

GP REFERRAL GUIDELINES

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Anaemia

Anaemia is defined as a haemoglobin of <13g/dl in an adult male or <11.5g/dl in an adult female. The patient's symptoms and initial FBC findings (particularly mean corpuscular volume and blood film features) will influence both the urgency and direction of initial clinical investigation.

Important: Iron deficiency should generally be referred to gastroenterology / gynaecology as appropriate for further investigation. Similarly, uncomplicated B12 / folate deficiency does not require routine referral to haematology (see macrocytosis guideline).

The following should be referred urgently for outpatient assessment:

- Leucoerythroblastic anaemia (based on blood film report)
- Unexplained progressive *symptomatic* anaemia
- Anaemia in association with:
 - splenomegaly or lymphadenopathy
 - other cytopenias

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Careful history focussing on duration, symptoms, bleeding, diet, drug and family history
- Blood film examination and reticulocyte count
- Ferritin, B12 and folate, nb serum iron, TIBC, Transferrin saturation will be more informative than ferritin if there is an inflammatory component.
- Immunoglobulins and protein electrophoresis, urine for Bence Jones proteins
- Renal and liver biochemistry
- Monitor FBC for evidence of progression over time

Referral for specialist opinion should be considered for:

- Persistent unexplained anaemia
- Iron deficiency showing sub-optimal response to oral iron therapy after a 6-8 week trial of iron.
- Patients intolerant of a single preparation of oral iron should be switched to an alternative as they may tolerate them more. We suggest Ferrous Sulphate, ferrous gluconate or liquid iron preparations e.g. synthron. If patients are intolerant and have significant side effects then they could be considered for intravenous iron therapy. The primary investigation of the iron deficiency e.g. gastroenterology or gynaecology should be carried out by the appropriate referrals either in primary or secondary care.

Haemoglobinopathy

We offer a twice weekly specialist haemoglobinopathy clinic, which provides comprehensive multidisciplinary care for patients with:

Sickle cell disease (HbSS, HbSC, HbSBthalassaemia and other compound heterozygotes)

B thalassaemia major

B thalassaemia intermedia HbH disease (α thalassaemia)

Diamond Blackfan anaemia

Other inherited haemolytic anaemias eg G6PD deficiency, Hereditary spherocytosis.

General practitioners can refer directly to these clinics. In addition we have specialist clinics with the orthopaedic, renal and neurology team which are accessed via referral to the sickle cell team via phone 02071882741 or fax 02071882728.

Leucocytosis

Leucocytosis is defined as an elevation of white cell count to $>10.5 \times 10^9/l$. It has a wide differential diagnosis ranging from normal response to infection through to haematological malignancies including acute leukaemias. Detection of a leucocytosis should prompt scrutiny of the differential white cell count, other FBC parameters and blood film examination.

The following should be referred by telephone for *immediate* haematology assessment:

- New suspected Acute leukaemia
- New suspected Chronic myeloid leukaemia with either:
White cell count $>100 \times 10^9/l$
Hyperviscosity symptoms (Headache, visual loss, acute thrombosis)

The duty haematologist will contact the general practice following the results of FBC and blood film examination and arrange urgent patient assessment / admission.

The following should be referred urgently for outpatient assessment:

- Leucoerythroblastic blood picture (from blood film report)
- New chronic myeloid leukaemia not meeting the above criteria
- Unexplained leucocytosis with white cell count $>50 \times 10^9/l$

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Blood film examination with differential white cell count
- Careful history and assessment for 'reactive' causes: smoking, infection, inflammation or neoplasia
- Examination for lymphadenopathy, splenomegaly
- A minor non-specific leucocytosis or neutrophilia is often seen in smokers

Referral for specialist opinion should be considered for:

- Persistent unexplained:
White cell count $>20 \times 10^9/l$
Neutrophilia $>15 \times 10^9/l$
Eosinophilia
Monocytosis
Basophilia

Lymphadenopathy

Lymphadenopathy occurs in a range of infective and neoplastic conditions and may be isolated, involving a single node or nodes within an anatomical grouping, or generalised. Isolated lymphadenopathy frequently results from local infection or neoplasia. Suspicions of lymphoma should be heightened by the presence of generalised or progressive lymphadenopathy, hepatosplenomegaly or accompanying 'B' symptoms (>10% weight loss in 6 months, soaking sweats, unexplained fevers). Repeatedly waxing and waning lymphadenopathy does not necessarily exclude a diagnosis of lymphoma.

The following should be referred urgently as 'suspected cancer':

- Lymphadenopathy >1cm persisting for >6 weeks with no obvious infective precipitant
- Lymphadenopathy for <6 weeks in association with:
 - B symptoms (see above)
 - hepatic or splenic enlargement
 - rapid nodal enlargement
 - disseminated / generalised nodal enlargement
 - anaemia / leucopenia / thrombocytopenia
 - hypercalcaemia

If in any doubt over whether to refer urgently or observe, we would strongly suggest discussion with the duty haematologist who will be pleased to offer advice on both the optimal timing and best route for referral

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Full blood count
- Glandular fever screen
- HIV test if considered appropriate
- Close monitoring of symptoms and progress of lymphadenopathy

Lymphocytosis

Lymphocytosis is defined as a lymphocyte count $> 4 \times 10^9/l$. A transient, reactive lymphocytosis is frequently seen in acute viral infection, particularly infectious mononucleosis. Chronic lymphocytosis is characteristic of chronic lymphocytic leukaemia (CLL), the incidence of which peaks between 60 and 80 years of age. In its early stages this condition is frequently asymptomatic with treatment only being required on significant progression.

The following should be referred urgently for outpatient assessment:

- Lymphocytosis in association with:
 - anaemia, thrombocytopenia or neutropenia
 - splenomegaly
 - painful or progressive lymphadenopathy
 - B symptoms (weight loss $>10\%$, soaking sweats, unexplained fever)
- Lymphocytosis in excess of $20 \times 10^9/l$ (or rapidly increasing)
- Confirmed presence of clonal B-cells / chronic lymphocytic leukaemia cells by haematology (immunophenotyping) laboratory

Appropriate investigation in primary care for patients with lymphocyte count $> 5 \times 10^9/l$ not meeting criteria for urgent referral:

- Glandular fever screen if appropriate
- Repeat FBC in 4-6 weeks – viral lymphocytoses are frequently transient
- Lifestyle modification – smoking is a well-recognised cause of reactive lymphocytosis (plus mild neutrophilia)

Referral for specialist opinion should be considered for:

- Persisting lymphocytosis $> 5 \times 10^9/l$ not fulfilling criteria for urgent referral

Macrocytosis

The differential diagnosis of red cell macrocytosis (mean corpuscular volume >100fl) includes B12 and folate deficiency, excess alcohol consumption, hypothyroidism, reticulocytosis and myelodysplastic syndrome. Macrocytosis is a normal physiological finding in pregnancy and is seen routinely in patients taking either hydroxyurea (hydroxycarbamide), or certain anti-retroviral agents.

Appropriate investigation in primary care prior to referral:

- B12 and folate levels (plus Intrinsic Factor Antibodies and coeliac screen)
- Blood film examination and reticulocyte count
- Liver and thyroid biochemistry
- Immunoglobulins and protein electrophoresis, urine for Bence Jones proteins
- Alcohol history and appropriate lifestyle modification

Referral for specialist opinion should be considered for:

- Suspected myelodysplastic syndrome (based on blood film report)
- MCV > 100fl with accompanying cytopenia (excluding B12 / folate def)
- Persistent *unexplained* MCV > 105fl

Guidance on the diagnosis of Vitamin B12 deficiency

Uncomplicated B12 or folate deficiency does not require routine referral for haematology outpatient assessment.

Clinical features of B12 deficiency are highly variable. Mildly reduced B12 levels are common and less than 10% of such patients show clinical evidence of deficiency. Only a limited correlation is seen between FBC abnormalities and the presence of neurological manifestations, with entirely normal FBC findings in 20-30% of cases presenting with neurological symptoms.

B12 levels above 300ng/l confirm adequate body stores and retesting within 2 years is unnecessary. Repeating the test once the patient is on replacement therapy is of no value. Vitamin B12 testing should also not be performed in pregnancy as results are entirely unreliable. Intrinsic factor antibodies may be found in up to 35% of cases of pernicious anaemia and, when detected, are considered diagnostic. A negative result is unhelpful however.

Suggested interpretation of serum B12 assay results

B12 level	Action
< 100 ng/l Low levels	B12 deficiency very likely - treat as indicated.
100-145ng/l Indeterminate.	Consider treatment, particularly if other evidence of deficiency e.g. neuropathy or macrocytosis. Check methymalonic acid (MMA) as more reflective of tissue B12 stores. Raised MMA reflect reduced B12

	levels which should normalise with B12 replacement
145-190ng/l	B12 deficiency unlikely, but seek further advice if suggestive features present, e.g. neuropathy. Check MMA if clinical symptoms suggestive.
> 300ng/l	B12 stores normal. Stores adequate for 2 years

Neutropenia

Neutropenia is defined as a neutrophil count of less than $2 \times 10^9/l$. Risk of infective complications is closely related to the depth of the neutropenia: a major increase in infections is seen with counts of $<0.5 \times 10^9/l$ while some increased risk of infection is seen with counts of $0.5-1 \times 10^9/l$. Causes of neutropenia include viral infection, sepsis, drugs, autoimmune disorders and bone marrow failure due to aplasia, malignant infiltration or severe B12 / folate deficiency.

The following should be referred urgently for outpatient assessment:

- Neutrophil count $< 1 \times 10^9/l$ (ND ethnic origin is important see below)
- Neutropenia in association with:
 - other cytopenia
 - lymphadenopathy
 - splenomegaly

Patients with active sepsis in association with unexplained neutropenia $< 1 \times 10^9$ should be discussed with the duty haematologist to arrange appropriate direct assessment

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Blood film examination
- Autoimmune screen
- Consider discontinuation of potentially precipitating medications
- Repeat FBC in 4-6 weeks – viral neutropenias are frequently transient

Please note:

Normal neutrophil count can be $<1.0 \times 10^9/L$ in individuals of Afro-Caribbean or Middle Eastern origin. This could be benign ethnic neutropenia (B.E.N.) and this has a high incidence in our local population.

Suggested assessment in primary care of a patient who is asymptomatic and has a neutropaenia without or without an accompanying mild thrombocytopaenia but normal haemoglobin. The blood test should be repeated 6-8 weeks later with a blood film and a review of medications that may contribute to lowering of neutrophil count e.g. anti-psychotic drugs Olanzapine or a high dose of Omeprazole. If the FBC is similar and there are no other precipitating causes then a diagnosis of B.E.N may be made.

Referral for specialist opinion should be considered for:

- Neutropenia associated with increased susceptibility to infection
- Other unexplained, *progressive* neutropenia

Paraproteins

Disorders characterised by the production of a paraprotein include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma and Waldenström's macroglobulinaemia. Paraproteins may also be a feature of CLL, NHL or amyloidosis. MGUS is a diagnosis of exclusion: 3% of over-70s have paraproteins which are frequently found incidentally and not associated with symptoms or physical findings. The overall risk of MGUS progression to myeloma is around 1% per year – this remains constant over time.

*Referrals to haematology should **not** be made for patients with raised immunoglobulin levels in the absence of a monoclonal paraprotein band on serum electrophoresis. Polyclonal gammopathy implies a non-specific immune reaction and is not associated with underlying haematological disorders.*

The following should be referred urgently for outpatient assessment:

- Any new paraprotein with accompanying features suggestive of multiple myeloma or other haematological malignancy these include:
 - hypercalcaemia
 - unexplained renal impairment
 - urinary Bence Jones proteins
 - increased urinary protein
 - bone pain or pathological fracture
 - radiological lesions reported as suggestive of myeloma
 - anaemia or other cytopenia
 - hyperviscosity symptoms (headache, visual loss, acute thrombosis)
 - lymphadenopathy or splenomegaly
 - lymphocytosis

Patients with suspected spinal cord compression should be discussed with duty haematologist to arrange appropriate direct assessment

Referral for specialist opinion should be considered for:

- Other newly-identified paraproteins not meeting the above criteria for urgent referral

Discharge policy for patients with MGUS

- Patients with uncomplicated paraproteins may be discharged to community monitoring after completing a period of initial investigation.
- Information at the time of discharge will include a plan for monitoring in primary care, as well as clearly defined individualised patient criteria for re-referral to the Haematology Department.

Polycythaemia

Elevated haemoglobin / haematocrit has a wide differential diagnosis including primary proliferative polycythaemia (polycythaemia vera), secondary causes (such as hypoxic lung disease and erythropoietin-secreting tumours) and relative polycythaemia resulting from plasma depletion. The threshold for therapeutic intervention with venesection or cytoreductive therapy in an individual patient depends on the cause, associated symptoms and thrombotic risk factors. Co-existing iron deficiency can sometimes mask the presence of primary polycythaemia.

The following should be referred urgently for outpatient assessment:

- Extreme raised haematocrit (Male $>.600$, Female $>.560$) in the absence of congenital cyanotic heart disease
- Persistently raised haematocrit (Male $>.510$, Female $>.480$) in association with:
 - recent arterial or venous thrombosis (including DVT / PE, CVA / TIA, MI / unstable angina, PVD)
 - neurological symptoms
 - visual loss
 - abnormal bleeding

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Confirm with repeat FBCs over time (uncuffed blood samples)
- Modify known associated lifestyle factors: smoking, alcohol, consider changing thiazides to non-diuretic anti-hypertensive agents
- Screen for diabetes

Referral for specialist opinion should be considered for:

- Elevated haematocrit (Male $>.510$, Female $>.480$) in association with:
 - past history of arterial or venous thrombosis
 - splenomegaly
 - pruritus
 - elevated white cell or platelet counts
- Persistent *unexplained* elevated haematocrit (Male $>.510$, Female $>.480$)

Discharge policy

- Following completion of investigation, only those cases requiring venesection or cytoreductive therapy will remain under outpatient follow-up
- All other cases will be discharged with a suggested frequency of FBC monitoring and a clearly-stated threshold haematocrit for re-referral

Suspected Haemochromatosis

Hereditary haemochromatosis is an autosomal recessive condition predisposing to pathological iron overload which may affect the liver, pancreas, heart, pituitary gland and joints. Over 90% of cases are caused by homozygous (C282Y) mutation of the HFE gene which can be detected by genetic screening. A raised ferritin may also be reactive to other conditions, particularly other causes of liver disease, alcohol excess, infection, inflammation or neoplastic disease.

The following should be referred urgently for outpatient assessment:

- Elevated ferritin with evidence of otherwise-unexplained 'end organ damage': congestive cardiac failure, liver dysfunction, diabetes or hypogonadism

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Repeat ferritin measurement in 4-6 weeks
- Check liver biochemistry, fasting glucose, transferrin saturation
- Careful alcohol history
- Consider 'reactive' cause: infection, inflammation, neoplasia
- Consider requesting genetic testing for HFE mutations

Referral for specialist opinion should be considered for:

- Persistent unexplained raised ferritin
- Genetic counselling / screening of first degree relatives of hereditary haemochromatosis cases

Thrombocythaemia

Thrombocythaemia / thrombocytosis is defined as a platelet count $> 450 \times 10^9/l$.

It may be due to a primary myeloproliferative disorder (essential thrombocythaemia) or closely related myelodysplastic conditions or is more commonly 'reactive': secondary to infection, inflammation, chronic bleeding or neoplasia. Very elevated platelet counts in the setting of myeloproliferative disorders carry risk of both thrombosis and abnormal bleeding (due to platelet dysfunction).

The following should be referred urgently for outpatient assessment:

- Platelet count $> 1000 \times 10^9/l$
- Platelet count $600 - 1000 \times 10^9/l$ in association with:
 - recent arterial or venous thrombosis (including DVT / PE, CVA / TIA, MI / unstable angina, PVD)
 - neurological symptoms
 - abnormal bleeding
 - age > 60 years

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Blood film examination
- Ferritin – treat and investigate iron deficiency
- Look for and treat reactive causes: infection, inflammation, neoplasia (suggest check CRP).

Referral for specialist opinion should be considered for:

- Persistent (ie lasting longer than 3 months), unexplained thrombocythaemia $> 450 \times 10^9/l$

Thrombocytopenia

Thrombocytopenia is defined as a platelet count $< 150 \times 10^9/l$.

Most patients with counts of $> 50 \times 10^9/l$ are asymptomatic, with the risk of spontaneous haemorrhage increasing significantly below $20 \times 10^9/l$. Differential diagnosis includes immune peripheral consumption (ITP), any cause of bone marrow failure (aplasia, malignant infiltration, myelodysplasia, B12 / folate deficiency), alcohol, drugs, sepsis, hypersplenism, disseminated intravascular coagulation (DIC) and TTP / HUS.

The following should be referred urgently for outpatient assessment:

- Platelet count $< 50 \times 10^9/l$
- Platelet count $50 - 100 \times 10^9/l$ in association with:
 - other cytopenia (Hb $< 10g/dl$, Neutrophils $< 1 \times 10^9/l$)
 - splenomegaly
 - lymphadenopathy
 - pregnancy
 - upcoming surgery

Patients with platelets $< 20 \times 10^9/l$ or active bleeding should be discussed with the duty haematologist to arrange appropriate direct assessment

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Blood film examination – may exclude platelet clumping artefact
- Autoimmune profile
- Liver biochemistry
- Alcohol history
- Consider discontinuation of potentially precipitating medications (discuss with haematologists if needed).
- Repeat FBC in 4-6 weeks

Referral for specialist opinion should be considered for:

- Persistent, unexplained thrombocytopenia $< 100 \times 10^9/l$
- Thrombocytopenia in patients with a history of thrombosis