The Newcastle upon Tyne Hospitals NHS Foundation Trust

GP Adult Haematology Guidelines

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1. Introduction

This document is designed to help general practitioners with routine haematological problems. It may also be useful to guide hospital doctors in further investigation of abnormal haematological parameters.

2. Guideline Scope

These guidelines do not apply to children or patients who are pregnant.

It is difficult to give advice for every clinical situation as all patients are different. Further monitoring or investigation may not be appropriate in some patient groups. Likewise patients may present with multiple different abnormalities and therefore further advice may be required.

Where major abnormalities are found on the blood film that require urgent attention e.g. acute leukaemia, microangiopathic haemolytic anaemia, platelet count less than 10×10^9/L etc. we will contact a general practitioner directly. When a blood film or coagulation screen is reviewed by a haematologist there may be specific suggestions made to guide referral or further investigations.

As pre-analytical variables can play a part in abnormal results we suggest repeating a sample if an unexpected result is encountered. Frequently our advice is based on the pattern of abnormalities and how these have developed and therefore reviewing older blood tests is useful to guide further management.

If we have advised you to perform a blood film please request this with relevant clinical details and request for 'medical review as per consultant haematologist'.

The laboratory is often able to add on tests to existing samples but this is only usually possible if done within 48 hours. Please see https://www.newcastlelaboratories.com/ for full details on our testing repertoire and how to request add on tests. If you send us an Advice and Guidance request within this time frame it often allows us to request more advanced tests and therefore advances patient management more quickly.

3. Useful resources:

- British Society for Haematology Guidelines: https://b-s-h.org.uk/guidelines
- GPNotebook: https://www.gpnotebook.co.uk
- Newcastle Laboratories. https://www.newcastlelaboratories.com/
- Newcastle upon Tyne Hospitals NHS Foundation Trust clinical haematology services http://www.newcastle-hospitals.org.uk/services/haematology.aspx
- Applications: Buku Haematology – all you need to know about haematology with GPs in mind – free to download on IOS and Android

4. Contacting the Haematology service

If advice is required about a haematological problem this should usually be via the Advice and Guidance service in the first instance. If help is required with a patient that is currently under our care or known to our service then please write to the appropriate haematologist directly. We aim to reply to all GP Advice and Guidance requests within two working days but an answer will often come sooner. If you need urgent or emergency advice that cannot wait then please contact the on call haematology registrar via switchboard.

5. Evaluation and feedback

This guideline has been prepared by Dr Andrew McGregor, consultant haematologist. It has been reviewed by Dr Brigit Greystoke, Dr Gail Jones, Professor Graham Jackson, Dr Tina Biss, Dr John Hanley, Dr Wendy Osborne, Dr Erin Hurst, Professor Steve O'Brien, Dr Kate Talks, Mr John Lambert and Mr Paul Murphy. Any feedback please contact andrewmcgregor1@nhs.net

6. Document changes

Any document changes must be updated in:

- NCCC Q Pulse
- Laboratory medicine Q Pulse
- Trust website (haematology departmental website and Newcastle Laboratories)
- Intranet

Contents

Anaemia

The haemoglobin concentration reference range for men is 130-180 g/L and women is 115-165 g/L. The cause of anaemia can generally be separated by the MCV – see separate sections on microcytosis or macrocytosis. However the MCV is not completely sensitive or specific and there may be more than one cause of anaemia occurring together so detailed investigation is often required.

Causes

- Iron deficiency and bleeding
- Anaemia of chronic disease/inflammation
- Malignancy including myeloma
- Renal failure especially if eGFR less than 30 ml/min or associated with diabetes
- Alcohol and liver disease
- Vitamin B12 or folate deficiency
- Haemolysis; including drug-induced
- Medications especially chemotherapy, anti-androgens and immunomodulatory drugs – check British National Formulary (BNF)
- Pregnancy
- Testosterone deficiency – common in elderly men
- Thyroid dysfunction
- Thalassaemia and haemoglobinopathy
- Bone marrow failure e.g. aplastic anaemia, myelodysplasia
- Bone marrow infiltration e.g. leukaemia, non-haematological cancer

History and examination

Look at causes and work through systematically. Look at older blood counts.

Suggested investigations

See sections on microcytosis and macrocytosis. If the anaemia is normocytic then all causes should be excluded.

- Check inflammatory markers
- Renal and liver function

Management

This depends on the underlying cause. If the above causes have been excluded then the most likely explanations are anaemia of chronic disease or a bone marrow failure syndrome. The latter is frequently associated with other cytopenia or changes on the blood film. In patients with otherwise normal full blood count and for whom there are no concerning features we suggest monitoring the full blood count in general practice. In anaemia of chronic disease the treatment is the underlying cause and if concerns then a referral to the appropriate speciality should be made.

If there is haemolysis or concerns about myelodysplasia then a referral to haematology is required.

If there is no evidence of inflammation please consider referring to haematology if the haemoglobin is persistently less than 110 g/L in men or less than 100 g/L in women for evaluation into possible myelodysplasia. If there is uncertainty of whether referral is required especially when the haemoglobin concentration is greater than 100g/L please discuss via Advice and Guidance. If the patient is not referred to haematology then continued monitoring for any changes is likely to be appropriate.

For cases of renal anaemia refer to nephrology.

Polycythaemia

The haemoglobin reference range for men is 130-180 g/L and women is 115-165 g/L. The haematocrit for men is 0.4-0.5 L/L and women is 0.36-0.46 L/L. Polycythaemia is usually a secondary phenomenon due to reduced plasma volume or respiratory disease. Primary polycythaemia vera is a clonal myeloproliferative neoplasm. Around 96% of patients with primary polycythaemia will have the *JAK2* V617F mutation and a further 1-2% will have mutations in *JAK2* exon 12. Patients with primary polycythaemia vera may have iron deficiency due to increased demand. In this scenario red cell indices may show a normal or high haemoglobin with an elevated haematocrit and elevated RBC but low MCV. This pattern is fairly unique to iron deficient polycythaemia. Please do not give iron in this setting as this will further increase the haemoglobin concentration.

Causes

- Apparent or relative or pseudo polycythaemia – reduction in plasma volume rather than increase in red cell mass
    - Smoking
    - Hypertension (Gaisbock's polycythaemia)
    - Alcohol
    - Diuretics
    - Dehydration
- Absolute or true polycythaemia
    - Inherited disorders
    - High affinity oxygen haemoglobin
    - Polycythaemia vera
    - Secondary polycythaemia
        - Chronic lung disease and hypoxia
        - Cyanotic heart disease
        - High altitude
        - Smoking
        - Sleep apnoea
        - Abnormal erythropoietin production
            - Local hypoxia e.g. polycystic kidneys, renal artery stenosis
            - Erythropoietin-producing tumour e.g. HCC, RCC, uterine
        - Renal transplant
        - Drugs e.g. erythropoietin, testosterone, anabolic steroids
    - Idiopathic

History and examination

This should focus on the more common causes – relative polycythaemia and secondary polycythaemia. Look at medications – especially diuretics, take an alcohol and smoking history and ask about respiratory symptoms. Ask about any illicit drugs or over the counter medications. Measure oxygen saturations and blood pressure. Ask about B symptoms, rashes, itch, aquagenic pruritus, erythromelalgia, gout, bleeding, thrombosis and examine for splenomegaly and plethora. Ask about symptoms of hyperviscosity e.g. headaches and visual disturbances. Look at older blood counts.

Suggested investigations

- Blood film
- Renal and liver function
- Calcium
- *JAK2* mutation – available in primary care
- Testosterone
- Erythropoietin level
- Ferritin
- Chest radiograph if respiratory issues

Management

- If the haematocrit or haemoglobin are only mildly elevated it is reasonable to offer lifestyle advice and repeat the test in three months.
- If any secondary causes are apparent these should be treated or modified accordingly (e.g. smoking cessation, stopping diuretics, optimising lung disease etc.).
- If there is an elevation in haematocrit or haemoglobin associated with a thrombotic event or symptoms of hyperviscosity then there should be a referral to haematology
- If the patient is hypoxic due to respiratory or cardiovascular diseases then advice should be sought from the appropriate specialist.
- If there is clinical suspicion for primary polycythaemia (constitutional symptoms, splenomegaly, no other secondary cause and persistent) please refer to haematology
- If secondary polycythaemia seems likely but primary polycythaemia needs to be ruled out please discuss via Advice and Guidance for *JAK2* testing which is available in primary care
- If the patient has the *JAK2* mutation please refer to haematology as this is indicative of a myeloproliferative neoplasm
- Please refer to haematology if the haematocrit is persistently (three months apart) above 0.52 L/L in men and 0.48 L/L in women and no secondary cause. If the haematocrit does not reach these thresholds and the MCV or ferritin is low please discuss with Advice and Guidance as this could be iron deficient polycythaemia vera.
- Do not give iron therapy to patients who are iron deficient but have an elevated haematocrit – discuss with Advice and Guidance.

- If the haemoglobin concentration or haematocrit is very high (e.g. haematocrit over 0.6 L/L in men and 0.56 L/L in women) or there are symptoms of hyperviscosity please discuss or refer urgently

References

- NICE Clinical Knowledge Summary. Polycythaemia / Erythrocytosis (January 2018). https://cks.nice.org.uk/polycythaemiaerythrocytosis
- McMullin MF, Mead AJ, Ali S, *et al*. A guideline for the management of specific situations in polycythaemia vera and secondary erythrocytosis: A British Society for Haematology Guideline. *Br J Haematol* 2019; **184**: 161-175. https://b-s-h.org.uk/guidelines/guidelines/management-of-specific-situations-in-polycythaemia-vera-and-secondary-erythrocytosis/
- McMullin MF, Harrison CN, Ali S, *et al*. A guideline for the diagnosis and management of polycythaemia vera. A British Society for Haematology Guideline. *Br J Haematol* 2019; **184**: 176-191. https://b-s-h.org.uk/guidelines/guidelines/diagnosis-and-management-of-polycythaemia-vera/

Macrocytosis

The normal MCV depends on age but is generally 83-101 fL. This can be present with or without anaemia.

Causes

- Artefact e.g. delay to analysis
- Alcohol and liver disease
- Vitamin B12 or folate deficiency
- Haemolysis (due to reticulocytosis)
- Medications especially hydroxycarbamide, methoxtrexate, chemotherapy and other immunomodulatory drugs
- Paraprotein
- Pregnancy
- Thyroid dysfunction
- Myelodysplasia and aplastic anaemia – often associated with neutropenia and/or thrombocytopenia

History and examination

Suggest looking at the above causes and look for signs of liver disease. Review older blood tests. Ask about diet and malabsorption.

Suggested investigations

- Liver function tests
- Vitamin B12 and folate
- Blood film
- Haemolysis screen (reticulocytes, blood film, DAT, LDH, haptoglobin)
- Pregnancy test
- Immunoglobulins and serum protein electrophoresis
- TSH

Management

- Correct any secondary cause and consider repeating test in first instance
- If haemolysis is suspected then please discuss or refer
- If myelodysplasia is suspected (other cytopenias or blood film abnormalities) then please discuss or refer
- Please consider referral for macrocytic anaemia when the haemoglobin is persistently less than 110 g/L in men or less than 100 g/L in women and there are no secondary causes. For cases when the haemoglobin is still greater than 100 g/L a discussion via Advice and Guidance may appropriate especially if the patient is asymptomatic.
- If the MCV is high with no anaemia or other cytopenia and no cause is identified then these patients can be monitored in primary care every six to 12 months
- If patient has liver disease please discuss with hepatology
- If a paraprotein is detected please see separate guideline on this

Microcytosis

The normal MCV depends on age but generally 83-101 fL.

Causes

- Iron deficiency
- Thalassaemia and haemoglobinopathy
- Anaemia of chronic disease
- Lead poisoning (rare)
- Inherited sideroblastic anaemia (rare)

History and examination

Look for signs of anaemia. Ask about diet, weight loss and potential blood loss. Review older blood tests.

This table can help differentiate between iron deficiency and thalassaemia (trait).

Factor	Iron deficiency	Thalassaemia (trait)
Haemoglobin	Low or normal	Low or normal
MCV/MCH	Low but can be normal	Low – often lower than would expect from haemoglobin concentration
RBC	Low or normal	High
RDW	Elevated	Normal
Previous FBC	May be normal	Persistently low MCV/MCH
Family FBC	May be normal	If inherited may have similar abnormalities
Blood film	May be normal or may show hypochromia and pencil cells.	Depends on type.
Ethnicity	Any	More common in certain ethnic groups

Suggested investigations

- Ferritin
- If suspect iron deficiency and ferritin normal check inflammatory markers (e.g. CRP) as inflammation may elevate ferritin into the normal range. In this case a blood film, reticulocyte haemoglobin, ZPP (zinc protoporphyrin) or transferrin saturation may be useful
- Haemoglobinopathy screen if suspected thalassaemia or haemoglobinopathy. Please note that alpha thalassaemia trait is the most common disorder and will not be picked up by a haemoglobinopathy screen. Alpha thalassaemia trait is a benign, asymptomatic disorder. The only two considerations are that firstly the MCV cannot (easily) be used to infer the cause of anaemia as it will always be low and secondly, depending on the level of MCH and ethnicity, partner testing may be required when family planning as per National Screening Programme.
- If lead poisoning is suspected please check ZPP, serum lead level and blood film
- In some patients a trial of iron may be a diagnostic and therapeutic manoeuvre

Management

- We do not review patients with iron deficiency in haematology.
- See section on iron deficiency for more details.
- We do not routinely review patients with thalassaemia trait but happy to be contacted via Advice and Guidance if concerns or further questions.

Thrombocytopenia

The normal platelet count is 150-450 × 10^9/L. It would be unusual to get any bleeding symptoms with a platelet count above 50 × 10^9/L. Spontaneous bleeding is more common when the platelet count is below 30 × 10^9/L.

Causes

- Artefact e.g. platelet clumping
- Medications – check BNF
- Viral infections including HIV and hepatitis
- Liver disease and alcohol
- Hypersplenism
- Vitamin B12 or folate deficiency
- Autoimmune diseases
- Pregnancy
- Thyroid dysfunction
- Sepsis
- Major haemorrhage
- Disseminated intravascular coagulation
- Immune thrombocytopenia (ITP)
- Anti-phospholipid syndrome
- Inherited bleeding disorders
- Thrombotic thrombocytopenic purpura (TTP) – very rare but an emergency
- Bone marrow failure e.g. myelodysplasia or aplastic anaemia
- Bone marrow infiltration e.g. acute leukaemia
- Post-transfusion purpura

History and examination

Think about asking questions to rule out above causes. Ask about bleeding symptoms, alcohol and a family history. Examine for hepatosplenomegaly, signs of liver disease, signs of autoimmune disease and any bruises. Review older blood tests.

Suggested investigations

These may depend on the history and examination.

- Blood film
- Vitamin B12 and folate
- Liver function tests
- HIV, hepatitis B and C
- TSH
- Coagulation screen
- Pregnancy test
- Consider autoimmune screen if history or examination suggestive
- Abdominal ultrasound if concerned about liver disease or palpable splenomegaly

Management

- Repeat the full blood count in case of artefact (unless significantly symptomatic in which please refer in to hospital for urgent evaluation)
- Asymptomatic patients with a stable platelet count above 80 × 10^9/L should be evaluated for the above conditions and have the above investigations but do not generally need to be seen by a haematologist. Discuss with Advice and Guidance if further information or help required in first instance. Repeat the blood count in four to six weeks and if stable monitor every four months for 12 months and then annually. Patients with a stable platelet count over 80 × 10^9/L for over a year and who are not on an anticoagulant do not generally require routine monitoring but should be advised to report any bleeding symptoms and get a full blood count prior to any invasive procedure.
- If there is another cytopenia or concern about haematological malignancy then please discuss or refer.
- Please refer to haematology if the platelet count is persistently under 80 × 10^9/L for over four months or if the platelet count is under 80 × 10^9/L and the patient is awaiting surgery.
- If the platelet count is below 50 × 10^9/L or there are bleeding concerns arrange urgent repeat and referral
- Anticoagulation or antiplatelet drugs are usually avoided when the platelet count is below 50 × 10^9/L and are safe when the platelet count is above 100 × 10^9/L. For most patients with a platelet count between 50 and 100 × 10^9/L anticoagulation is safe but at the lower end of this range a risk verses benefit decision is required. Bleeding risks are influenced by the stability and aetiology of the thrombocytopenia. In the absence of bleeding symptoms serial monitoring over the first 12 months to confirm stability should be considered.
- If the platelet count is low due to liver disease suggest discuss with hepatology in first instance.

Thrombocytosis

Thrombocytosis (or thrombocythaemia) is defined as a platelet count over 450 × 10^9/L. This is frequently a reactive transient problem relating to infection or inflammation. If persistent it may represent a myeloproliferative neoplasm. In patients with myeloproliferative neoplasms there is an increased risk of thrombosis but also bleeding if the platelet count is very high e.g. over 1500 × 10^9/L.

Causes

- Infection
- Inflammation e.g. autoimmune disease, malignancy, trauma
- Bleeding
- Iron deficiency
- Hyposplenism
- Medications e.g. rebound post chemotherapy and thrombopoietin agonists
- Spurious e.g. bacteria, fragments, cryoglobulin
- Myeloproliferative neoplasms e.g. essential thrombocythaemia, chronic myeloid leukaemia, polycythaemia vera, myelofibrosis.

History and examination

This should focus on ruling out the above causes. Look for splenomegaly which can be seen in myeloproliferative neoplasms and look for features of autoimmune disease. Ask about itch, rashes, sweats and weight loss. Ensure that there has been no prior splenectomy and that there is no bleeding or risk factors for iron deficiency or other malignancy. Review older blood tests.

Suggested investigations

- Liver function tests
- Calcium
- Inflammatory markers
- Ferritin
- Blood film

Management

- Refer to haematology if platelet count over 800 × 10^9/L with no reactive cause
- If platelet count 450-800 × 10^9/L then suggest repeat the blood count in four to six weeks in first instance or discuss with the Advice and Guidance team if concerns, high thrombosis risk or constitutional symptoms/splenomegaly.
- If the platelet count is persistently above 450 × 10^9/L with no secondary cause for over four months then suggest referral to haematology.
- If there is a history of thrombosis or bleeding this may require more urgent referral

References

- Harrison CN, Butt N, Campbell P, *et al*. Diagnostic pathway for the investigation of thrombocytosis. *Br J Haematol* 2013; **161**: 604-606. https://b-s-h.org.uk/guidelines/guidelines/diagnostic-pathway-for-the-investigation-of-thrombocytosis/
- Harrison CN, Bareford D, Butt N, *et al*. Guideline for investigation and management of adults and children presenting with a thrombocytosis. *Br J Haematol* 2010; **149**: 352-375. https://b-s-h.org.uk/guidelines/guidelines/investigation-and-management-of-adults-and-children-presenting-with-thrombocytosis/

Neutropenia

A normal neutrophil count is 2-7 × 10^9/L and neutropenia is defined if the neutrophil count is less than 1.5 × 10^9/L. Mild neutropenia is 1-1.5 × 10^9/L, moderate neutropenia is 0.5-0.99 × 10^9/L and severe neutropenia is less than 0.49 × 10^9/L. Patients are at risk of more serious infection when the neutrophil count falls below 1 × 10^9/L and especially when less than 0.5 × 10^9/L.

Causes

- Medications – check BNF
- Viral infections
- Autoimmune disease
- Vitamin B12 or folate deficiency
- Sepsis
- Ethnic variations – particularly in Black Africans. These are not at increased risk of infection and show a normal neutrophil response to inflammation and infection.
- Hypersplenism
- Felty's sydnrome
- Thyroid dysfunction
- Nutritional deficiencies e.g. anorexia nervosa
- Bone marrow failure disorders e.g. myelodysplasia, aplastic anaemia
- Bone marrow infiltration e.g. acute leukaemia, T-cell large granular lymphocytic leukaemia
- Congenital syndromes e.g. cyclical neutropenia

History and examination

Ask about the above causes, recurrent infections, mouth ulcers and family history. Examine for signs of autoimmune disease, liver disease and lymphadenopathy and splenomegaly. Review older blood tests.

Suggested investigations

- Liver function tests
- HIV, hepatitis B and C
- Blood film
- TSH
- Vitamin B12 and folate
- Ferritin
- Autoimmune screen if history or examination suggestive

Management

The management will vary from patient to patient depending on differential diagnosis, prior blood counts and clinical concern. Causative medications may not need to be stopped if they are important and the neutrophil count is above 1 × 10^9/L and there are no recurrent infections. In neutropenia associated with viral infections this may persist for weeks and less commonly for a few months.

In general

- Neutrophil count 1.5 × 10^9/L and above – rule out secondary causes as per suggested history, examination and investigations. Repeat in four weeks' time and if stable and no concerns then no further investigation.
- Neutrophil count 1-1.49 × 10^9/L – rule out secondary causes as per suggested history, examination and investigations. Repeat in two to four weeks' time and if still low seek advice through Advice and Guidance service for specific management plan.
- Neutrophil count below 1 × 10^9/L – discuss immediately with haematologist via Advice and Guidance. A blood film will have been performed in these situations and the results can guide frequency and timing of further tests. In general someone with a neutrophil count persistently below 1 × 10^9/L needs haematological assessment but if it is above 1 × 10^9/L and there are no associated full blood count abnormalities, film abnormalities or clinical concern patients can be monitored in primary care.
- If the neutropenia is associated with other blood count or film abnormalities or abnormalities on examination or recurrent infections then make a formal referral
- If the patient is of Black African or Middle-Eastern ethnicity then a neutrophil count is commonly 1-2 × 10^9/L with no clinical consequence. This is a diagnosis of exclusion after ruling out other causes and seeing a persistent low count without increased risk of infection. Please perform the above investigations and if normal and the neutrophil count remains above 1 × 10^9/L then no further investigation is required.
- If a patient with a neutrophil count less than 1 × 10^9/L presents with fever they should be admitted and treated with intravenous antibiotics as per the policy for neutropenic sepsis

Neutrophilia

This is usually a reactive phenomenon and only rarely will represent a primary haematological malignancy. It is unusual for a reactive neutrophilia to be above 100 × 10^9/L. The finding of basophilia points towards a myeloproliferative neoplasm; especially chronic myeloid leukaemia. If there is an associated monocytosis which is persistent see section on monocytosis.

Causes

- Infection – especially bacterial
- Malignancy (haematological or solid tumour)
- Stress events e.g. trauma, seizures, myocardial infarction, eclampsia etc.
- Autoimmune diseases or other inflammatory processes
- Hyposplenism
- Smoking
- Medications e.g. corticosteroids, GCSF, lithium
- Myeloproliferative neoplasms such as chronic myeloid leukaemia, myelofibrosis and chronic neutrophilic leukaemia (these conditions are often identified or suspected on the blood film)

History and examination

Careful clinical evaluation asking about infective symptoms, travel history, smoking history and into the above causes. Examine for features of autoimmune disease, lymphadenopathy and splenomegaly. Review older blood tests.

Suggested investigations

- CRP or ESR
- Blood film
- Dependant on history and examination

Management

The management will vary from patient to patient depending on differential diagnosis, prior blood counts, result on repeat and clinical concern.

- If persistent basophilia suggest referral or discussion via Advice and Guidance
- If neutrophil count persistently above 20 × 10^9/L without a reactive cause suggest referral
- If there is neutrophilia and splenomegaly or blood film abnormalities then suggest referral
- If unexplained inflammatory process suggest refer to general medicine depending on localising features

Lymphopenia

The reference range depends on age but in adults is generally 1.5-4 × 10^9/L.

Causes

- Acute infections especially bacterial
- Chronic infections e.g. tuberculosis
- HIV
- Increasing age
- Medications e.g. steroids
- Autoimmune diseases
- Cardiac failure
- Congenital immunodeficiency syndromes
- Lymphoma

History and examination

Look to exclude the above causes. Examination for lymphadenopathy and ask about B symptoms and recurrent infections. Look for symptoms or signs of autoimmune disease. Review older blood tests.

Suggested investigations

- HIV test

Management

- If the lymphopenia is persistent with no secondary causes and no clinical concerns then no further action is required
- It would be extremely unusual for a patient to have lymphopenia as the sole presenting feature of lymphoma however if there are other clinical concerns e.g. lymphadenopathy, B symptoms then please refer.
- If the patient has recurrent infections and is lymphopenic (and HIV negative) then suggest check immunoglobulins and discuss with immunology

Lymphocytosis

The reference range depends on age but in adults is generally 1-5-4 × 10^9/L. In younger patients lymphocytosis is often reactive but this is less common in the elderly where a clonal (malignant) disorder is more likely. Please note that a normal full blood count does not rule out lymphoma.

Causes

- Viral infection
- Bacterial infection especially tuberculosis, pertussis
- Hyposplenism
- Smoking
- Non-Hodgkin lymphoma e.g. chronic lymphocytic leukaemia

History and examination

Review older blood tests. Ask about recent viral infections. Ask about weight loss, B symptoms, recurrent infections and smoking. Examine for lymphadenopathy and hepatosplenomegaly.

Suggested investigations

- Blood film
- Monospot if EBV suspected

Management

- Repeat the full blood count in four to six weeks to look for resolution
- If there are B symptoms or palpable lymphadenopathy or hepatosplenomegaly or associated cytopenia and lymphocytosis is persistent then refer to haematology
- If there are concerning blood film features please refer to haematology
- In older patients a persistent lymphocytosis most likely represents a haematological malignancy (*i.e.* non Hodgkin lymphoma). The most common malignancy is chronic lymphocytic leukaemia. There is no advantage of early treatment in these patients and therefore, depending on age and comorbidities, there is frequently no rush to make definitive diagnoses in patients with mild persistent lymphocytosis who are asymptomatic. Making a diagnosis of malignancy which may not influence life expectancy in asymptomatic patients may cause anxiety and affect insurance coverage.
- If the lymphocyte count is persistently above 10 × 10^9/L suggest discussion with Advice and Guidance to determine the best management strategy. If the lymphocyte count is persistently above 20 × 10^9/L then suggest formal referral.

If your patient is found to have chronic lymphocytic leukaemia based on a blood count and immunophenotyping they may not necessarily require referral to haematology. Please discuss with the Advice and Guidance service. In general patients can be monitored in primary care if:

- No B symptoms
- No (or only minor) lymphadenopathy
- Normal haemoglobin, platelet and neutrophil count
- Stable lymphocyte count 30 × 10^9/L or less

At diagnosis we usually monitor at three months and then six monthly for two years and then annually if stable. Please refer back to haematology if:

- Falling platelets, haemoglobin or neutrophil count without other cause (e.g. iron deficiency)
- Progressive lymphadenopathy or splenomegaly (please note that in viral infections lymph nodes will become more prominent but will return to baseline on resolution)

- Lymphocyte doubling time over one year
- B symptoms
- Patient anxiety

Many patients will not fall neatly into one box so please discuss with us if concerns.

References

- Bloodwise patient information (CLL) 2019. https://bloodwise.org.uk/info-support/chronic-lymphocytic-leukaemia
- Macmillan patient information (CLL) 2019. https://www.macmillan.org.uk/information-and-support/leukaemia/chronic-lymphocytic

Eosinophilia

The normal eosinophil count is 0.04 to 0.4 × 10^9/L. Eosinophils play a part in allergic, parasitic and malignant disease processes as well as tissue repair and remodelling. Hypereosinophilia is defined as an elevation of the eosinophil count 1·5 × 10^9/L or greater persisting for at least six months for which no underlying cause can be found. It can be associated with signs of organ dysfunction (cardiac, respiratory, gastrointestinal and neurological).

Causes

- Atopy and/or allergy e.g. asthma, eczema
- Infections – parasites, fungal, HIV
- Medications – ACE inhibitors, penicillin, anti-epileptics, PPI – check BNF
    - DRESS syndrome (occurs three to six weeks after the introduction of a new drug and is characterised by a triad of a skin eruption, fever and internal organ involvement)
- Autoimmune
    - Eosinophilic granulomatosis with polyangitis
    - Polyarteritis nodosa
    - SLE
    - Idiopathic eosinophilic synovitis
    - Eosinophilic fasciitis (Shulman disease)
    - Rheumatoid arthritis
- Dermatological
    - Wells syndrome (eosinophilic cellulitis)
    - Pemphigoid
- Gastrointestinal
    - Chronic pancreatitis
    - Inflammatory bowel disease
    - Coeliac
- Respiratory
    - Allergic broncho-pulmonary aspergillosis
    - Asthma
    - Sarcoidosis
    - Löffler syndrome
    - Eosinophilic pneumonia
- Malignant disorders
    - Solid organ tumour with aberrant production of cytokines
    - Hodgkin lymphoma
    - T-cell non-Hodgkin lymphoma
    - Mastocytosis – the eosinophilia may be clonal or non-clonal or a mixture
    - Clonal or malignant eosinophilic disorders e.g. CML
- Hyposplenism
- Adrenal insufficiency

History and examination
There is such a wide variety of differentials that a systematic approach is required. Travel history is important. Look at older blood counts.

Suggested investigations
- Blood film
- Inflammatory markers
- Renal and liver function
- Calcium
- Stool ova cysts and parasites and other markers of infection as guided by history
- Coeliac screen
- Autoimmune screen and ANCA
- IgE
- Chest radiograph if respiratory features

Management
Please refer urgently if:
- Eosinophil count over 10×10^9/L without an obvious secondary cause
- Eosinophil count over 1.5×10^9/L with suspected end organ damage

A routine referral can be made if the eosinophil count is persistently over 1.5×10^9/L and no secondary cause has been found.

References
Butt NM, Lambert J, Ali S, *et al*. Guideline for the investigation and management of eosinophilia. *Br J Haematol* 2017; **176**: 553-572. https://b-s-h.org.uk/guidelines/guidelines/investigation-and-management-of-eosinophilia/

Basophilia

The normal reference range is 0-0.1 × 10^9/L. There are very few causes of basophilia and if this is persistent – particularly if above 0.4 × 10^9/L this is strongly suggestive of a myeloproliferative neoplasm.

Causes

- Chronic myeloid leukaemia
- Other myeloproliferative neoplasms e.g. myelofibrosis
- Atypical chronic myeloid leukaemia
- Ulcerative colitis
- Hypothyroidism
- Recovery from acute illness
- Allergy
- Chicken pox
- Hyposplenism

History and examination

Look for signs of infection including atypical infections. Examine for splenomegaly and hepatomegaly. Ask about weight loss, and night sweats. Look at older blood counts.

Suggested investigations

- Blood film
- Inflammatory markers
- TSH

Management

Basophilia is seldom seen in reactive states save for very mild elevations e.g. 0.2 × 10^9/L. If the basophil count is elevated it should be repeated in three to four weeks to see if persistent and a blood film should be requested. If the basophilia is persistent then please discuss via Advice and Guidance. If a blood film is reported as concerning for chronic myeloid leukaemia or a myeloproliferative neoplasm please refer directly to haematology.

Monocytosis

The normal reference range is 0.2-0.8 × 10^9/L and monocytosis is frequently transient.

Causes

- Infections e.g. tuberculosis, brucella, malaria, syphilis, endocarditis
- Autoimmune and inflammatory diseases
- Sarcoidosis
- Hyposplenism
- Chronic myelomonocytic leukaemia
- Malignancy

History and examination

Look for signs of infection including atypical infections. Ask about a travel history. Examine for splenomegaly and hepatomegaly. Ask about weight loss, rashes and night sweats. Look at older blood counts.

Suggested investigations

- Blood film
- Inflammatory markers
- Renal and liver function
- Calcium

Management

If the monocytosis is persistent this may represent chronic myelomonocytic leukaemia. This is a chronic and generally incurable disorder. Some cases behave indolently and others can be more aggressive.
Suggest referral if:

- Persistent monocyte count over 5 × 10^9/L
- Monocyte count over 1.2 × 10^9/L with other cytopenia or concerning symptoms or abnormal features on blood film

If the monocyte count is between 1.2 and 5 × 10^9/L with no other cytopenia and no constitutional symptoms or splenomegaly then please discuss via Advice and Guidance and monitor every six to 12 months.

Paraprotein

There is a separate guideline on this located on the Newcastle Laboratories website: https://secure.newcastlelaboratories.com/test-directory/test/immunoglobulins-igg-iga-igm/ and also on Q Pulse NUTH_0062

Splenomegaly

The size of the spleen is determined by sex, age and height. We recommend using this calculator to determine the expected spleen size: https://qxmd.com/calculate/calculator_384/expected-spleen-size. Mild splenomegaly (14cm or less) is usually not concerning.

Causes

- Liver disease with portal hypertension
- Viral infection e.g. EBV, CMV
- Other infections e.g. tuberculosis, infective endocarditis, tropical diseases, syphilis
- Autoimmune diseases e.g. rheumatoid arthritis
- Metabolic storage disorders e.g. Gaucher's disease
- Sarcoidosis
- Lymphoma
- Myeloproliferative neoplasms e.g. chronic myeloid leukaemia, myelofibrosis
- Haemolytic anaemias, thalassaemia and haemoglobinopathies

History and examination

Look at previous imaging if available. Ask about symptoms relating to spleen size e.g. pain, early satiety. Clinically evaluate for above causes including asking about B symptoms, recent viral infection, features of autoimmune disease, family history and travel history. Review any previous imaging.

Suggested investigations

- Full blood count and blood film (urgent)
- Ultrasound scan of abdomen
- Liver function tests
- Viral screen e.g. EBV, CMV, HIV, hepatitis B and C
- Haemolysis screen (blood film, reticulocyte count, LDH, LFTs, haptoglobin, DAT)
- Immunoglobulins and serum protein electrophoresis
- Autoimmune screen if history suggestive
- Others depending on clinical history and examination and differential diagnosis

Management

- If spleen size is enlarged for height and sex but 14cm or less and no other cause and no suspicion regarding haematological aetiology then suggest repeating ultrasound scan in four to six months to see if resolving and to ensure not increasing in size.
- If persistently enlarged over 14cm or 2cm above predicted or if concerns regarding haematological malignancy then suggest referral to haematology unless underlying liver disease or infective cause
- Discuss with Advice and Guidance team if concerns

Lymphadenopathy

Lymph node enlargement can occur in infective and neoplastic conditions. Neoplastic lymph nodes tend to be non-tender and progressive. In the case of lymphoma, lymphadenopathy may be associated with B symptoms (over 10% weight loss in 6 months, drenching sweats or unexplained fevers), alcohol-induced lymph node pain, itch or full blood count abnormalities. However frequently in lymphoma the blood count is normal so this should not necessarily reassure if other clinical concerns. Repeatedly waxing and waning lymphadenopathy does not necessarily exclude a diagnosis of lymphoma.

Causes

- Infections – particularly localised infection, tuberculosis, syphilis
- Lymphoma or other haematological malignancy
- Non-haematological malignancy e.g. Virchow's node in left supraclavicular fossa from lung or gastrointestinal malignancy
- Sarcoidosis
- Skin conditions e.g. eczema
- Kikuchi disease

History and examination

To look at causes above. Ask about infections, itch, alcohol-induced pain, weight loss, sweats and fevers. A travel history may be informative. Systemic enquiry is required. Examination for splenomegaly and hepatomegaly as well as other lymph node areas. Ask about symptoms suggestive of superior vena cava obstruction or stridor.

Suggested investigations

- Full blood count and blood film (urgent)
- Inflammatory markers
- Renal and liver function
- Calcium
- LDH
- Immunoglobulins and serum protein electrophoresis
- HIV test
- Monospot test if possible EBV or syphilis, toxoplasma, CMV and EBV serology as appropriate
- Autoimmune screen in appropriate

Management
Please refer if:

- Lymphadenopathy for less than six weeks in association with: B symptoms, hepatomegaly or splenomegaly, rapid nodal enlargement, disseminated or generalised nodal enlargement, anaemia or thrombocytopenia, hypercalcaemia, itch. Two-week wait referral appropriate.
- Lymphadenopathy over 1cm persisting for more than 6 weeks with no obvious infective precipitant. Two-week wait referral appropriate.
- If there is concern that the patient may have a haematological malignancy and does not fall neatly into one box please discuss with Advice and Guidance

We are happy to see patients with lymphadenopathy but please note that to diagnose lymphoma a lymph node biopsy is required and depending on features and clinical concern direct referral to a surgeon may be a more direct route. In general ENT surgeons deal with neck lymph nodes, breast surgeons with axillary nodes and general surgeons with inguinal nodes. Please use Advice and Guidance if uncertainty.

If the lymphadenopathy is associated with a lymphocytosis please refer to haematology directly.

For some patients with mild lymphadenopathy and no concerning symptoms an ultrasound scan can be of value to assess size and appearances of the lymph node architecture which can often point towards the aetiology of the lymphadenopathy.

References

- NICE Clinical Knowledge Summary. Neck lump (January 2016) https://cks.nice.org.uk/neck-lump
- NICE Haematological cancers – recognition and referral (November 2016) https://cks.nice.org.uk/haematological-cancers-recognition-and-referral

Night sweats

Nights sweats are associated with lymphoma but night sweats as the sole presenting feature of lymphoma with no palpable lymphadenopathy, no weight loss and no blood count abnormalities would be unusual. The sweats should be drenching (e.g. need to change the bedclothes), often occur at night and affect the whole body (not just one area e.g. back of neck).

Causes

- Infections – e.g. tuberculosis, endocarditis, osteomyelitis, abscesses, tropical infections
- Lymphoma
- Other malignancy e.g. lung cancer
- Endocrine issues
    - Hypoglycaemia
    - Phaeochromocytoma
    - Hyperthyroidism
    - Menopause
    - Carcinoid
- Autoimmune diseases
- Neurological diseases e.g. autonomic dysfunction, Parkinson's
- Medications e.g. antidepressants, hormones e.g. tamoxifen – check BNF
- Withdrawal syndromes e.g. drugs, alcohol
- Acid reflux
- Idiopathic

History and examination

Think about above causes and rule out systematically. Examine for lymphadenopathy and splenomegaly. Ask about travel.

Suggested investigations

- Full blood count and film (urgent)
- Renal and liver function tests
- Inflammatory markers
- Calcium
- TSH
- Glucose or HBA1c
- Hormonal profile as appropriate
- HIV
- LDH
- Immunoglobulins and serum protein electrophoresis
- Chest radiograph
- Autoimmune screen if history suggestive

Management
This depends on the underlying cause. If there is associated weight loss or palpable lymphadenopathy then refer to haematology via 2WW.

References

- NICE Haematological cancers – recognition and referral (November 2016) https://cks.nice.org.uk/haematological-cancers-recognition-and-referral

Raised ESR

The reference range here depends on the patient's age and may be falsely elevated if the patient is anaemic or the sample has taken a long time to reach the laboratory.

Causes

- Infection
- Inflammation e.g. autoimmune disease, polymyalgia rheumatica
- Malignancy
- Increased immunoglobulins
- Myeloma or lymphoma
- Trauma
- Sarcoid

History and examination

Evaluate for any infective cause and look for any signs or symptoms of autoimmune disease. Ask about night sweats, bone pains and weight loss. Examine for lymphadenopathy and splenomegaly. Look at older blood results.

Suggested investigations

- Full blood count and blood film
- Autoimmune screen if appropriate or suggestive
- Tests for infective aetiology
- Calcium
- Immunoglobulins and serum protein electrophoresis
- If no obvious cause consider chest radiograph and abdominal imaging

Management

This depends on the underlying cause and degree of suspicion. If there are no results or features to suggest haematological malignancy we do not review patients with an elevated ESR.

Iron deficiency

Ferritin less than 12 µg/L indicates complete absence of stored iron and less than 20 µg/L indicates iron depletion. Between 30 and 50 µg/L can also be consistent with iron deficiency; especially in elderly patients and in inflammatory states where ferritin may be 'falsely' elevated. Less than 30 µg/L has a 92% sensitivity and 98% specificity for diagnosing iron deficiency and a ferritin less than 40 µg/L is 98% sensitivity and specific for iron deficiency. A ferritin above 50 µg/L excludes iron deficiency unless there is inflammation.

Whilst a low MCV and MCH are often seen in iron deficiency they are not completely sensitive so a normal full blood count does not rule out iron deficiency. 50% of patients with iron deficiency will have a normal MCV. When there are concerns of iron deficiency but the ferritin is normal due to co-existent inflammation further testing may help including blood film, reticulocyte haemoglobin, zinc protoporphyrin and transferrin saturation. In the vast majority of cases ferritin is all that is required and we do not advise routine testing for 'iron studies'. The serum iron is not a good test for iron deficiency as it varies depending on time of day, recent meals and does not reflect iron stores.

Causes

- Blood loss
    - Blood donor
    - Gastrointestinal, gynaecological or urological blood losses
- Poor dietary intake of iron
- Malabsorption
- Increased requirements e.g. pregnancy, infancy
- Paroxysmal nocturnal haemoglobinuria (very rare)

History and examination

Look for causes of blood loss. Ask about blood donation. Ask about malabsorption symptoms and diet. Enquire about travel history.

Suggested investigations

- Full blood count
- Coeliac screen
- *Helicobacter pylori*
- Stool parasite if relevant travel history and/or eosinophilia
- Urinalysis
- Ferritin (CRP if ferritin normal and suspect iron deficiency)
- If elevated inflammatory markers the following may be helpful: blood film, reticulocyte haemoglobin, zinc protoporphyrin and transferrin saturation
- As directed by gastroenterology or gynaecology or urology e.g. endoscopies etc.

Management

- We do not review patients with iron deficiency in haematology.
- Iron deficiency should be managed as per local and national guidelines
- If further investigations are required patients should be referred to another speciality depending on the history and examination (e.g. gastroenterology, gynaecology, urology).
- If oral iron is required suggest that this is taken with vitamin C or orange juice and without acid suppressant
    - Repeat full blood count in four weeks to ensure responding – there should be a 20 g/L rise in haemoglobin after four weeks of therapy
    - Carry on iron therapy for three months after anaemia resolved and MCV normalised to build stores and/or aim ferritin over 50 µg/L
    - Ongoing monitoring e.g. every three months and then annually for those at risk of further iron deficiency
    - Continuous replacement may be required if ongoing losses e.g. heavy menstrual bleeding or malabsorption. Once daily or even alternate daily iron supplementation is usually all that is required when on long term prophylaxis. These patients should have their full blood count and ferritin monitored every six to 12 months.
- Please note that commercial preparations claiming to be better tolerated often have low amounts of elemental iron and may not be sufficient in someone with iron deficiency anaemia but may be considered as maintenance therapy
- Dietary changes are usually insufficient once patients are deficient in iron and supplementation is usually required
- For patients who do not tolerate oral iron:
    - Laxatives if constipation
    - Use alternative preparation (ferrous gluconate has less elemental iron than ferrous sulphate or ferrous fumarate and therefore may be better tolerated)
    - Use lower dose of elemental iron
    - Take with food (although this may impair absorption)
    - Use liquid paediatric formulation e.g. sodium feredetate
    - There is some evidence to suggest that alternate day oral iron is as effective as traditional TDS regimes and may be better tolerated
- If oral iron does not work (there should be a rise in haemoglobin of 20 g/L in four weeks)
    - Check compliance
    - Take on empty stomach with vitamin C
    - Take in the morning when hepcidin levels are usually lower
    - Avoid acid suppressants
    - Avoid taking with calcium-containing products and tannins (e.g. tea and wine)
    - Check coeliac serology, *H pylori* test and enquire about malabsorption
    - Avoid slow-release or enteric-coated preparations (these often release their iron late in the small bowel after the optimal sites of absorption)
    - Ensure no other nutritional deficiencies e.g. vitamin B12 or folate
    - Intravenous preparations may be needed if inflammation as this reduces the amount of iron absorbed
- Patients should store iron supplements carefully to avoid accidental overdose

There is a specialist iron deficiency clinic at the RVI (run by gastroenterology) if further advice is required

Intravenous iron is generally only considered when patients are truly intolerant of oral supplements. There is some limited evidence that intravenous iron may work slightly more quickly than oral iron and could be considered where a rapid rise in haemoglobin is required. In general some indications for intravenous iron are below:

- Iron deficiency anaemia with intolerance of oral iron, especially in inflammatory bowel disease, or where oral iron is ineffective.
- To support the use of erythropoiesis stimulating agents (including patients on renal dialysis).
- Persistent bleeding where taking oral iron is insufficient e.g. hereditary haemorrhagic telangiectasia
- Anaemia of chronic disease/inflammation where oral iron is poorly absorbed
- As an alternative to blood transfusion when a rapid increase in haemoglobin is required (e.g. perioperative anaemia, severe anaemia in late pregnancy or postpartum anaemia).

If intravenous iron is required urgently then this can be accessed via ambulatory care. In general speak to the relevant specialist or discuss with the iron deficiency service.

References

- Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. *Gut* 2011; 60: 1309-1316. https://www.bsg.org.uk/resource/guidelines-for-the-management-of-iron-deficiency-anaemia.html
- NICE Clinical Knowledge Summary. Anaemia – iron deficiency (September 2018). https://cks.nice.org.uk/anaemia-iron-deficiency
- Thomas DW, Hinchliffe RF, Briggs C, Macdougal IC, Littlewood, T, Cavill I. Guideline for the laboratory diagnosis of functional iron deficiency. *Br J Haematol* 2013; **161**: 639-648. https://b-s-h.org.uk/guidelines/guidelines/laboratory-diagnosis-of-functional-iron-deficiency/
- Pavord S, Daru J, Prasannan N, *et al*. UK guidelines on the management of iron deficiency in pregnancy. *Br J Haematol* 2020; **188**: 819-830 https://b-s-h.org.uk/guidelines/guidelines/uk-guidelines-on-the-management-of-iron-deficiency-in-pregnancy/

Hyperferritinaemia

Ferritin is high if over 200 µg/L in women and over 300 µg/L in men.

Causes

- Any infection or inflammation including autoimmune conditions
- Liver disease and metabolic syndrome
- Malignancy
- Genetic haemochromatosis
- Renal failure
- Chronic blood transfusion
- Thalassaemia (even without blood transfusion)
- Myelodysplasia
- Porphyria cutanea tarda
- Inherited anaemias including sideroblastic anaemia, congenital dyserythropoietic anaemia and some inherited haemolytic syndromes
- Hereditary hyperferritinaemia cataract syndrome
- Haemophagocytic lymphohistiocytosis
- Gaucher's disease
- Acaeruloplasminaemia

We do not see patients with high ferritin in haematology unless there is a suspected haematological cause such as thalassaemia, transfusion overload, other inherited anaemia or myelodysplasia. This should be obvious from the history or blood count. We suggest following these two comprehensive guideline documents from the British Society for Haematology:

- Investigation and management of a raised serum ferritin: https://b-s-h.org.uk/guidelines/guidelines/investigation-and-management-of-a-raised-serum-ferritin/
- Diagnosis and therapy of genetic haemochromatosis: https://b-s-h.org.uk/guidelines/guidelines/diagnosis-and-therapy-of-genetic-haemochromatosis-review-and-2017-update/

If genetic haemochromatosis is suspected due to hyperferritinaemia and transferrin saturations above 40% in women or 50% in men then check *HFE* genotyping. This is available from primary care. If the patient is homozygous for *HFE* C282Y mutation or a compound heterozygote C282Y/H36D then suggest refer to Dr Steven Masson, consultant hepatologist. There are rare iron loading syndromes not due to mutations in the *HFE* gene and therefore if these are suspected (e.g. persistently elevated transferrin saturations above 40% in women or 50% in men or ferritin above 1000 µg/L and no secondary cause) then you may wish to discuss this with Dr Masson in the first instance.

References

- Cullis JO, Fitzsimons EJ, Griffiths WJ, Tsochatzis E, Thomas DW. Investigation and management of a raised serum ferritin. *Br J Haematol* 2018; **181**: 331-340. https://b-s-h.org.uk/guidelines/guidelines/investigation-and-management-of-a-raised-serum-ferritin/
- Fitzsimons EJ, Cullis JO, Thomas DW, Tsochatzis E, Griffiths WJ. Diagnosis and therapy of genetic haemochromatosis (review and 2017 update). *Br J Haematol* 2018; **181**: 293-303. https://b-s-h.org.uk/guidelines/guidelines/diagnosis-and-therapy-of-genetic-haemochromatosis-review-and-2017-update/

Vitamin B12 or folate deficiency

We do not routinely see patients with vitamin B12 or folate deficiency. The cause of vitamin B12 or folate deficiency is usually dietary, due to malabsorption or autoimmune gastroenterological disorders.

We suggest following this guideline from the British Society for Haematology: Devalia V, Hamilton MS, Molloy AM. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. *Br J Haematol* 2014; **166**: 496-513. https://b-s-h.org.uk/guidelines/guidelines/diagnosis-of-b12-and-folate-deficiency/

Prolonged clotting times and bruising

Coagulation tests are useful to screen for bleeding disorders in those with a suggestive bleeding history but alone are poorly predictive in assessing risk of bleeding pre procedure. An abnormal coagulation screen does not necessarily increase the risk of bleeding and a normal coagulation screen does not necessarily rule out a bleeding disorder.

Indications for coagulation screens include:

- Before starting anticoagulation
- When investigating thrombocytopenia
- To look for a lupus anticoagulant
- Monitor anticoagulant (only request specific assay e.g. INR for warfarin)
- In the presence of a bleeding history
- Monitor severity of liver disease
- In patients with liver disease and high ASA grade pre surgery

A common cause of a prolonged APTT is the presence of an antibody which interferes with the assay. The commonest example is a lupus anticoagulant (LA). When a prolonged APTT is found, the lab will often automatically do further tests to try to work out the cause. The confirmatory test for a LA is the DRVVT. A LA is a type of anti-phospholipid antibody and is often not clinically significant but is associated with anti-phospholipid syndrome (APS) and other autoimmune diseases. Anti-cardiolipin and anti-beta-2 glycoprotein-1 antibodies are also seen in patients with APS. Anti-phospholipid antibodies are detectable in up to 5% of the normal population and can be a transient phenomenon and therefore we may advise to repeat after three months to ensure resolution. However this is only indicated in patients with symptoms suggestive of APS (pregnancy morbidity, thrombosis, neurological symptoms, thrombocytopenia etc.). In asymptomatic patients where a LA has been picked up coincidentally, no further tests are indicated.

Causes

Prolonged PT (or PT>APTT)	Prolonged APTT (or APTT>PT)	Prolonged PT and APTT	Bleeding disorders with normal coagulation
Warfarin	Lupus anticoagulant or other antibody interfering with assay	Disseminated intravascular coagulation	von Willebrand disease
Liver disease	Heparin	Anticoagulants	Platelet function defects
Vitamin K deficiency	Dabigatran	Coagulopathy due to trauma	Drugs e.g. antiplatelets, apixaban
Factor VII deficiency	Factor VIII, IX and XI deficiency	Major haemorrhage	Mild factor deficiency
Rivaroxaban	Factor XII deficiency (not a bleeding disorder)	Dysfibrinogenaemia	Factor XIII deficiency
	von Willebrand disease	High haematocrit	Connective tissue disorders e.g. Ehlers Danlos
	Dysfibrinogenaemia	Liver disease	Vitamin C deficiency
	High haematocrit	Severe vitamin K deficiency	Uraemia
		Inherited deficiencies of factors II, V, X	Hereditary haemorrhagic telangiectasia

If the coagulation screen is unexpectedly abnormal suggest repeat in first instance as pre-analytical variables heavily affect results.

History and examination

Look at older results – is this a new problem? Ensure sample not taken from a line or the patient is on an anticoagulant. Ask about personal and family history of bleeding:

- Bleeding associated with trauma or surgical challenges including dental procedures – was there abnormal bleeding, was blood transfusion required, did the patient need to have additional intervention to secure haemostasis?
- Heavy menstrual bleeding from menarche
- Bleeding around pregnancy or delivery
- Bruising or excess bleeding in minor injuries
- Spontaneous bleeding – gastrointestinal, joint/muscle bleeds, intracranial haemorrhage, epistaxis

If there is easy bruising look at medications and ask about alcohol history. In addition to anticoagulants, NSAIDS and anti-platelet agents, antidepressants may also cause bruising. Rarely if a patient is malnourished vitamin C deficiency causes bruising. Bruising is common in elderly patients due to lack of skin tone and also in patients taking long-term steroids. Examine for lymphadenopathy or splenomegaly and look for signs of liver disease, hypermobility or hypothyroidism. Ask about a family history of bleeding disorder. Please bear in mind the risk of non-accidental injury and abuse if unexplained bruising. See separate guideline on non-accidental injury.

Suggested investigations

- Full blood count and blood film (urgent)
- Repeat coagulation screen
- Renal and liver function
- TSH
- Urinalysis if a petechial rash
- Further investigations may have already been reflexed from the laboratory e.g. investigation for an antibody such as lupus anticoagulant or factor assays

Management

This depends on why the test was done and the results. If there is clinical concern about a bleeding disorder due to a suggestive personal or family history we would suggest referral even if the coagulation screen is normal. If there is an alternative cause of the abnormal coagulation e.g. liver disease then suggest discussion with the relevant speciality. If uncertainties please discuss via Advice and Guidance.

Sudden onset bruising may be the first sign of acute leukaemia. Other features that point towards this diagnosis includes: weight loss, fever, hepatosplenomegaly, petechial rash, pallor. If this is suspected then arrange an urgent full blood count and coagulation screen.

Patients frequently complain of easy bruising. This is more common in the elderly due to reduction in skin tone and may be exacerbated by steroid therapy and anti-platelet or anticoagulant medication. If the bruising is localised to one area (e.g. legs), if there are no other bleeding symptoms (especially if previous unremarkable surgical challenges), if the bruising is a recent phenomenon and the full blood count and coagulation screen is normal then the likelihood of finding an underlying inherited bleeding disorder is slim.

References

- NICE Clinical Knowledge Summary. Bruising (March 2016). https://cks.nice.org.uk/bruising

Thrombophilia

A “thrombophilia screen” is a test for a variety of factors predisposing for venous thrombosis. With the exception of lupus anticoagulant (see above), the results are irrelevant for the management of arterial thrombosis. For patients with unexplained arterial thrombosis different tests may be appropriate and should be discussed with the appropriate specialist (e.g. stroke physician, cardiologist, vascular surgeon). There are surprisingly few indications for thrombophilia testing and it is not usually appropriate outside of specialist coagulation clinics. This is because:

1) The test is not exhaustive so a negative test does not rule out an inherited tendency to thrombosis.
2) Most people who carry the most common prothrombotic abnormalities e.g. factor V Leiden will never have a thrombosis, so a positive result should not influence management. Screening asymptomatic family members is therefore not advised.
3) Patients with a provoked thrombosis would usually have a time-limited period of anticoagulation and stop regardless of a thrombophilia screen result.
4) Patient with unprovoked thrombosis are often offered on going anticoagulation, regardless of a thrombophilia screen result.
5) A family history of venous thrombosis in a first degree relative is a relative contraindication to the use of oestrogen containing contraceptives/HRT irrespective of the presence or absence of a defined thrombophilia

A demand management process is in place to screen requests and contact numbers for the Consultant Haematologists involved in this provided to allow requestors to discuss processing of individual samples.

When deciding on whether to perform a thrombophilia screen we generally follow this guideline from the British Society for Haematology: Baglin T, Gray E, Greaves M, *et al*. Clinical guidelines for testing for heritable thrombophilia. *Br J Haematol* 2010; **149**: 209-220. https://b-s-h.org.uk/guidelines/guidelines/testing-for-heritable-thrombophilia/

Venous thromboembolism and travelling

Venous thromboembolism occurs in travellers due to immobility, direct compression of the venous system at the back of the knee and possible activation of the coagulation system in response to air travel. However, the absolute risk of VTE in travellers is low. The absolute risk of VTE in healthy people has been calculated as one event per 106 667 flights for flights lasting less than four hours, and one event per 4656 flights, for flights lasting over four hours. Risk increases with the duration of flight. There is little evidence with which to make firm recommendations.

Risk factors for VTE include:

- Previous DVT or PE off anticoagulants
- Active malignancy
- Recent surgery or trauma, particularly to the abdomen, pelvis, or legs in last four weeks
- A family history of VTE in first degree relative
- Aged over 60 years
- Inherited thrombophilia
- Large varicose veins or chronic venous insufficiency
- Limited mobility (for example, a lower-limb fracture in plaster)
- Obesity (body mass index greater than 30 kg/m^2)
- Polycythaemia
- Pregnancy, or up to six weeks postpartum
- Prothrombotic state e.g. autoimmune or inflammatory conditions
- Use of oestrogens, such as oral contraceptives or hormone replacement therapy.

Management

Counsel patients with higher risk of VTE and allow them to make a decision as to whether flights should be postponed until the risk reduces.

In patients with a personal history of VTE we take the pragmatic solution of offering either a prophylactic dose of LMWH or rivaroxaban in all flights over four hours. If their thrombotic event was associated with a flight less than four hours we offer this for all flights. There is little good quality evidence for which to advise on other scenarios but if there are multiple risk factors then a similar regime can be considered. Rivaroxaban has the advantage of not requiring any sharps bins. We advise to take one 10mg dose prior to flying (each way) for every 24 hours in flight. For example a six hour flight would need one 10mg dose outbound and one dose for the return but if a fight or journey lasted more than 24 hours then a second dose would be required each way. If LMWH is used, use a pre-filled syringe and ensure patients are able to administer. Provide written information on the need for needles and provide a sharps bin.

For patients with other risk factors class 1 stockings (exerting a pressure of 14–17 mmHg at the ankle) or proprietary flight socks can be considered.

These are contraindicated if the ABPI is less than 0.8. Aspirin is not advised. Patients should move around frequently and perform calf compression exercises.

Keeping hydrated seems sensible but there is no evidence to suggest it reduces risk of VTE. Patients need to inform their travel insurance company of any pre-existing medical problems. It is sensible to offer advice on the signs and symptoms of VTE in those at risk and the need to present if these develop.

References

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

Superficial thrombophlebitis

Please see separate guideline on this.

Blood parasite investigation

A number of parasites can be detected by blood film microscopy including malaria, microfilaria, trypanosomes and babesia. Timing of sample and clinical details is critical for accurate interpretation.

Malaria

There are five recognised species of malaria parasites affecting humans: *Plasmodium falciparum*, *P vivax*, *P ovale*, *P malariae* and *P knowlesi*. Patients can present with fever, myalgia, headache, nausea, diarrhoea, vomiting, lethargy, anorexia and rigors. Rarely symptoms of malaria can manifest many years after exposure.

In patients returning from a malarial endemic region presenting with symptoms concerning for malaria the following initial investigations are suggested

- Full blood count
- Thick and thin blood films (the laboratory will automatically calculate level of parasites in cases of *P falciparum* and *P knowlesi*)
- Malaria rapid diagnostic test (this will be done automatically by the laboratory)
- Renal and liver function
- CRP

It is vital that details of anti-malarial medication and travel history are given with each request. When investigation for malarial parasites is requested the sample should be transported to the laboratory as soon as possible. A negative malarial screen does not exclude a diagnosis of malaria. If there is strong clinical suspicion of malaria repeat the test in 12, 24 and 48 hours. If concerns please discuss with an infectious diseases specialist registrar or consultant.

Microfilaria

Filariasis in humans can give rise to a variety of clinical features; these include eosinophilia, chyluria, elephantiasis, lymphadenopathy, Calabar swelling, urticaria, subcutaneous nodules and blindness.

In patients returning from an endemic region presenting with symptoms concerning for microfilaria the following initial investigations are suggested

- Full blood count
- Thick and thin blood films
- Filaria serology

The timing of specimen sampling is critical in the detection of microfilaria. Times for collection should be selected in accordance with the patient's clinical symptoms and travel history. An absolute minimum of a sample taken during the day (around 1pm) and one at night (around midnight) should be examined. It is vital that details of travel history are given with each request. If concerns please discuss with an infectious diseases specialist registrar or consultant as normal blood film microscopy does not exclude this diagnosis.

Trypanosomes

Patients infected with trypanosomes can present with fever, headaches, joint pains, itching and lymphadenopathy. The symptoms can vary depending on the type of trypanosome.

In patients returning from an endemic region presenting with symptoms concerning for trypanosome infection the following initial investigations are suggested

- Full blood count
- Thick and thin blood films
- Trypanosome serology

If concerns please discuss with an infectious diseases specialist registrar or consultant as normal blood film microscopy does not exclude this diagnosis.

Babesiosis

Babesiosis occurs following tick bites; particularly in immunocompromised patients and patients who have hyposplenism. Babesia infection is characterised by the presence of haemolytic anemia and nonspecific flu-like symptoms (e.g. fever, chills, myalgia, weakness, fatigue). Some patients have splenomegaly, hepatomegaly, or jaundice. Risk factors for severe babesiosis include asplenia, advanced age and other causes of impaired immune function (e.g. HIV, malignancy, corticosteroid therapy, chemotherapy).

In patients returning from an endemic region presenting with symptoms concerning for Babesiosis the following initial investigations are suggested

- Full blood count
- Thick and thin blood films

It is vital that details of travel history are given with each request. If concerns please discuss with an infectious diseases specialist registrar or consultant as normal blood film microscopy does not exclude this diagnosis.