General Practice Referral Guidelines
Haematology Department
Southend University Hospital NHS Foundation Trust
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Dear Colleague

The attached protocols have been designed with the aim of streamlining referrals from primary care to the Department of Haematology by offering guidance to allow prioritisation of urgent cases while avoiding the unnecessary referral of patients who are unlikely to benefit from a specialist opinion. For non-urgent conditions, a suggested series of investigations, appropriate for the primary care setting, is included for use prior to referral.

These guidelines are likely to encompass more than 90% of referrals to Haematology. It is inevitable that a small minority of cases will fall outside their scope. In such cases and in others where a General Practitioner considers a specialist opinion to be required and appropriate, patients should still be referred to secondary care. Following receipt of a referral, it is felt by the reviewing consultant, that outpatient attendance is not required, written or telephone advice will be provided.

We are always happy to answer telephone enquiries, as in many cases advice can be provided on the basis of test results without necessarily seeing a patient.

Cases requiring rapid, direct assessment by the Haematology Department (as indicated in the guidelines) should be discussed by telephone with either the on call Haematology Staff Grade/SpR via the main switchboard (Bleep 1175) or the on call Consultant Haematologist via Haematology secretaries (01702 38 5206/5207/5410).

These guidelines are available online at:
http://www.southend.nhs.uk/media/22256/referralguidelineshaematology.pdf

Yours sincerely

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Referral Guidelines for Neutropenia

Neutropenia is defined as a neutrophil count of less than 2 x 10^9/l. Please note, that the normal range for Africans/Afrocaribbeans is 1.0-7.0 x 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 x 10^9/l while some increased risk of infection is seen with counts of 0.5-1 x 10^9/l. Causes of neutropenia include viral infection, sepsis, drugs, autoimmune disorders and bone marrow failure due to aplasia, malignant infiltration or B12 / folate deficiency.

The following should be referred urgently for outpatient assessment:

- Neutrophil count < 1 x 10^9/l
- Neutropenia in association with:
  other cytopenia (Hb < 10g/dl, Platelets < 50 x 10^9/l)
  lymphadenopathy
  splenomegaly

Patients with active sepsis in association with unexplained neutropenia < 1 x 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
- B12 and folate levels
- Autoimmune screen
- Consider discontinuation of potentially precipitating medications
- NB Normal neutophil count often <2 x 10^9/l in individuals of Afro-Caribbean or Middle Eastern origin
- Repeat FBC in 4-6 weeks – viral neutropenias are frequently transient

Referral for specialist opinion should be considered for:

- Persistent (at least on two occasions 4-6 weeks apart), unexplained neutropenia 1 – 1.5 x 10^9/l

Referral Guidelines for 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 20 x 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 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
  - upcoming surgery

Patients with platelets <20 x 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
- B12 and folate levels
- Alcohol history
- Consider discontinuation of potentially precipitating medication**s**
- Repeat FBC in 4-6 weeks

Referral for specialist opinion should be considered for:

- Persistent (at least on two occasions 4-6 weeks apart, no clumping noted on the blood film), unexplained thrombocytopenia < 80 x 10^9/l

Referral Guidelines for Thrombocytosis

Thrombocytosis/thrombocythaemia / is defined as a platelet count > 450 x 10^9/l. It may be due to a primary myeloproliferative disorder (essential thrombocythaemia) or 'reactive': secondary to infection, inflammation, chronic bleeding or neoplasia. Very high 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 x 10^9/l
- Platelet count 600 – 1000 x 10^9/l in association with:
  - recent arterial or venous thromboembolism
  - neurological symptoms
  - abnormal bleeding

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

Referral for specialist opinion should be considered for:

- Persistent (at least on two occasions 4-6 weeks apart), unexplained thrombocythaemia > 600 x 10^9/l on at least two occasions
- Persistent thrombocythaemia 450 – 600 x 10^9/l in association with:
  - previous history of arterial or venous thrombosis
  - splenomegaly
  - elevated haemoglobin or white cell count

Referral Guidelines for Polycythaemia

Elevated haemoglobin 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.

The following should be referred urgently for outpatient assessment:

- Hb > 20g/dl (PCV >0.60) in the absence of chronic hypoxia
- Raised Hb in association with:
  - recent arterial or venous thrombosis
  - 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 if possible)
- Modify known associated lifestyle factors: smoking, alcohol, consider changing thiazides to non-diuretic anti-hypertensive agents

Referral for specialist opinion should be considered for:

- Elevated PCV (Male >0.52, Female >0.48) in association with:
  - past history of arterial or venous thrombosis
  - splenomegaly
  - pruritus
  - elevated white cell or platelet counts
- Persistent (at least on two occasions 4-6 weeks apart), *unexplained* elevated PCV (Male >0.52, Female >0.48)

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 PCV for re-referral

Referral Guidelines for Paraproteins

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 the age of 70 and 5% of over the age of 80 have a paraprotein which is 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 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:
  - hypercalcaemia
  - unexplained renal impairment
  - urinary Bence Jones proteins
  - bone pain or pathological fracture
  - radiological lesions reported as suggestive of myeloma
  - anaemia or other cytopenia
  - hyperviscosity symptoms (headache, visual loss, acute thrombosis)

Patients with suspected spinal cord compression should be discussed with on call haematologist or oncologist 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[1]

Very low risk patients: IgG paraprotein, less than 15 g/L and normal Free Light Chains ratio.

Patients with IgM paraproteins will generally remain under haematology follow-up

Monitor FBC, U&E, Creatinine and Ca++ and Serum Electropheresis annually

Dipstick urine for protein annually

Reasons to re-refer:

Monoclonal Band rising unexpectedly (>50% increase compared to baseline)

Developing a significant cytopenia (for instance):

Hb dropping below 10 g/dl
Neutrophils below 1.5 x 10^9/l
Platelets < 80 10^9/l

Developing renal impairment
Severe proteinuria with 24 hrs proteins >1,5g/24 hours or ++ or +++ on Dip stick examination.
Unexplained hypercalcaemia
Pathological fracture
Unexplained bone pain
L nodes enlargment with >3 lymph nodes >3 cm diameter
Unexplained weight loss > 3 kg within <3 months of time.

General Advice:

No specific dietary advice required.
Administer all usual vaccines (Flu Pneumovax etc.)

[1]South Essex Cancer Network; Haem NSSG: Approved Feb 2014

Referral Guidelines for Anaemia

Anaemia is defined as a haemoglobin of <13g/dl in an adult male or <11.5g/dl in an adult female. Treatment is determined by its cause - this will be identified through systematic clinical evaluation and supplementary investigation. 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.

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.

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

*Patients with **suspected aplastic anaemia** (neutrophils < 0.5 x 10^9/l, platelets < 50 x 10^9/l) or **acute haemolytic anaemia** should be discussed with duty haematologist to arrange appropriate direct assessment*

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
- Immunoglobulins and protein electrophoresis
- 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
- B12 deficiency of uncertain cause requiring further investigation

Referral Guidelines for Macrocytosis

The differential diagnosis of red cell macrocytosis (mean corpuscular volume >98fl) includes B12 and folate deficiency, excess alcohol consumption, hypothyroidism, reticulocytosis, hypothyroidism and myelodysplastic syndrome.

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

Appropriate investigation in primary care prior to referral:

- B12 and folate levels (plus intrinsic factor and GPC Abs in B12 deficiency)
- Blood film examination and reticulocyte count
- Liver and thyroid biochemistry
- Lipids/cholesterol levels
- Immunoglobulins and 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 > 100 fl with accompanying cytopenia (excluding B12 / folate deficiency)
- Persistent *unexplained* MCV > 104 fl
- B12 deficiency of uncertain cause requiring further investigation

Referral Guidelines for 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. 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 x 10^9/l

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

- Glandular fever screen, if appropriate
- Repeat FBC in 4-6 weeks: if lymphocytosis persists, a blood film will be normally reviewed by a Consultant Haematologist with a comment suggesting further action (e.g. “Please, refer, if clinically appropriate”, “Forwarded for immunophenotyping” e.t.c)

Referral for specialist opinion should be considered for:

- Persisting lymphocytosis > 5 x 10^9/l not fulfilling criteria for urgent referral (please, discuss with a Haematologist)

Referral Guidelines for 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 PCR. 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

Referral for specialist opinion should be considered for:

- Persistent unexplained raised ferritin >600 mcg/L, and/or transferring saturation >50%.
- Genetic counselling / screening of first degree relatives of hereditary haemochromatosis cases

Referral Guidelines for 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, progressive or painful lymphadenopathy, hepatosplenomegaly or accompanying 'B' symptoms (>10% weight loss in 6 months, soaking sweats, unexplained fevers).

The following should be referred urgently for outpatient assessment:

- 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

Solitary neck nodes should generally be referred for ear, nose and throat assessment in the first instance while isolated axillary or groin nodes should be referred to general surgery

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

- FBC with a blood film FAO Consultant Haematologist
- Biochemistry, LDH, Immunoglobulins and electrophoresis, Ca++
- Glandular fever screen, serology for CMV, Hep B, Hep C, HIV
- CXR

Referral Guidelines for Leucocytosis

Leucocytosis is defined as an elevation of white cell count to >10.5 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.

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 >50x 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 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
- Careful history and assessment for 'reactive' causes: infection, inflammation or neoplasia
- Examination for lymphadenopathy, splenomegaly
- Biochemistry, uric acid, LDH
- CXR

Referral for specialist opinion should be considered for:

- Persistent (at least on two occasions 4-6 weeks apart), unexplained:

  White cell count >20 x 10^9/l
  Neutrophilia >15 x 10^9/l
  Eosinophilia
  Monocytosis