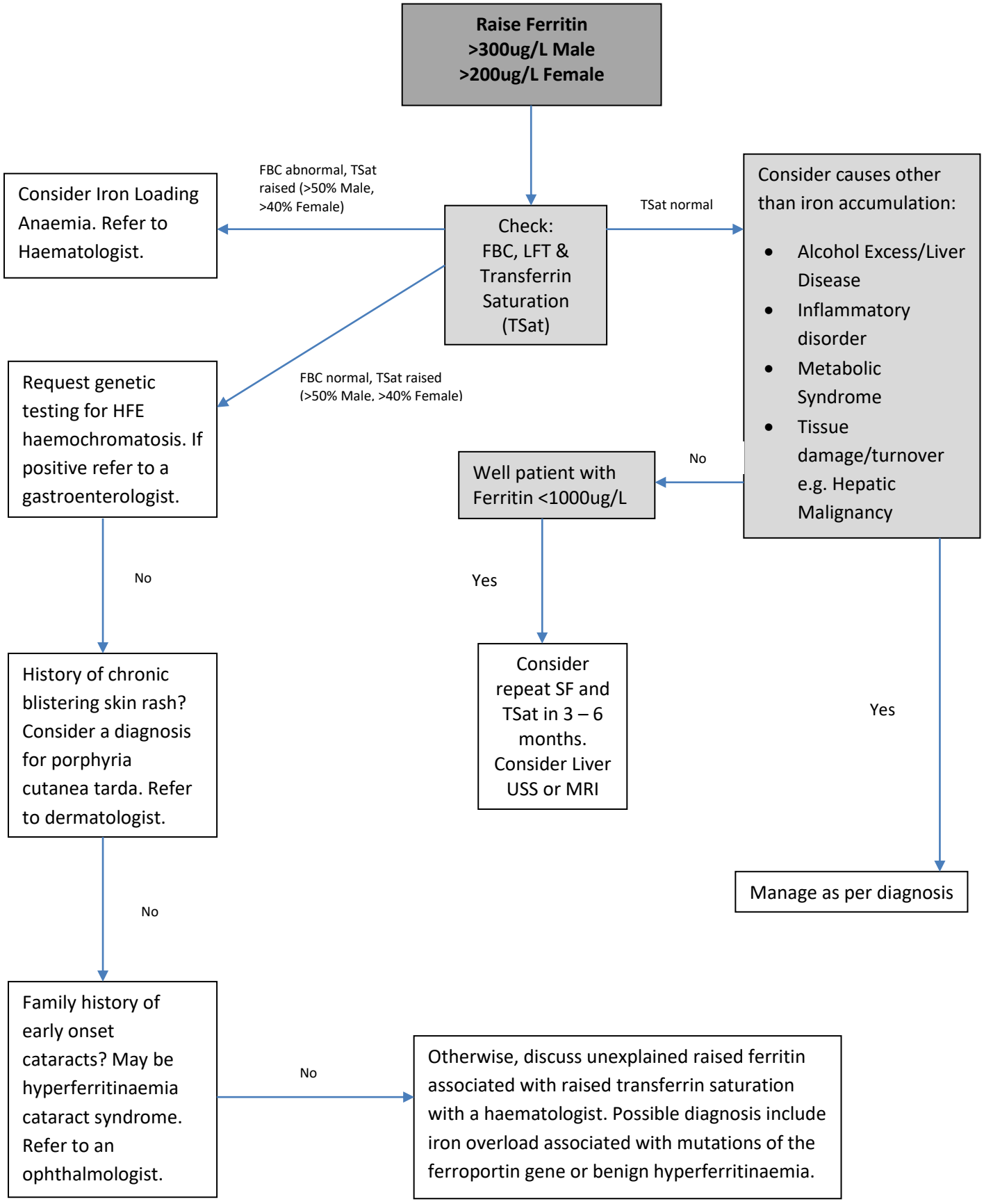
- If genetic haemochromatosis confirmed then patient management is usually overseen by Gastroenterology, although venesections are undertaken by Haematology. A referral to Gastroenterology would also be appropriate in patients found to have suspected liver disease on investigation of a high ferritin value.
- If family screening is required for genetic haemochromatosis (parents, siblings, children) then this can be undertaken in General Practice. Screening includes ferritin, transferrin saturation and possibly genetic studies. If genetic counselling is required then we suggest refer to the Clinical Genetics service.
- For raised serum ferritin associated with an acute phase response then the underlying condition may require further investigation and management.
- Refer to Haematology if true iron overload (raised ferritin and transferrin saturation) with uncertain cause (e.g. negative tests for genetic haemochromatosis) or known haemochromatosis to commence venesection.

References

- Cullis JO, Fitzsimmons EJ, et al. Investigation and management of a raised serum ferritin. Br J Haematol 2018; 181: 331-340

- Fitzsimmons EJ, Cullis JO, et al. Diagnosis and therapy of genetic haemochromatosis (review and 2017 update). Br J Haematol 2018; 181: 293-303

Assessment of an unexpected finding of a raised Ferritin level in primary care



Clinical Problem: Macrocytosis (high MCV)

The most common cause of a high MCV is alcohol excess, however other causes should be considered.

Differential diagnosis:

- *Artefact* – e.g. delayed sample processing or cold haemagglutinins.
- *Physiological* – mild macrocytosis normal in pregnancy (approx. 4fl rise from baseline).
- *Reticulocytosis* – reticulocytes are ~25% larger than normal RBC. High count suggests a marrow response to red cell destruction or blood loss.
- *Excess alcohol intake* - target cells or stomatocytes on a blood film report suggests alcohol excess or liver dysfunction.
- *Abnormal liver function* – often anaemic and low platelets if advanced.
- *Hypothyroidism* - can also give a normocytic anaemia
- *Vitamin B12 or folate deficiency* - hypersegmented neutrophils and / or oval macrocytes on a blood film report suggest a megaloblastic anaemia.
- *Drugs* e.g. hydroxycarbamide, azathioprine and many chemotherapy agents. Can give the appearances of a megaloblastic anaemia.
- *Bone marrow disorder*, e.g. myelodysplastic syndrome – blood film may be suggestive and may also have leucopenia or thrombocytopenia.

Baseline investigations:

- Repeat FBC (ensure sample gets to laboratory on same day), blood film, reticulocytes, LFT, TFT, B12 / folate.
- Note that a mild reduction in vitamin B12 levels can be seen as an artefact in pregnancy or women taking COC / HRT. There is also significant overlap in vitamin B12 levels between those with true deficiency and those with a level at the lower end of the normal range. A trial of therapy may be necessary- the MCV should normalise in 3 months if due to B12 deficiency.

Vitamin B12 / folate:

- NICE have produced a very useful Clinical Knowledge Summary. https://cks.nice.org.uk/anaemia-b12-and-folate-deficiency

Referral:

- Further management / referral based on suspected cause.
- Consider haematology referral if suspected red cell haemolysis or bone marrow disorder.
- We do not see patients with an unexplained macrocytosis but an otherwise normal blood count. These patients can be monitored in General Practice with 6-12 monthly blood counts. Refer if develop cytopenias.

Clinical Problem: Low White Cell Count (<4 x10^9/L)

A low white cell count (WCC) is most commonly seen as a transient feature following viral infection. Where there has been no recent history of infection, or where the low WCC is persistent, then other causes should be considered.

Differential Diagnosis
Neutropenia:

- *Constitutional* – Ethnic variation in Black Africans and some Arab or Mediterranean patients includes a neutrophil count down to 0.8 x10^9/L.
- *Congenital* – uncommon but consider in young patients if no previous normal blood counts. Variable inheritance and severity.
- *Post-viral*- may persist for several weeks and be followed by a prolonged autoimmune neutropenia lasting for several months.
- *Drug-induced*- long list of possibilities: especially chemotherapy; phenothiazines and other anti-psychotics; anti-epileptics; anti-arrhythmics, anti-thyroid drugs; antibiotics; ACE-inhibitors; sulphasalazine and NSAIDs.
- *Autoimmune*- may be seen alone or with other autoimmune disease.
- *Vitamin B12 / folate deficiency*
- *Bone marrow failure*- may give isolated neutropenia but more commonly associated with anaemia and / or thrombocytopenia.
- Unusual causes such as Felty's syndrome.

Lymphopenia, is non-specific and has many possible causes including:

- *Infection*- acute or chronic infection, especially HIV or TB
- *Autoimmune disease / connective tissue disease*
- *Steroid therapy*
- *Cardiac failure*
- *Malignancy*

Examination:

- Should include baseline observations. Examine for hepato-splenomegaly and for lymphadenopathy. Local signs of infection

Baseline investigations:

- Blood film should be examined. Consider autoimmune screen or viral serology (including HIV) as appropriate.

Management:

- Consider switching non-essential medications if suspicion of drug-induced neutropenia. Neutrophil count should begin to recover within a few days / weeks depending on the medication. If neutrophils >1.0 x10^9/L with no increase in infections then I would not change important medications.
- If neutrophil count <1.0x10^9/L then patients should report any fever or symptoms of infection immediately and may need hospitalisation for intravenous broad spectrum antibiotics.

Referral:

- Consider Haematology referral if:
  - Unexplained neutropenia <1.0x10^9/L.
  - Unexplained neutropenia <1.5 x10^9/L if persistent or with other cytopenias.
- We do not routinely investigate isolated lymphopenia.

Clinical Problem: Raised White Cell Count (see separate sheet for lymphocytosis)

Note the particular cell line increased, i.e. neutrophilia, monocytosis, eosinophilia or lymphocytosis.

Differential Diagnosis:

Neutrophilia

- *Reactive* - most commonly seen as a reactive feature secondary to infection, inflammation, trauma or malignancy. May have increased monocytes and platelets. May develop anaemia of chronic disease.
- *Medication* - e.g. corticosteroids or G-CSF. Cigarette smoking
- *Post-splenectomy*
- *Chronic myeloid leukaemia* (CML) – rare condition, often very high white cell count with coexisting splenomegaly, eosinophilia, basophilia and primitive cells in the peripheral blood. These characteristic features will usually be picked-up by the haematology laboratory.

Monocytosis

- *Reactive* - most commonly seen as a reactive feature, often with a neutrophilia.
- *Chronic myelomonocytic leukaemia* (CMML) – often with cytopenias and dysplastic features on a blood film.

Eosinophilia

- Most common causes are allergy / atopy or drug reaction.
- Less common causes are wide-ranging, including parasitic infection, tuberculosis, HIV, malignancy, connective tissue disease / vasculitis, sarcoidosis, skin disease or pulmonary disease (e.g. allergic bronchopulmonary aspergillosis, Loffler's syndrome). Can be seen in haematological malignancies.

Examination:

- Difficult to give specific recommendations given the wide-range of possible causes.
- Examine for hepatomegaly and splenomegaly if suspect CML or CMML.
- If unexplained eosinophilia then consider eosinophil related organ damage which can cause cardiac, pulmonary, gastrointestinal, renal, musculoskeletal, neurological and skin damage.

Baseline investigations:

- FBC, blood film, U&E, LFT, inflammatory markers.
- Other investigations as directed by symptoms and suspected underlying cause.

Referral:

- Consider Haematology referral if:
  - Suspicion of haematological malignancy - chronic myeloid leukaemia or chronic myelomonocytic leukaemia.
  - Sustained eosinophilia (>1.5 $x10^9$/L) in absence of a secondary cause or with suspicion of associated end organ damage.
- If unexplained inflammatory process then consider referral to General Medicine, or other speciality based on any localising features.

Clinical Problem: Lymphocytosis (>4 x 10^9/L)

A mild lymphocytosis has two main causes, either reactive (especially in children) or related to a lymphoproliferative disorder, e.g. CLL (especially in the elderly).

Differential Diagnosis:

- *Normal* - mild lymphocytosis is normal post-splenectomy or in children <5 years.
- *Viral infection*
- *Bacterial infection* - especially pertussis or chronic tuberculosis.
- *Low-grade lymphoproliferative disorder* – blood film report comment such as `smear cells` or 'small, mature lymphocytes' may point towards this diagnosis.

Examination:

- Look for evidence of recent infection.
- Check for lymphadenopathy, hepatomegaly or splenomegaly.

Baseline investigations:

- Consider likelihood of viral aetiology and relevance of viral serology.
- If isolated lymphocytosis with no other disturbance in blood counts then repeat in 6-8 weeks to see if resolved.

- If persisting lymphocytosis >10 x10^9/L, or if blood film comments suggest a lymphoproliferative disorder, then consider sending a second EDTA (purple) tube to haematology marked `immunophenotyping – chronic panel` to assess for a clonal population.

Note that the diagnosis of an asymptomatic early-stage lymphoproliferative disorder (e.g. CLL) generally requires no treatment and often does not influence the life expectancy of an elderly patient. Consider the possibility of monitoring the blood count 6-12 monthly in General Practice rather than causing undue concern to the patient by confirmatory testing.

Referral:

Consider Haematology referral if:

- Immunophenotyping confirms lymphoproliferative disorder.
- Associated anaemia or thrombocytopenia.
- Lymphadenopathy, hepatomegaly or splenomegaly.
- B-symptoms – unexplained weight loss, fevers, drenching night sweats, recurrent infections, extreme lethargy. It would be unusual to have significant symptoms with a lymphocyte count <20-30 x10^9/L and no palpable lymphadenopathy.

Patients who are referred to ourselves with early, asymptomatic, low risk disease may be offered ongoing community follow-up. See following letter for recommendations on monitoring and re-referral.

Diagnosis: Chronic lymphocytic leukaemia (CLL)

Dear Doctor,

We have reviewed the above patient in our haematology clinic and have diagnosed chronic lymphocytic leukaemia (CLL). Patients with early stage, low-risk disease tend to progress very slowly and may not require any treatment for many years, possibly never. The annual risk of significant progression is approximately 4%.

We would like to discharge the patient from regular clinic follow up and would be grateful if you could review the patient 6 monthly to check the following:

- Full blood count
- Check symptoms and examine for lymphadenopathy and hepatosplenomegaly

If there are any of the following changes, we would be grateful if you could refer the patient back to haematology clinic:

- Drop in haemoglobin to <105g/dl, or >20g/dL below baseline, which is not due to haematinic deficiency.
- Drop in platelets to $<100x10^9$/l.
- Doubling of the lymphocyte count in <12 months (to an absolute value >25 x 10^9/l, and not due to acute transient cause such as infection), or absolute lymphocyte count >100 x 10^9/l.
- Development or progression of hepatomegaly, splenomegaly or lymphadenopathy.
- Unexplained weight loss of >10% in 6 months.
- Unexplained fevers or drenching night sweats.
- Low IgG levels with recurrent (>3/yr) proven bacterial infections

Patients should receive:

- Annual influenza vaccination (ideally also household contacts).
- Pneumococcal vaccination: patients should be offered a single dose of Prevenar 13 (PCV13) followed by Pneumovax II (PPV23) at least two months later, irrespective of previous pneumococcal vaccinations. If Pneumovax has already been administered, then wait at least six months afterwards to give Prevenar 13. Going forward, give 5-yearly boosters with Pneumovax II.
- COVID vaccination as per national guidance (ideally also household contacts).
- Live vaccines are not recommended (yellow fever, polio, MMR). Note, the standard varicella zoster vaccine [Zostavax] is a live vaccine, however Shingrix is available as an alternative.

Yours

Clinical Problem: Low platelets (platelets <150 x 10^9/L)

A low platelet count is defined a count <150 x10^9/L. This is usually asymptomatic until the platelet count falls <50 x10^9/L, with spontaneous bleeding being more common once <20-30 x10^9/L.

Symptoms tend to include bruising, petechiae and mucosal bleeding, however more serious bleeds, e.g. intra-cerebral, can also occur. Due to the risk of bleeding, drugs such as NSAIDs or anticoagulants should generally be avoided when the platelet count is <70 x10^9/L.

Differential diagnosis:

- *Spurious*: e.g. platelet aggregation in an EDTA blood sample.
- *Infection related*, especially viral, including HIV.
- *Alcohol excess*
- *Liver disease / splenomegaly*
- *Autoimmune*, especially if history of autoimmune disease, e.g. SLE.
- *Vitamin B12 / folate deficiency*
- *Chronic DIC*, e.g. malignancy
- *Drug effect or post-radiotherapy*
- *Bone marrow failure*- for example haematological malignancy or metastatic solid tumour. Often with low haemoglobin / white cell count and suspicious blood film features.

Examination should include assessment of haemorrhagic features, e.g. bruising, petechiae or mucosal bleeding. Also check for lymphadenopathy, hepatomegaly or splenomegaly.

Baseline testing: FBC, blood film, coagulation screen (PT, APTT, fibrinogen), U+E, LFT, TSH. Patients should be considered for HIV testing, especially if no other cause of thrombocytopenia is apparent.

Referral:
Consider Haematology referral if:

- Co-existing unexplained anaemia or leucopenia.
- Immediate referral if platelet count <20 x10^9/L or active bleeding
- Urgent referral if platelet count <20-50 x10^9/L (repeat immediately to ensure not a sample error).
- Unexplained platelet count 50-100 x10^9/L for >3 months.

Haematological referral is inappropriate where there is a known non-haematological cause, for example metastatic solid tumour or liver disease.

References:

- NICE CKS. Platelets – Abnormal Counts and Cancer (June 2021)

Clinical Problem: High platelets (platelets >450 x 10^9/L)

A high platelet count is most often reactive, in the same way that a plasma viscosity, CRP or ESR may be elevated. If there is no obvious reactive cause then other possibilities should be considered.

Differential diagnosis:

- *Normal* – post-splenectomy
- *Reactive* to infection, inflammation or malignancy*. May be associated with neutrophil leucocytosis and anaemia of chronic disease.
  **Thrombocytosis can be a marker for cancer, including lung, endometrial, gastric, oesophageal or colorectal.*
- *In response to blood loss or trauma*. If chronic blood loss may also see iron deficiency anaemia.
- *Related to a myeloproliferative disorder*, e.g. essential thrombocythaemia (isolated thrombocytosis); polycythaemia vera (also raised haematocrit); or proliferative phase myelofibrosis (splenomegaly often a feature). Most patients will have a JAK2, CALR or MPL mutation (WebICE "Pathology > Haemat/Coag > JAK2/MPL/CALR > JAK2 ET/MF").

Examination:

- Examine for hepatomegaly or splenomegaly.

Baseline investigations:

- FBC, blood film, U+E, LFT, calcium, inflammatory markers
- Ferritin if anaemia (may be falsely elevated if raised inflammatory markers)
- Chest x-ray
- Other investigations depending on history / examination and clinical suspicion

Referral:

Consider haematology referral if:

- Persistently raised platelets (>450x10^9/L) with no obvious underlying cause / normal inflammatory markers.
- Splenomegaly or blood film suggestion of a primary bone marrow disorder.

If a raised platelet count is part of an unexplained inflammatory condition (e.g. raised WCC, anaemia of chronic disease, raised inflammatory markers) then consider referral to General Medicine.

References:

- Harrison CN, *et al*. Guideline for investigation and management of adults and children presenting with a thrombocytosis. Br J Haematol 2010; 149: 352-375.
- Harrison CN et al. Diagnostic pathway for the investigation of thrombocytosis. Br J Haematol 2013; 161: 604-606
- NICE CKS. Platelets – Abnormal Counts and Cancer (June 2021)

Clinical Problem: Paraprotein

A paraprotein is a monoclonal band of immunoglobulin found in the serum or urine. In the urine it is uncommon to find intact immunoglobulin, as this is a large unfiltered protein, however immunoglobulin light chains can be identified if present above the renal threshold for reabsorption (Bence-Jones protein). Free light chains can also be detected in the serum (SFLC) and this is now a more sensitive test than BJP.

Monoclonal immunoglobulin is produced by a clonal B-lymphocyte population which can be benign (e.g. monoclonal gammopathy of undetermined significance [MGUS]) or malignant (e.g. multiple myeloma or B-cell lymphoma). An IgM paraprotein is extremely rare in myeloma but can be seen as a MGUS or B-cell lymphomas.

Testing for a paraprotein is normally performed when there is a concern over underlying multiple myeloma (e.g. unexplained bone pain, pathological fracture, anaemia, renal impairment, hypercalcaemia, increased total protein or decreased immunoglobulins) or to investigate an unexplained raised plasma viscosity or ESR. Testing is performed by serum protein electrophoresis and free light chain analysis (SFLC), present in ~99% cases myeloma. Non-directed screening is not recommended.

Differential Diagnosis:

- *MGUS*- benign condition found in 3% of the population over the age of 50 years or 5% of those over 70 years. Risk of progression ~ 1-2% per year.
- *Multiple myeloma* – 25% have no serum paraprotein (abnormal SFLC ratio only). <1% have no serum paraprotein or abnormal SLFC ratio.
- *Solitary plasmacytoma* – solitary area of plasma cell infiltration which can be present in the bone or as an extramedullary mass.
- *Amyloidosis*- rare disorder but poor outlook as often diagnosed late due to non-specific symptoms. Amyloid protein deposition in various organs including heart, liver, kidneys, gastrointestinal tract, peripheral nerves and spleen. Features can include proteinuria (can be nephrotic), non-dilated cardiomyopathy, hepatomegaly and autonomic or peripheral neuropathy. Requires specialist investigation if suspected.
- *B-cell lymphoproliferative disorder*- usually presents with features such as lymphadenopathy, or systemic symptoms such as weight loss or drenching night sweats.
- Rare disorders such as osteosclerotic myeloma (POEMS syndrome) or heavy chain disease.

Examination:

- Examine for lymphadenopathy and splenomegaly.

Baseline investigations:

- FBC, plasma viscosity, U+E, calcium, serum immunoglobulins and serum free light chains (SFLC).
- Serum free light chains measurement is looking for a discrepant kappa / lambda light chain ratio. If both light chains are raised, but the ratio remains normal, then this is usually reactive or due to renal impairment.
- If patients do have renal impairment then the normal ratio will be altered (renal reference range 0.37 – 3.1) due to differing excretion of kappa and lambda light chains.

- Borderline SFLC ratios of 0.2 – 5.0 are often also benign, consider referral only if clinical concern of haematological malignancy.
- As immunoglobulins and light chains will be increased in acute illness, repeat mildly abnormal results after resolution of illness (unless levels meet referral criteria below).
- Any symptoms of bone pain should be investigated by plain radiography.

Distinguishing MGUS from symptomatic multiple myeloma can largely be done with simple tests available in the community. This involves looking for signs of myeloma-related organ damage such as anaemia, hypercalcaemia, renal impairment, bone lesions, symptomatic hyperviscosity or recurrent bacterial infections.

Referral:

- 2 week wait: symptoms or signs suggestive of a serious paraprotein-related disorder (e.g. myeloma, amyloidosis, plasmacytoma, lymphoma) rather than MGUS, e.g. paraprotein with unexplained anaemia, renal impairment, hypercalcaemia, bone lesions, splenomegaly or lymphadenopathy.
- Lytic lesions or unexpected osteoporosis on plain radiography.
- Refer if IgG paraprotein >15 g/l; IgA or IgM paraprotein >10 g/l; any value of IgD or IgE paraprotein; kappa or lambda light chains >1000; or SFLC ratio of either <0.01 or >100.
- Any patient with a newly discovered paraprotein, regardless of the absolute value, if there is clinical concern (routine referral).

URGENT REFERRAL if acute kidney injury, symptomatic hypercalcaemia (Ca >2.9 mmol/L), hyperviscosity or suspicion of spinal cord compression.

Follow-up of MGUS:

Over time, MGUS may progress or the underlying condition may reveal itself, so long-term follow up is required. Progression is not just to multiple myeloma, but also to other paraprotein disorders (e.g. B-cell lymphoma, amyloidosis). The approximate yearly risk of disease progression is about a tenth of the paraprotein value in grams per litre (e.g. 10 g/l = about 1% per year) and the vast majority of patients will therefore die from unrelated conditions.

If patients are being monitored in the community, recommendations are for blood testing (FBC, U+E, LFT, calcium, immunoglobulins) initially 3 monthly, and up to 6 monthly if the paraprotein is stable.

The attached policy gives full details of follow-up and re-referral criteria:

Low risk MGUS Pathway.docx

References:

- Bird J, et al. UK Myeloma Forum (UKMF) and Nordic Myeloma Study Group (NMSG): Guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS). Br J Haematol 2009; 147: 22-24
- NICE Clinical Knowledge Summary. Multiple Myeloma. April 2022 https://cks.nice.org.uk/multiple-myeloma

Clinical Problem: Polyclonal immunoglobulins / hypergammaglobulinaemia

Raised levels of immunoglobulins are a common finding as part of an acute phase response. If a distinct monoclonal protein is detected then refer to separate protocol for paraprotein investigation.

Differential Diagnosis:
The list of potential causes is vast and includes many infectious, inflammatory, malignant or autoimmune conditions.

Particularly high levels (IgG >30g/L) are most commonly associated with:

- *Liver disease* (~50%), inc. autoimmune hepatitis, viral hepatitis, primary biliary cirrhosis or alcohol induced liver disease
- *Connective tissue disease* (~25%), inc. Sjögren syndrome, rheumatoid arthritis or systemic lupus erythematosus
- *Solid tumour* (~5%)
- *Chronic infection* (~5%) including HIV
- *Haematological disorders* (<5%) such as lymphoma or leukaemia

Examination:
Given the wide range of possible causes a thorough general examination should be performed. The finding of lymphadenopathy should raise concern over an underling haematological malignancy, however, as shown above, this is not a common cause of a polyclonal gammopathy.

Baseline investigations:

- It is difficult to give specific recommendations given the wide range of possible causes so investigations should be led by clinical features.
- If no obvious cause then as a baseline consider: FBC, U+E, LFT, calcium, CRP and autoimmune screen. Consider viral serology (hepatitis, HIV). Consider radiological imaging such as CXR and abdominal ultrasound.

Consider Haematology referral if:

- Features suggesting haematological malignancy (laboratory results, signs or symptoms).
- If no obvious cause but systemically unwell then consider referral to General Medicine.

References:

- Dispenzieri A, et al. Retrospective cohort study of 148 patients with polyclonal gammopathy. Mayo Clinic Proc 2001; 76: 476-487.

Clinical Problem: Raised erythrocyte sedimentation rate (ESR) or plasma viscosity (PV)

A raised plasma viscosity (PV) or erythrocyte sedimentation rate (ESR) is a non-specific marker of underlying infection, inflammation, trauma or malignancy. High values can also be seen in multiple myeloma due to the serum paraprotein.

Note that the ESR, and less so the PV, are both affected by patient age and pregnancy. The ESR is also affected by the age of the sample (should be received within 4 hours) and by the haemoglobin value (can be falsely high if anaemia).

Differential diagnosis:

- *Acute or chronic infection*, including tuberculosis or HIV.
- *Other inflammatory disorders*, e.g. inflammatory bowel disease, sarcoidosis.
- *Malignancy-* solid organ or haematological (esp. multiple myeloma).
- *Collagen disorders*, e.g. rheumatoid arthritis, SLE, temporal arteritis, vasculitis.

Baseline investigations:

- Full history and examination to look for potential cause.
- If no obvious explanation then screen for multiple myeloma: FBC, U+E, serum calcium, serum immunoglobulins & serum free light chains. Plain x-ray if bone pain.

  Note that polyclonal raised immunoglobulins can be seen with an underlying inflammatory condition, but do not suggest multiple myeloma (see separate protocol for polyclonal hypergammaglobulinaemia).

- Consider occult infection, inflammation or malignancy. 'Routine' investigations such as CXR, autoimmune screen and urinalysis are often performed however investigations should be led by the clinical history.

Referral

Haematology referral if:

- Features suggesting haematological malignancy / multiple myeloma (laboratory results, signs or symptoms).
- Serum paraprotein or significantly abnormal SFLC ratio. See paraprotein investigation. Urgent referral if hyperviscosity symptoms – e.g. headaches, lethargy, visual disturbance / retinal haemorrhages, breathlessness (often only seen if PV >4 cp).

An unexplained persistent raised PV without the above features may warrant referral to General Medicine if there is clinical concern.

Clinical Problem: Lymphadenopathy

Palpable lymph nodes are most commonly noted in the neck, axillae or groin. The most common cause will be inflamed lymph nodes in response to a local infection, however if no obvious inflammatory cause is present, or if nodes are persistent, then other causes should also be considered. Concerning features include unexplained fever, night sweats, shortness of breath, pruritus, weight loss or alcohol-induced lymph node pain.

Differential diagnosis:

- *Infection*: bacterial, viral, parasitic or fungal. Often tender. Can be acute or chronic e.g. tuberculosis, HIV.
- *Local skin disease*
- *Haematological malignancy*, esp. lymphoma or leukaemia
- *Metastatic solid tumour* e.g. Virchow's node in left supraclavicular fossa from lung or gastrointestinal malignancy
- Others: collagen disorder (SLE, RA), sarcoidosis, Kikushi disease and other rarer causes.

Investigation:

- FBC (urgent <48 hours), blood film and inflammatory markers.
- Viral serology, if appropriate (e.g. EBV, CMV, toxoplasma, HIV)
- NICE guidelines also recommend as urgent chest x-ray with persistent cervical or supraclavicular lymphadenopathy.

Examination:

- Look for local cause, e.g. infection, skin disorder.
- Examine for cervical, supraclavicular, axillary and inguinal lymph nodes.
- Palpate abdomen for hepatomegaly or splenomegaly.

Referral:

- Features suggesting haematological malignancy may include drenching night sweats, fever, shortness of breath, weight loss (>10% within 6 months), cytopenias, generalised itch, alcohol-induced nodal pain (rare but associated with Hodgkin lymphoma) or hepato-splenomegaly.
- Neck lumps should initially be referred to ENT for assessment +/- biopsy
- If suspicion of haematological malignancy then should be referred (2WW) to Haematology (or ENT if neck lump).
- If there is a peripheral blood lymphocytosis then flow cytometry of peripheral blood lymphocytes may give a diagnosis without need for a biopsy (see separate protocol for investigation of lymphocytosis).

References:

- NICE. Suspected cancer: recognition and referral. June 2015
- NICE Clinical Knowledge Summary. Neck lump (October 2020) https://cks.nice.org.uk/neck-lump
- NICE Clinical Knowledge Summary. Haematological Cancers - Recognition and Referral (February 2021). https://cks.nice.org.uk/haematological-cancers-recognition-and-referral

Clinical Problem: Splenomegaly

Splenomegaly may be detected due to local symptoms, such as left upper quadrant discomfort or early satiety, but more commonly it is an incidental finding on radiological imaging.

An enlarged spleen is >12-13cm length, although with borderline splenomegaly (up to approximately 14cm) and no associated systemic symptoms we often find no underlying cause. Normal spleen size varies with gender and height – see expected spleen size calculator.

Differential Diagnosis:

- *Liver disease with portal hypertension*
- *Haematological* (red cell destruction) - acquired haemolytic anaemia, red cell membrane disorder or **haemoglobinopathy.**
- *Haematological* (malignancy) – related to **myeloproliferative disorder**, **lymphoma** or **leukaemia** (may be related to systemic symptoms such as weight loss or fevers/drenching night sweats).
- *Autoimmune disease* – such as rheumatoid arthritis or systemic lupus.
- *Infection* – bacterial (e.g. endocarditis, tuberculosis), viral (e.g. HIV, EBV, CMV, hepatitis) or protozoal (e.g. tuberculosis, **malaria**, **leishmaniasis, schistosomiasis**).
- *Rare causes*, e.g. sarcoidosis, amyloidosis or storage disorders such as **Gaucher disease**.

Massive splenomegaly (>20cm) is usually only seen with the causes shown in **bold**.

Examination:
Depends on suspected cause but include basic observations, stigmata of endocarditis, hepatomegaly / signs of liver disease and lymphadenopathy.

Baseline investigations:

- Full blood count, blood film, reticulocytes, U+E, LFT, LDH, immunoglobulins, Direct Coombs test. Check HIV serology.
- Other testing depending on suspected cause, e.g. haemoglobinopathy screen, autoimmune screen, infection serology / cultures, serum ACE, etc.

Referral:
Haematology referral (NICE suggest 2WW, especially if concern over malignancy – night sweats, fever, shortness of breath, itch or weight loss):

- Suspected haematological disorder – red cell disorder or malignancy.
- Unexplained splenomegaly with systemic symptoms or clinical concern.
- Unexplained splenomegaly >14cm in size.

If systemically well, no obvious cause and only borderline splenomegaly then we suggest repeat US scan in 4-6 months to look for evidence of further enlargement.

References:

- NICE. Suspected cancer: recognition and referral. June 2015
- NICE Clinical Knowledge Summary. Haematological Cancers - Recognition and Referral (February 2021). https://cks.nice.org.uk/haematological-cancers-recognition-and-referral

Splenectomy - antibiotic prophylaxis and vaccination

Patients without a functioning spleen are at increased risk of severe life-threatening infection but this risk can be reduced by education, vaccination and antibacterial prophylaxis.

Patients may have had their spleen removed surgically or have poor splenic function from a variety of conditions (e.g. sickle cell disease, amyloidosis, tumour infiltration, chronic GVHD, splenic irradiation, coeliac disease, inflammatory bowel disease).

The lack of splenic function may be obvious (e.g. post splenectomy or congenital asplenia) or may be assumed from Howell-Jolly bodies on a blood film (specific but not completely sensitive). The radiological finding of a small spleen does not always indicate poor function so a blood film should also be examined.

The risk of severe infection comes from encapsulated bacteria (pneumococcus, haemophilus, meningococcus) as well as more unusual infections such as malaria, babesia (tick borne infection mainly seen in north-eastern USA and southern Europe) and capnocytophaga (dog or cat bites).

Patient Education

- Patients should be aware that they have an increased risk of severe infection.
- They should know about the need for vaccination and antibacterial prophylaxis.
- They should know what actions to take if they suspect infection. They may wish to wear a Medic Alert bracelet and should carry a card with written information about their condition, relevant clinical details and contact telephone details.
- They should be aware of the risks from animal bites, mosquito bites and from tick bites. Travel advice should include appropriate malaria chemoprophylaxis and strategies to reduce mosquito bites.

Vaccination (age 10 and above, assuming completed childhood vaccination programme) *[for younger patients see details in Green Book, referenced]*

Vaccines should preferably be given at least 2 weeks before splenectomy (or at least two weeks post-splenectomy if not done previously). Patients on a short-course of chemotherapy or immunosuppressants may get a better response if vaccines are given at least 3 months after completion.

Pre-splenectomy:

- Pneumococcal polysaccharide vaccine: Pneumovax-23 0.5ml i.m. or s.c.
- Conjugate meningococcus A, C, W125 and Y vaccine: Menveo 0.5ml i.m.
- Meningitis B vaccine: Bexsaro 0.5ml i.m.

Four weeks later:

- Meningitis B vaccine: Bexsaro 0.5ml i.m.

Long-term:

- Annual influenza vaccine
- Booster pneumococcal vaccine (PPV-23) – 5 yearly
- Booster meningococcal vaccine if travelling to high-risk area (e.g. sub-Saharan Africa or Saudi Arabia). Country specific recommendations at www.travax.nhs.uk

Antibacterial prophylaxis

Antibacterial prophylaxis should be offered to all patients. It should be actively encouraged in patients with high risk features, however patients without these features may decide not to use regular antibiotics after appropriate counselling. Regardless, all patients should have a supply of antibiotics at home to take in an emergency.

High risk features:

- Age less than 16 years or age greater than 50 years
- Inadequate response to pneumococcal vaccination
- Previous invasive pneumococcal infection
- Underlying haematological malignancy or immunosuppression

Patients are also at a higher risk in the immediate post-operative period and for the first two years after splenectomy.

Antibacterial prophylaxis should be with penicillin V 250mg BD (or erythromycin 500mg BD if penicillin allergic).

See attached patient information leaflet:
https://www.gov.uk/government/publications/splenectomy-leaflet-and-card

References:

- Davies JM, Lewis MPN et al. Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen: Prepared on behalf of the British Committee for Standards in Haematology by a Working Party of the Haemato-Oncology Task Force. Br J Haematol 2011; 155: 308-317
- Public Health England. Immunisation against infectious disease. Chapter 7: Immunisation of individuals with underlying medical conditions. Update January 2020.

Clinical Problem: Sweats

We are often referred patients with 'sweats' for investigation of possible haematological malignancy. Although it is true that haematological malignancy can cause *drenching night* sweats, it is unusual for this to be the sole presenting feature. Other systemic features may include unexplained weight loss (>10% body weight within 6 months), lymphadenopathy / splenomegaly or an abnormal full blood count.

Differential Diagnosis:

- *Obesity*
- *Infection* – acute or chronic infections including tuberculosis, endocarditis and HIV infection.
- *Endocrine* – menopause, hyperthyroid, diabetes mellitus, phaeochromocytoma, carcinoid syndrome or acromegaly.
- *Neurological* – Parkinsonism or autonomic neuropathy.
- *Malignancy* – Haematological malignancy including myeloproliferative disorders or lymphoma.
- *Medication* – in particular antidepressants (SSRIs, especially venlafaxine, and tricyclics), hormonal agents (e.g. tamoxifen, GnRH agonists) or NSAIDs.
- Withdrawal from alcohol or illicit substances.

Examination:

- Examine for lymphadenopathy, splenomegaly or hepatomegaly.

Baseline investigations:

- Full blood count, blood film, basic biochemistry, LDH, immunoglobulins, TSH, glucose.
- Other tests depending on suspected cause, e.g. chest x-ray, hormone levels, withdrawal of suspected medications.

Referral:

- NICE recommends considering a 2 week wait referral for patients having night sweats *with unexplained splenomegaly or lymphadenopathy*
- Other speciality referrals depending on suspected cause.

References:

- Paisley AN, Buckler HM. Investigating secondary hyperhidrosis. Br Med J 2010; 341: 4475.
- NICE. Suspected cancer: recognition and referral. June 2015
- NICE Clinical Knowledge Summary. Haematological Cancers - Recognition and Referral (February 2021). https://cks.nice.org.uk/haematological-cancers-recognition-and-referral
- NICE Clinical Knowledge Summary. Hyperhidrosis (April 2021). https://cks.nice.org.uk/topics/hyperhidrosis/

Clinical Problem - Easy bruising (also relevant for other bleeding symptoms)

Easy bruising is a relatively common symptom, especially in females or the elderly. In a published survey of 500 healthy individuals, 18% felt they bruised easily.

Easy bruising as a solitary symptom is unlikely to be significant, however suspicion is higher when accompanied by other haemorrhagic problems (e.g. epistaxis, gum bleeding, menorrhagia or bleeding at previous childbirth, surgery or dental extraction) or if there is a family history of a bleeding disorder.

A life-long history of a bleeding tendency may point towards an inherited disorder while a more recent history suggests an acquired cause.

Differential diagnosis:
Acquired:

- *Trauma*, often arms & legs but can be atypical if non-accidental injury
- *Low platelets*, especially if <50 x10^9/l, multiple causes – see above.
- *Abnormal platelet function* – e.g. uraemia, liver disease, NSAIDs, clopidogrel, anti-depressants (SSRI), anticonvulsants.
- *Abnormal coagulation* – e.g. liver disease, anticoagulants.
- *Vascular defect* – e.g. amyloid, corticosteroids, scurvy, senile purpura (usually dorsum of hands and extensor surfaces of forearms).
- *Autoimmune disease* – e.g. thyroid disease.

Inherited:

- *Vascular disorders*, all rare and generally associated with other features, e.g. Marfan syndrome, Ehlers-Danlos syndrome, hereditary haemorrhagic telangiectasia.
- *Inherited platelet disorders*, rare and generally mild.
- *Inherited coagulation factor deficiency*, e.g. all rare except Von Willebrand disease. Haemophilia A & B can present in later life if mild (a third have no family history).

Easy bruising or other haemorrhagic symptoms are very subjective. An anxious patient may worry about minor symptoms while a patient with a true bleeding disorder may disregard significant symptoms as being normal for their experience. Patients with bleeding disorders often have multiple haemorrhagic symptoms or symptoms which have required medical intervention.

Examination should look for current bruises (size, distribution), petechiae (very suggestive of vascular or platelet disorder) or mucosal bleeding. Also check for lymphadenopathy, hepatomegaly or splenomegaly.

Baseline investigations therefore include: FBC (NICE suggest urgent <48hr), blood film, coagulation screen (inc. PT, APTT and fibrinogen), U+E, liver function and thyroid function. NICE also suggest urine dipstick for haematuria.

Referral: Patients with significant or multiple symptoms or abnormal baseline investigations should be referred to Haematology.

References:
NICE Clinical Knowledge Summary. Bruising (March 2021).
https://cks.nice.org.uk/bruising

Clinical Problem: Abnormal Coagulation

Blood clotting tests should be performed when there is a suspicion of an underlying bleeding disorder. Screening in the absence of symptoms rarely detects significant abnormalities but may detect insignificant problems prompting unnecessary referral and further testing. It should be remembered that abnormal clotting tests usually do not indicate a bleeding disorder and that not all bleeding disorders produce abnormal clotting results (e.g. some von Willebrand disease, mild factor deficiencies, platelet disorders, vascular disorders, factor XIII deficiency, fibrinolytic disorders…).

Local audit of "routine" pre-operative coagulations screens found an abnormal PTr in 5.7% of samples and abnormal APTTr in 7.4% of samples, however, on further testing, only 0.7% of patients were felt to have a potentially significant disorder.

Isolated prolonged prothrombin time (PT) or PT > APTT	**Isolated prolonged activated partial thromboplastin time (APTT) or APTT > PT**	**Prolonged PT and APTT**
Warfarin, rivaroxaban, apixaban, edoxaban Vitamin K deficiency Liver disease (early) Inherited – FVII deficiency	Lupus anticoagulant Heparin Dabigatran Inherited – FXII, FXI, FIX or FVIII deficiency	Liver disease (late) Disseminated intravascular coagulation (DIC) Inherited – Fibrinogen, FX, FV or prothrombin deficiency.

Examination:

- Evidence of bleeding disorder (e.g. unexplained bruising or bleeding).
- Features of liver disease

Baseline investigations:

- FBC, PT, APTT, mixing studies, thrombin time, fibrinogen, U+E, LFT

Any further relevant coagulation tests may be performed automatically by the laboratory if enough sample is available and if the clinical details suggest bleeding symptoms.

If unexplained consistently prolonged PT then repeat sample after a trial dose of 10mg vitamin K.

If unexplained consistently prolonged APTT then initially screen for a lupus anticoagulant, especially if mixing studies do not show complete correction.

If unexplained consistently prolonged APTT with complete correction on mixing then consider coagulation factor assays, especially if personal or family history of abnormal bleeding.

Referral:

- Haematology referral if suspicion of inherited or acquired bleeding disorder regardless of clotting test results (see protocol on easy bruising for more specific details).
- Abnormal results can also be discussed via our Advice & Guidance service.
- Not for haematology referral if a non-haematological cause is apparent, e.g. liver disease.

Clinical Problem: Thrombophilia

Individuals who have an increased risk of developing a pathological thrombosis are described as having a thrombophilia. There are both inherited and acquired causes of thrombophilia. Low-risk thrombophilias such as the factor V Leiden mutation or the prothrombin G20210A mutation are common in the population (each ~3-5% population) and are weak risk factors for thrombosis. Rarer thrombophilias such as deficiencies of antithrombin, protein C or protein S (~0.1-0.2% population) are stronger risk factors for thrombosis.

Requests for thrombophilia testing are most commonly encountered following an episode of venous thrombosis or if there is a family history of thrombosis or thrombophilia. Thrombophilia testing should only be performed if it will influence clinical management and should not be performed indiscriminately in these situations. Inherited thrombophilia testing is also not recommended following unprovoked, early (<50yr) arterial thrombosis (consider anti-phospholipid syndrome +/- exclusion of a myeloproliferative disorder or PHN if clinical suspicion).

It should be noted that results are unlikely to influence the intensity or duration of anticoagulation following VTE and are only weakly related to the risk of recurrence. Even in the absence of an identifiable thrombophilia, NICE currently advise to consider continuing anticoagulation beyond 3 months (6 months for people with active cancer) after an unprovoked DVT or PE. Base this decision on the balance between the person's risk of venous thromboembolism recurrence (which is only weakly influenced by common, low risk thrombophilias) and their risk of bleeding. Discuss the risks and benefits of long-term anticoagulation with the person and take their preferences into account.

Indications for screening:

Venous thrombosis

- Patients with unprovoked (or provoked by minor risk factor) VTE – test for antiphospholipid syndrome alone, unless meets further criteria below
- Patients with unprovoked VTE at an unusual site, especially intra-abdominal thrombosis - testing to exclude a myeloproliferative disorder, PNH or anti-phospholipid syndrome
- Patients with an unprovoked (or provoked by minor risk factor) VTE where a first degree relative has also had VTE. This is the *only* patient group where NICE (NG158) suggest performing inherited thromobophilia testing, however opinions and guidelines vary.
- Also consider testing patients who develop unprovoked venous thromboembolism at <40 years old, especially if family history of VTE.

Patients who have recurrent unprovoked VTE will likely need long term anticoagulation regardless of the result. In this case testing will not influence management and anticoagulation should not be stopped so that testing can be performed.

Family screening (NOT recommended by NICE NG158)

- First degree family members of patients with a known high-risk thrombophilia (esp. AT, PC, PS), where knowledge of a thrombophilic defect may be useful (e.g. daughters of child-bearing age).

Family screening for low-risk inherited thrombophilias is not routinely recommended.

Family screening in the context of a family history of VTE, but without a known inherited thrombophilia, is not routinely recommended. It is important to recognise that thrombophilia testing is not comprehensive and only includes the most common and serious abnormalities. A negative screen does not exclude a familial predisposition to thrombosis unless there is a known identifiable thrombophilia in the symptomatic relatives.

Obstetrics / Neonates

- Testing before commencing COC/HRT is **not** recommended, as even if a first degree family member is known to have a thrombosis, a negative result does not exclude an increased risk of venous thrombosis. This is especially true where it is not known if a thrombophilia is present in the index case.
- Test for anti-phospholipid syndrome if history of previous unprovoked VTE or adverse pregnancy outcomes (e.g. recurrent or late pregnancy loss). Testing during pregnancy itself can be unreliable.
- Test for antithrombin deficiency if known family history of AT deficiency or evidence of heparin resistance.
- Test for protein S and protein C deficiency if neonatal / childhood purpura fulminans

Testing cannot be performed at the time of an acute thrombotic event or while a patient is on anticoagulation. The majority of patients will require samples to be taken 4–6 weeks after the completion of anticoagulation.

Referral:

- Consider haematology referral if patient meets criteria for testing as mentioned above. We would prefer to perform the counselling and testing ourselves rather than see patients following testing performed in the community (samples also need to arrive at the laboratory as soon as possible)

References:

- Arachchillage D, Mackillop L, et al. Thrombophilia testing: a British Society for Haematology Guideline. Br J Haematol 2022. DOI: 10.1111/bjh.18239
- NICE. NG158 Venous Thromboembolic diseases: diagnosis, management and thrombophilia testing. 26th March 2020

Clinical Problem: VTE Prevention in travellers

Although the risk of venous thrombosis is approximately doubled by long-haul travel (>6 hours), the absolute risk remains low for most people. The risk is increased regardless of the mode of travel, and it is uncertain if air travel confers any additional risk. Long-haul flights are not advised for 3 months following hip or knee replacement.

Low risk:
No previous DVT / PE (or previous event and still taking anticoagulation)
No moderate or high risk factors

Moderate risk:
Age >60 years
Obese (BMI >30 kg/m^2)
Family history of VTE (1st degree relative)
Taking OCP or HRT
Height >1.9m or <1.6m
Polycythaemia
Inherited thrombophilia
Pregnant or post-partum
Large varicose veins or venous insufficiency
Reduced mobility, e.g. lower limb fracture in plaster
Previous provoked DVT / PE and not on anticoagulation
Recent surgery or trauma (esp. abdomen, pelvis or legs)
Clinically evident cardiovascular disease (e.g. recent MI or symptomatic CCF)
Chronic inflammatory disease (e.g. inflammatory bowel disease).
Recent major acute illness (e.g. pneumonia)

High risk:
Active malignancy – untreated or on active treatment
Major surgery (anaesthesia >30 minutes) within past 4 weeks
Previous unprovoked or travel related VTE and not taking anticoagulation
Multiple risk factors as listed in "moderate risk" category

Management:
Low risk – no specific measures. General advice includes avoiding prolonged immobility (recline seat when possible, loose clothing, calf / leg exercises when sitting, short walks or breaks when possible), maintaining a normal fluid intake and avoiding alcohol or sedatives.
Moderate risk – General advice plus class 1 compression stockings or propriety flight socks (unless ABPI <0.8).
High risk – As per moderate risk but also consider LMWH (would need prophylactic dose for outbound and return flights, instruction on use & storage, sharps bin, and letter for customs / security).

Class 1 stockings should provide 14-17mmHg compression at the ankle. Not available on prescription for VTE prevention (class 1 can be prescribed for varicose veins). Propriety flight socks widely available.

Aspirin (either commencing aspirin or increasing the dose if already using) is not recommended for VTE prevention during travel.

References:
NICE Clinical Knowledge Summary. DVT Prevention for Travellers (August 2018). https://cks.nice.org.uk/dvt-prevention-for-travellers

GP Guidelines for Patients with Clinically Significant Haemoglobinopathies (Sickle Cell Disease or Thalassaemia Major)

The haematology department at South Tees NHS Foundation Trust provides specialist care for all people with clinically significant haemoglobinopathies; this includes all patients with sickle cell disease (HbSS, HbSC, etc) or thalassaemia major (B thalassaemia, HbH disease or transfusion dependent thalassaemia). As this is a low prevalence area, the majority of care relating to the haemoglobin disorder is provided within secondary care. This guideline aims to cover information for general practitioners in helping to care for this group of people.

Patients who are carriers of a haemoglobinopathy eg. sickle cell carrier, carrier of B thalassaemia trait do not require secondary care follow up. At diagnosis these patients will be sent an information leaflet via the requesting clinician which explains the condition. If further advice is required please use Advice and Guidance available through the Choose & Book system. Newborn screening results will be communicated by the newborn screening coordinator.

Clinical Team
Dr Dianne Plews (lead clinician, consultant haematologist)
Dr Ahmed Hageb (paediatric consultant)
Sr Lindy Defoe (lead nurse / newborn screening)

Open Access & Clinical Advice
All patients with a clinically significant haemoglobinopathy have 24 hour open access to hospital services in the event that they are unwell.

Adults – Haematology Day Unit, JCUH. 01642 282763 (9am – 5pm, Monday – Friday)
Ward 33, JCUH. 01642 835996 (out of hours)

Children – Paediatric Day Unit, JCUH. 01642 854896 (24 hours)

If a patient presents to primary care acutely unwell please contact the open access numbers. Patients should not be advised to attend A&E unless they have been involved in acute trauma or have central chest pain which seems cardiac in origin.

Urgent clinical advice for both adult and paediatric patients can be obtained from the haematology registrar on-call (via hospital switchboard 01642 850850). For non urgent queries please use the Advice and Guidance choose service or telephone Dr Plews' secretary if the patient is known to the service (01642 854381).

Prevention of Infection
All patients with sickle cell disease are considered to be hyposplenic. Some patients with thalassaemia major will have had a splenectomy. Guidelines for management of hyposplenism should be followed for these patients.

Guidance on antibiotic prophylaxis and vaccinations can be found in the DOH Green Book.

1. Prophylactic penicillin

- All patients should receive prophylactic penicillin or equivalent. This will be initiated in the paediatric clinic at the initial consultation, but should be continued on a regular prescription in primary care.

Penicillin dosage

• **Age**	• **Dose of penicillin**
• 3 months – 1 year	• 62.5mg twice daily
• 1 year – 5 years	• 125mg twice daily
• 5 years - adult	• 250mg twice daily

- If patients do not wish to take regular penicillin they should have an emergency supply of antibiotics at home to take in the event of infection (eg. amoxicillin 250mg tds).
- In the event of penicillin allergy, prophylactic erythromycin may be prescribed, although is not as effective and patients over 16 years may wish to consider using emergency antibiotics instead.
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2. Vaccinations

- All patients should be encouraged to receive vaccinations according to the standard UK childhood immunisation schedule, including meningitis vaccines. People with haemoglobin disorders should receive the following additional vaccinations:
- Pneumovax at age 2 years. This is repeated 3 years after the initial vaccination (aged 5 years) and five yearly thereafter.
- Hepatitis B
- Annual influenza vaccine
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3. Travelling

- Patients receiving hydroxycarbamide should not receive live vaccines eg. yellow fever.
- Patients are at increased risk of malaria infection and it is important that they take appropriate anti-malarials when travelling to an ‘at risk’ area.

Pain Management

People with sickle cell disease may experience frequent episodes of severe pain relating to sickling crises. We encourage patients to manage their crises at home, where possible. Patients are advised to drink 1.5 – 2 x daily maintenance fluids (for an adult this will be 3-4 litres) and to take analgesia using an analgesic ladder according to the severity of the pain. Patients will usually take paracetamol and ibruprofen initially, but require access to opiate analgesia at home for more severe pain – this will usually be Oramorph or equivalent. Pethidine should be avoided. If a patient presents with severe pain they should receive analgesia according to their emergency health care plan (of which they should have a copy).

Hydroxycarbamide

Hydroxycarbamide has been shown to reduce mortality and morbidity is both adults and children with sickle cell disease by reducing the frequency of chest and painful crises. It is currently offered to patients with recurrent painful crises, chest crises, raised transcranial Doppler velocities and more recently to children. Hydroxycarbamide works by increasing the percentage of haemoglobin F and changes in nitric oxide metabolism which reduce haemolysis and increase the baseline haemoglobin level.

In South Tees NHS Hospitals hydroxycarbamide is prescribed and monitored by the haematology team. General practitioners will not be expected to be involved in the prescribing of hydroxycarbamide, but should be aware of the potential side effects and actions to take in the event that a patient presents to primary care.

Potential presentations and clinical actions required:

Pregnancy or breast feeding	Stop drug
Family planning	Men and women should use safe contraceptive methods whilst taking hydroxycarbamide and for 3 months after stopping. Patients who want to father a child or get pregnant should stop hydroxycarbamide for at least 3 months prior to conception
Blistering rash	Stop drug and contact haematology team
Alopecia	Usually mild, stop only on patient request
Hyperpigmentation of nails	Usually mild, stop only on patient request
Fever and hepatitis	Stop drug and contact haematology team
Sore throat or mouth ulceration	Stop drug and contact haematology team
Cytopenias (Hb <45g/L, neutrophils <1.0, platelets<80)	Stop drug and contact haematology team

Iron Chelation

People with haemoglobin disorders often require blood transfusions and can become iron overloaded as a result of this. Iron overload is monitored in secondary care using ferritin, transferrin saturation and T2* MRI of the liver and heart. Those with evidence of iron overload will be prescribed iron chelation. In this region all iron chelation is prescribed and monitored in secondary care.

Commonly used medications are:

- Deferasirox (Exjade FCT, oral preparation)
- Desferrioxamine subcutaneous or intravenous infusion

Side effects which may present to primary care:

Fever, abdominal pain and diarrhoea	Consider Yersinia infection. Stop iron chelation and prescribe ciprofloxacin 500mg bd
Skin reactions	Topical corticosteroid may be helpful in reducing local erythema

Tinnitus or worsening hearing loss	Withhold chelation and discuss with haemoglobinopathy team
Visual disturbance (night blindness or central scotoma)	Withhold chelation and discuss with haemoglobinopathy team
Drug interactions	Avoid phenothiazines due to increased risk of neurological toxicity
Abnormal blood tests: raised transaminases or cytopenias	Withhold chelation and discuss with haemoglobinopathy team