UNIVERSITY HOSPITAL LIMERICK GP REFERRAL GUIDE FOR HAEMATOLOGY

Contents

1 Anaemia

Anaemia is defined as a haemoglobin of <13.0 g/dL in an adult male or <12.0g/dL in an adult female. The patient's symptoms and initial FBC findings (particularly mean corpuscular volume (MCV) 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/urology as appropriate for further investigation. Similarly, uncomplicated B12/folate deficiency does not require routine referral to haematology (see macrocytosis guideline).

Urgent Referral: 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 or 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
- Blood film is automatically made by lab for :
    - first Hb < 8.5 g/dL OR
    - Hb <10g/dL if RDW >17% in the presence of a reticulocytosis
- Ferritin, B12 and folate, serum iron, TIBC, Transferrin saturation (this will be more informative than ferritin if there is an inflammatory component)
- Immunoglobulins and protein electrophoresis
- Renal and liver biochemistry
- Monitor FBC for evidence of progression over time

Referral for specialist opinion should be considered for:

- Persistent unexplained anaemia

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2 Leucocytosis

Leucocytosis is defined as an elevation of white cell count to >11 x 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.

Urgent Referral: 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 x 10^9/L

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

- Blood film examination with differential white cell count
- Blood film is automatically made by lab for:
    - WBC > 30 x 10^9/L
    - Monocytes > 2x 10^9/L (persistently >1.5x 10^9/L for at least 3 months reviewed by Medical Scientist for blood film determination)
    - Lymphocytes >5 x 10^9/L
    - Eosinophils > 2 x10^9/L
- Inflammatory markers
- 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 x 10^9/L
- Neutrophilia >15 x 10^9/L
- Monocytosis
- Basophilia

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3 Polycythaemia/Erythrocytosis

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.

Urgent Referral: The following should be referred urgently for outpatient assessment:

- Extreme raised Packed Cell Volume (PCV; Male >0.60, Female >0.56) in the absence of congenital cyanotic heart disease
- Persistently raised PCV (Male >0.49, Female >0.48) in association with: recent arterial or venous thrombosis (including DVT/PE, CVA/TIA, MI/unstable angina, PVD), neurological symptoms, visual loss or abnormal bleeding

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

- Confirm with repeat FBCs over time (non-fasting blood samples with patient in well-hydrated state)
- Blood film is automatically made by lab for PCV >0.52 (males) or >0.49 (females) on second presentation
- 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 PCV (Male >0.49, Female >0.48) in association with: past history of arterial or venous thrombosis, splenomegaly, pruritus, elevated white cell or platelet counts
- Persistent (>3 months) unexplained elevated haematocrit (Male >0.49, Female >0.48)

Discharge policy:

- Patients with Polycythaemia Vera will remain in follow up with Haematology
- Most patients with reactive or secondary erythrocytosis will be discharged back to primary care as there are no Haematology interventions required

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4 Thrombocytosis/thrombocythaemia

Thrombocythaemia/thrombocytosis is defined as a platelet count > 450 x 10^9/L.
It is commonly 'reactive': secondary to infection, inflammation, chronic bleeding or neoplasia, but may be due to a primary myeloproliferative disorder (essential thrombocythaemia) or closely related myelodysplastic conditions.
Very elevated platelet counts in the setting of myeloproliferative disorders carry risk of both thrombosis and abnormal bleeding (due to platelet dysfunction).

Urgent Referral: The following should be referred urgently for outpatient assessment:

- Platelet count > 1000 x 10^9/L
- Platelet count 600 – 1000 x 10^9/L in association with: recent arterial or venous thrombosis (including DVT/PE, CVA/TIA, MI/unstable angina, PVD), neurological symptoms or new abnormal bleeding

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

- Blood film made by lab for persistently elevated platelet count >450 x 10^9/L (for at least 6 months)
- Ferritin and iron studies – treat and investigate iron deficiency
- Look for and treat reactive causes: infection, inflammation, neoplasia (suggest check CRP)
- An elevated CRP is associated with a reactive thrombocytosis rather than a primary haematological disorder

Referral for specialist opinion should be considered for:

- Persistent (ie lasting longer than 6 months), unexplained thrombocythaemia >450 x 10^9/L

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5 Paraproteins/MGUS

Disorders characterised by the production of a paraprotein include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma and Waldenströms 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 and/or*
- *raised Serum free light chains with abnormal ratio and/or*
- *presence of urinary Bence jones proteins.*

Polyclonal gammopathy implies a non-specific immune reaction and is not associated with underlying haematological disorders.

Urgent Referral: The following should be referred urgently for outpatient assessment:

- A new paraprotein of ≥30g/L and/or SFLC ratio ≥100
- Any new paraprotein with accompanying features suggestive of multiple myeloma or other haematological malignancy. These include:
  - unexplained hypercalcaemia
  - unexplained renal impairment
  - urinary Bence Jones proteins
  - increased urinary protein
  - bone pain or pathological fracture and radiological lesions reported as suggestive of myeloma
  - unexplained anaemia or other cytopenia
  - hyperviscosity symptoms (headache, visual loss, acute thrombosis)
  - lymphadenopathy or splenomegaly

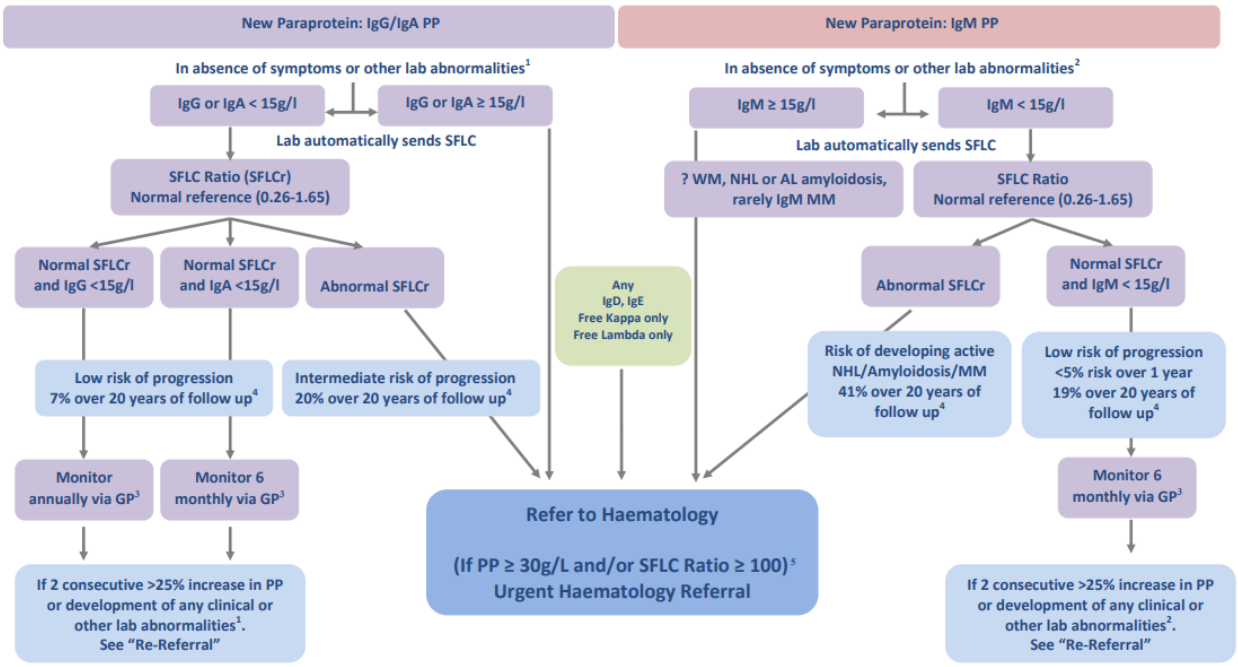
Referral for specialist opinion should be considered for:

- Newly-identified IgG, IgA or IgM paraproteins ≥15g/l not meeting the above criteria for urgent referral
- Newly-identified IgG, IgA or IgM paraproteins <15g/l with an abnormal SFLC ratio.
  The reference range for SFLC is 0.26-1.65 for patients with GFR > 90 ml/min and 0.37-3.1 for patients with renal impairment (GFR < 90ml/min)
- Any new IgD, IgE, kappa light chain or lambda light chain band

Discharge policy for patients with MGUS:

- Patients with uncomplicated paraproteins may be discharged to community monitoring after completing a period of initial investigation
- Patients should be re-referred according to the algorithm below, which is taken from the 'UHL Guidance on Management of MGUS in Primary Care Document' available on the HSE website

University Hospital Limerick: Haematology & Clinical Biochemistry
UHL Guidance on Management of MGUS in Primary Care



[1]Clinical symptoms: bone pain, anaemia, renal impairment, hypercalcaemia, neuropathy, lymphadenopathy.
[2]Clinical symptoms: Bruising, bone pain, anaemia, renal impairment, hypercalcaemia, neuropathy, lymphadenopathy.
[3] Lab monitoring: FBC/Renal/Liver/Bone/Immunoglobulins/SPEP and PP.
[4] Kyle et al, NEJM, 2018 Long term follow-up of Monoclonal Gammopathy of Undetermined Significance.
[5]Serum involved / uninvolved free light chain ratio ≥ 100 (involved free light chain, either kappa or lambda, is the one that is above the normal reference range; the uninvolved free light chain is the one that is typically in, or below, the normal range)

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6 Lymphocytosis

Lymphocytosis is defined as a lymphocyte count >4 x 10^9/L.
A transient, reactive lymphocytosis is frequently seen in acute viral infection, particularly infectious mononucleosis.
Smoking is a well-recognised cause of reactive lymphocytosis (plus mild neutrophilia)
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.

Urgent Referral: The following should be referred urgently for outpatient assessment:

- Lymphocytosis in association with unexplained: anaemia, thrombocytopenia or neutropenia, splenomegaly, painful or progressive lymphadenopathy, 'B' symptoms (weight loss >10%, drenching sweats, unexplained fever)
- Lymphocytosis in excess of 20 x 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 x 10^9/L not meeting criteria for urgent referral:

- Bloods film automatically made by lab for lymphocytes >5 x 10^9/L
- Infectious mononucleosis 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:

- Persistent lymphocytosis >5 x 10^9/L not fulfilling criteria for urgent referral

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7 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, drenching sweats, unexplained fevers).
Repeatedly waxing and waning lymphadenopathy does not necessarily exclude a diagnosis of lymphoma.

Urgent Referral: 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, unexplained anaemia/leucopenia/thrombocytopenia, hypercalcaemia

If in any doubt over whether to refer urgently or observe, we would strongly suggest discussion with the haematologist on call 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 and blood film
- Infectious mononucleosis screen
- HIV test if considered appropriate
- Close monitoring of symptoms and progress of lymphadenopathy

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8 Macrocytosis

The differential diagnosis of red cell macrocytosis (mean corpuscular volume >100 fl) 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), methotrexate or certain antiretroviral agents.

Appropriate investigation in primary care prior to referral:

- B12 and folate levels (plus Intrinsic Factor Antibodies and Coeliac screen if low)
- Blood film automatically made by lab for MCV >105fL
- Reticulocyte count
- Liver and thyroid biochemistry
- Immunoglobulins and serum protein electrophoresis
- 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

Vitamin B12 and folate deficiency are not primary haematological conditions and do not require referral for Haematology outpatient assessment.

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9 Neutropenia

Neutropenia is defined as a neutrophil count of less than 1.5 x 10^9/L. Risk of infective complications is related to the depth of the neutropenia: severe neutropenia <0.5 x 10^9/L is associated with a significantly increased risk of infection, while moderate neutropenia 0.5-1 x 10^9/L is less commonly associated with serious infections.

Causes of neutropenia include viral infection, sepsis, drugs, autoimmune disorders and bone marrow failure due to aplasia, malignant infiltration or severe B12/folate deficiency.

Urgent Referral: The following should be referred urgently for outpatient assessment:

- Neutrophil count < 1 x 10^9/L associated with recurrent or severe sepsis/l (NB ethnic origin is important see below)
- Neutropenia in association with: other cytopenia, lymphadenopathy or splenomegaly

Patients with active sepsis in association with unexplained neutropenia <1 x 10^9/L should be discussed with the duty haematologist on consults (during working hours) or haematologist on call to arrange appropriate direct assessment.

Appropriate investigation in primary care for patients with neutrophil count <1.5 x 10^9/L not meeting criteria for urgent referral:

- Blood film is automatically made by lab for neutrophils <1.5 x 10^9/L
- Virology - hepatitis B and C, HIV
- Haematinics – Serum B12 and folate
- Autoimmune screen
- Review of medications – many medications are associated with neutropenia. Consider discontinuation of potentially precipitating medications (depending on risk benefit assessment)
- Repeat FBC in 4-6 weeks – viral neutropenias are frequently transient

Referral for specialist opinion should be considered for:

Neutropenia associated with increased susceptibility to infection
Other unexplained, progressive neutropenia <1 x 10^9/L

Please note:

Benign ethnic neutropenia (B.E.N.) may be seen in in individuals of Afro-Caribbean or Middle Eastern Origin. For patients with B.E.N. a normal neutrophil count may be <1.0 x 10^9/L. This may be accompanied by mild thrombocytopenia (platelets 100-150 x 10^9/L).
For asymptomatic patients of the relevant ethnic origin with neutropenia, with or without an accompanying mild thrombocytopenia but normal haemoglobin, the blood count 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.

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10 Thrombocytopenia

Thrombocytopenia is defined as a platelet count <150 x 10^9/L.
Most patients with counts of >50 x 10^9/L are asymptomatic, with the risk of spontaneous haemorrhage increasing significantly below 20x 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.

Urgent Referral: The following should be referred urgently for outpatient assessment:

- Platelet count <50 x 10^9/L
- Platelet count 50-100 x 10^9/L in association with: other cytopenia (Hb < 10g/dL, Neutrophils <1 x 10^9/l), splenomegaly, lymphadenopathy, pregnancy or upcoming surgery

Patients with platelets <20 x 10^9/L or active bleeding should be discussed with the haematologist on consults (during working hours) or haematologist on call to arrange appropriate direct assessment.

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

- Bloods film is automatically made by lab for first presentation platelets <75x10^9/L
- Autoimmune profile
- Liver biochemistry
- Alcohol history
- Haematinics
- HIV, hepatitis B and hepatitis C
- Review of medications – many medications are associated with thrombocytopenia. Consider discontinuation of potentially precipitating medications (depending on risk benefit assessment)
- Repeat FBC in 4-6 weeks

Referral for specialist opinion should be considered for:

- Persistent, unexplained thrombocytopenia < 80 x 10^9/L
- Thrombocytopenia in patients with a history of thrombosis

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11 Eosinophilia and suspected systemic mastocytosis

Eosinophilia is defined as an elevation of the eosinophil count above levels observed in healthy individuals, usually above $0{\cdot}5 \times 10^9$/L. Hypereosinophilia (HE) is defined as an elevation of the eosinophil count $1{\cdot}5 \times 10^9$/L or greater persisting for at least 6 months for which no underlying cause can be found. It can be associated with signs of organ dysfunction (cardiac, respiratory, gastrointestinal, neurological). Investigation and treatment should not be delayed in patients with hypereosinophilia of less than 6 months duration who have evidence of end-organ damage.

Detection of hypereosinophilia should prompt assessment for underlying cause. A detailed medical history and a thorough physical examination should be performed. The history should include assessment for allergic disorders, skin rashes, cardiorespiratory, gastrointestinal and constitutional symptoms as well as detailed tropical travel history and drug history.

The causes of eosinophilia are numerous and are divided into three main categories: secondary (reactive e.g. atopy, parasites, drugs, pulmonary eosinophilias), primary clonal eosinophilia and idiopathic.

Urgent Referral: The following should be referred urgently for outpatient assessment:

- Leucoerythroblastic film, ANC >50 x10^9/L
- Eosinophil count >10 x10^9/L
- Eosinophils >1.5 x10^9/L with evidence of organ damage

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

- Blood film is automatically made by lab for eosinophils > 2 x10^9/L
- Inflammatory markers - CRP and ESR
- Renal, liver and bone profile
- LDH
- Vitamin B12
- Allergy/atopy status
- Stool cultures for parasites
- Chest x-ray

Referral for specialist opinion should be considered for:

- Unexplained persistent (>3 months) eosinophilia >1.5 x10^9/L

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12 Suspected haemochromatosis

Hereditary haemochromatosis is not a primary haematological disorder.
It is not diagnosed or managed by the Haematology service.
The Irish College of General Practitioners have issued guidance on diagnosis and management in primary care and is available on the ICGP website.