

# UH Bristol Haematology Referral Guidelines for Primary Care

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## INTRODUCTION

University Hospital Bristol (UHBristol) hosts a regional adult haematology clinical service and offers diagnosis and on-going management of non-malignant and malignant haematological disorders.

The aims of this guideline are to help interpret common abnormalities of routine haematology tests done in primary care and to indicate appropriate further investigations in the community. The guideline also suggests indications for referral to the UHBristol haematology service. Since these guidelines may not be applicable to all patients, the haematology liaison team also offers advice for queries about individual patients.

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## ROUTES FOR REFERRAL AND ADVICE QUERIES

### *Urgent advice:*

9am to 5pm weekdays- Haematology SpR bleep 2677  
 This bleep should be reserved for emergency advice  
 Out of hours and weekends- On call Haematology SpR via UHBristol switchboard

### *Non urgent advice:*

Please use the haematology advice and guidance service which can be accessed through e referral service. Your query will be responded to by a consultant haematologist within 3 working days.

### *Referral:*

Through e-referral system OR by postal referral to- Liaison Haematology Service (or named Consultant if relevant), Level 8, BHOC, Horfield Rd, Bristol BS2 8ED

### *Minimal Information:*

We would be grateful if the referral letter could include the full blood count results and any other relevant test results.

***PLEASE do not fax referrals or send referral letters to the Haematology Laboratory.***

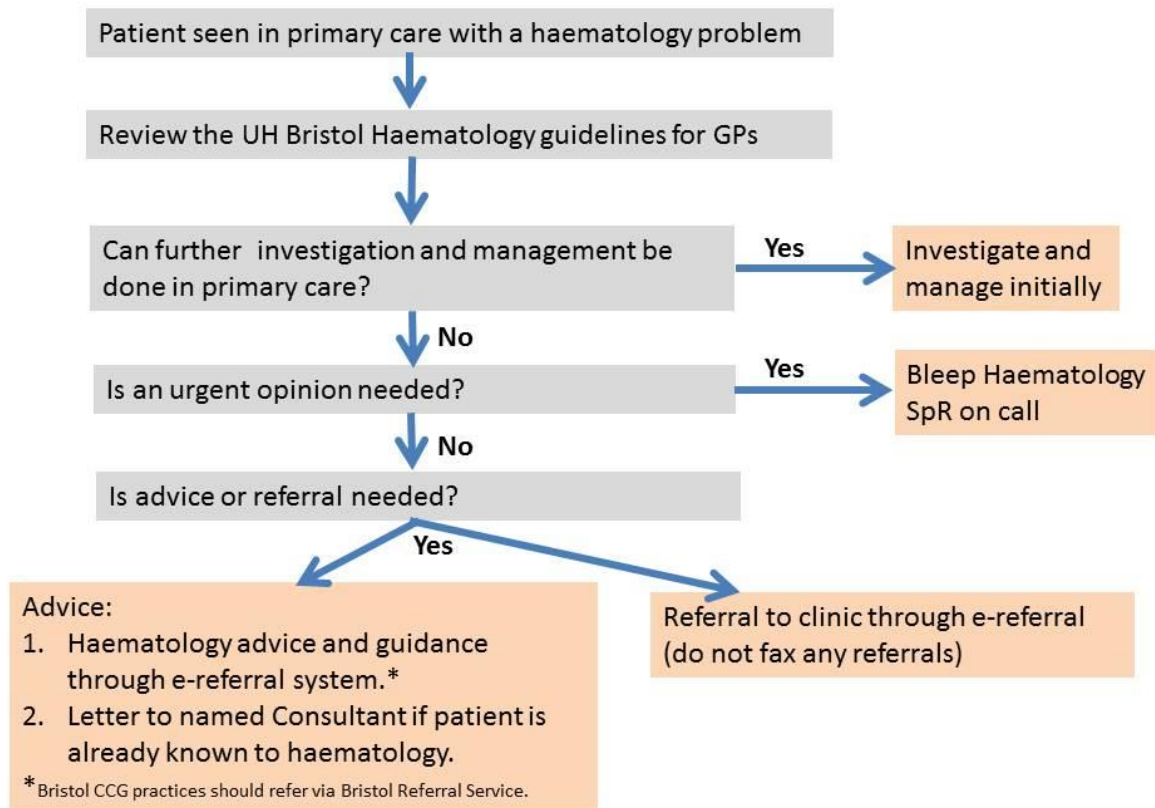
## HAEMATOLOGY CLINICS AVAILABLE FOR INITIAL REFERRAL

Most new referrals should go to one of the general haematology clinics (CH/LL or CH/CB). Exceptions include:

- Suspected high grade lymphoma, acute leukaemia or symptomatic myeloma (2 week wait referral or contact haematology SpR on call)
- Haemoglobinopathy (PM1/51)
- Bleeding/thrombosis (ADM/21)

Ref	Name	Surgery Day	Surgery Details
ADM/21	Bleeding and thrombosis	Tuesday am	Bleeding or thrombosis referrals
CH/LL	General Haematology	Wednesday pm	This clinic is most appropriate for new paraproteins, lymphocytosis, lymphadenopathy, pancytopenia, persistent neutrophilia (possible CML).
PM1/51	Sickle Cell/Thalassaemia	Wednesday pm	
CH/CB	General Haematology	Thursday pm	This clinic has a specialist interest in non-malignant haematology (including isolated cytopenias, haemochromatosis, polycythaemia, thrombocytosis).

## SUGGESTED ALGORITHM FOR INVESTIGATION, ADVICE AND REFERRAL PATHWAYS



## ANAEMIA

### *Definition:*

- <130g/l Hb in an adult male
- <115g/l Hb in an adult female

### *Important points:*

- The MCV is the best starting point to direct further investigations of the cause of anaemia.
- Anaemia may be multifactorial.
- The reticulocyte count may help to differentiate between a red cell production problem versus increased consumption or loss.
- A raised reticulocyte count or a rapidly falling Hb would suggest either bleeding or haemolysis. A raised LDH, bilirubin and low haptoglobins is consistent with haemolysis (blood film and DCT will be helpful to distinguish type).
- Transfusions should generally be avoided in patients with reversible causes (e.g. haematinic deficiency or haemolysis) unless there is cardiovascular instability. For other patients the decision to transfuse is based on degree of symptoms directly attributable to anaemia. Erythropoietin may be indicated in specific circumstances after discussion with the relevant specialist (e.g. renal physician or haematologist).

*Further investigation is initially directed by the MCV:*

Microcytic (Low MCV <81 fl)	
Common causes:	Iron deficiency Thalassaemia trait Anaemia of chronic disease (AoCD)
Assess: Previous FBC results History: Ethnicity, diet, menstruation, Weight loss, change in bowel habit, bleeding, chronic disease	
Step 1: Check ferritin – If low =iron deficiency. Treat with iron and investigate for a cause (Including GI investigations and coeliac screen if appropriate)	
Step 2: If ferritin normal - differential diagnosis: Iron deficiency with a normal ferritin (suspect if CRP raised), thalassaemia trait or AoCD  Check CRP, ZPP and reticulocyte Hb and consider a trial of iron if microcytosis is acquired (previous normal FBC) and ZPP raised/reticulocyte Hb low, rechecking FBC in 6 weeks.  Consider Hb electrophoresis if no previous normal FBC (especially if RBC raised and MCV/MCH lower than expected for iron deficiency). Ethnicity may provide a clue. N.B Hb electrophoresis does not exclude $\alpha$ thalassaemia trait.	

Macrocytic (raised MCV>99 fl )	
Common causes:	B12 or folate deficiency Alcohol, Liver Pregnancy* Medications, hypothyroidism MDS, Myeloma or other marrow cause Haemolysis, recent bleed (reticulocytosis)
Assess: Previous FBC results History: Alcohol, diet, meds, Weight loss, Jaundice, dark urine, GI symptoms	
Step 1: Check B12, folate, LFTs, GGT, Renal function, reticulocyte count, LDH, Blood film, calcium, TFTs If B12 and folate low treat and investigate cause.	
Step 2: If no obvious cause from above, also exclude myeloma (Immunoglobulins, serum protein electrophoresis, Urine Bence Jones protein)  Consider referral to haematology either if no cause found (possible MDS) or a primary haematological cause likely.  In elderly frail patients there is an option to monitor in the community following exclusion of reversible causes (as above) and refer if symptomatic or progressive or significant anaemia	

\*Pregnancy can cause macrocytosis and Hb below the "normal range" (physiological not pathological): investigations only required if significant (MCV>108) or associated with anaemia (Hb<105 g/L) in the absence of iron deficiency.

Normocytic (Normal MCV 81-99 fl)	
Common causes:	Renal failure Anaemia of chronic disease Medications MDS, Myeloma or other marrow cause Haemolysis, recent bleed Iron, B12 or folate deficiency
Assess previous FBC results	
History and examination:	as for microcytic and macrocytic anaemias. Also assess lymph nodes, liver and spleen
Step 1: B12, folate, ferritin, LFTs, Cr, retics, LDH, Blood film, calcium, CRP Immunoglobulins, serum protein electrophoresis, Urine Bence Jones protein If ferritin, B12 or folate low treat and investigate cause.	
Step 2: Consider referral to haematology either if no cause found (possible MDS) or a primary haematological cause likely.  In elderly frail patients there is an option to monitor in the community following exclusion of reversible causes (as above) and refer if symptomatic or progressive or significant anaemia	

*Haematology referral is recommended if the anaemia is associated with:*

- An **abnormal blood film** that suggests a primary haematological disorder.
- **Thrombocytopenia** or **neutropenia**.
- An **enlarged spleen** or **lymphadenopathy** (see sections below)
- A high reticulocyte (without obvious bleeding)
- Unexplained, progressive, symptomatic anaemia.
- A paraprotein or positive urine bence jones protein
- Persistent unexplained MCV>105

*Haematology referral may not be appropriate for:*

- Patients who are elderly or frail who have a mild, unexplained asymptomatic anaemia (following exclusion of reversible causes). Instead, consider monitoring in the community or discussion (by email or letter) with the haematology service. In the elderly the cause of anaemia is not found in one third of cases.
- Following discussion with or clinic review by haematology, if transfusion support guided by symptoms is considered the most appropriate management plan, there is an option to arrange this directly from the community (request through ICE).

*Haematology referral is usually inappropriate for:*

- Patients with iron deficiency anaemia - please refer to gastroenterology or gynaecology as appropriate. GI investigations (Upper and lower endoscopy) are recommended for all men, women >50 years old, and those with a strong family history of Colorectal carcinoma.
- For women <50 with upper GI symptoms, upper GI endoscopy is recommended. If required, direct referral for parenteral iron can be made from primary care (Pathology day unit via GP support unit).
- B12 or folate deficiency – can usually be managed in the community unless there is failure to respond to treatment or diagnostic difficulty.
- Patients with anaemia of chronic disease or renal failure– please consider referral to the specialist appropriate to the underlying cause.



## HAEMOGLOBINOPATHY:

### *Affected patients:*

- Patients with known Sickling disorders or thalassaemia who have moved to the area (e.g. University Students) should be referred to the specialist haemoglobinopathy clinic. This clinic 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 (a thalassaemia) and Diamond Blackfan anaemia.
- Please refer to Dr Priyanka Mehta, by letter or choose and book.
- Urgent advice can also be obtained from the haematology SpR on call on bleep 2677

### *Unaffected carriers of important haemoglobinopathies:*

Carrier status may be suspected because of family history, ethnicity, or FBC abnormalities which are not acquired. In general, these patients do not need to be referred to haematology. National screening is routinely done for neonates and pregnant women.

It may be important to diagnose asymptomatic carriers because:

- i. Partner testing with prenatal and antenatal genetic counselling may be indicated. This can be arranged through Nicole Paterson (sickle and thal nurse specialist) 0117 3422774  
Partner testing is warranted for asymptomatic carriers of HbS, C, D, E, O,  $\beta_0$ ,  $\beta^+$ ,  $\alpha_0$ .

This is because HbS can combine with HbS, HbC,  $\beta_0$ ,  $\beta^+$ , (*More rarely with: HbD-Punjab, HbO-Arab*) to result in sickle cell anaemia,

$\alpha_0$ -thalassaemia can combine with  $\alpha_0$  (*More rarely can combine with non-deletional  $\alpha^+$  (e.g.  $\alpha\text{CS}\alpha$ )*) to result in HbBarts Hydrops and Beta thalassaemia major or intermedia can result from various combinations of  $\beta_0$ ,  $\beta^+$ , E and more rarely  $\delta\beta_0$  and Hb Lepore thalassaemia (fusion of  $\delta$  &  $\beta$  genes).

- ii. Results may explain FBC abnormalities, avoiding unnecessary further investigations and ineffective or harmful treatment.
- iii. Rarely, in extreme circumstances carriers may become symptomatic (HbS trait)

## LEUCOCYTOSIS

### *Definition:*

- White cell count  $>10.5 \times 10^9/l$ .
- Assessment in primary care:
  - Leucocytosis is most commonly a normal response to systemic illness. In those without an overt reactive cause it may be important to exclude a primary (clonal) haematological diagnosis.
  - Is there an obvious reactive cause (infection, inflammation or neoplasia)?
  - Is it due to an increase in the lymphocytes, neutrophils, monocytes or a combination? (If lymphocytosis and neutrophilia reactive cause is more likely than a clonal haematological disorder)
  - Is the leucocytosis persistent and stable or progressive (and time scale of the latter)?
  - Is it isolated or associated with any other cytopenias?
  - Smoking commonly causes a low level neutrophilia and/or lymphocytosis.
  - Are there symptoms or signs associated with a myeloproliferative or lymphoproliferative condition (especially ask about sweats, fevers, weight loss, itching and examine for spleen and lymph nodes).
  - A blood film and CRP are useful initial investigations

## NEUTROPHILIA

A neutrophilia is a common occurrence and rarely secondary to a haematological disorder. Bacterial infection is the commonest cause and (suspected by clinical context, high CRP, *myeloid left shift with toxic granulation* on the blood film)

### *Common causes:*

- Infection
- Necrosis
- Inflammation
- Ischaemia
- Drugs (Steroids)
- Pregnancy
- Smoking
- Myeloproliferative neoplasms including CML

### *Look for Significant associations:*

- Rapidly increasing WCC
- An unwell patient
- Splenomegaly
- Cytopenias
- Abnormal blood film
- Basophilia may suggest MPN

### *Haematology Referral:*

#### *Immediate haematology assessment by telephone:*

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

#### *Urgent outpatient assessment:*

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

#### *Referral for routine specialist opinion should be considered for:*

- Persistent unexplained white cell count  $>20 \times 10^9/L$
- Persistent unexplained monocytosis  $>1 \times 10^9/L$
- Neutrophilia  $>15 \times 10^9/L$
- Eosinophilia or basophilia

For patients not meeting the criteria for referral, consider repeating the FBC in 3 months to assess for progression (or sooner if clinical context changes).

#### *Haematological referral is generally not appropriate for:*

Suspected reactive cause of neutrophilia (e.g. an unwell patient with sepsis should initially be referred for admission to general medicine). We suggest treating the underlying cause and reassessing the FBC following resolution of the intercurrent illness. In uncertain cases, request a blood film and consider discussion with a haematologist.

## LYMPHOCYTOSIS

### *Definition:*

Lymphocytosis is defined as a lymphocyte count  $> 4 \times 10^9/l$ .

### *Important points:*

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.

### *Haematology Referral:*

#### *Urgent outpatient assessment:*

- Suspected acute leukaemia (Immediate referral)
- Rapidly rising lymphocyte count
- Lymphocytosis in association with:
  - anaemia, thrombocytopenia or neutropenia
  - splenomegaly or progressive lymphadenopathy
  - B symptoms (weight loss  $>10\%$ , soaking sweats, unexplained fever)

#### *Referral for prompt specialist opinion is usually appropriate for:*

- Lymphocytosis in excess of  $20 \times 10^9/l$
- Associated lymphadenopathy
- Confirmed presence of clonal B-cells / chronic lymphocytic leukaemia cells by haematology (immunophenotyping) laboratory

#### *Referral for specialist opinion is also an option for:*

- Persisting lymphocytosis  $> 10 \times 10^9/l$  not fulfilling criteria above (In elderly, frail patients consider discussion with haematology first as monitoring in the community may be the most appropriate option).

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

- Glandular fever screen if appropriate
- Consider HIV screen
- 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)

## LYMPHADENOPATHY

### *Assessment in Primary care:*

- Is it localised or generalised?
- If localised, is there a local infective or neoplastic cause (examine area that drains nodal group)?
- Duration of lymph node enlargement and any change in size (especially progressive enlargement)?
- Any accompanying 'B' symptoms (>10% weight loss in 6 months, soaking sweats, unexplained fevers)?
- Any hepatosplenomegaly, lymphocytosis or cytopenias?
- Repeatedly waxing and waning lymphadenopathy does not necessarily exclude a diagnosis of lymphoma.

### *Haematology Referral:*

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

- Lymphadenopathy >1cm persisting for >6 weeks with no obvious infective precipitant
- Small volume inguinal lymphadenopathy is a common normal finding. Refer if >2cm
- 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

## MACROCYTOSIS (mean corpuscular volume >99fl)

### *Common causes:*

- B12 and folate deficiency
- Excess alcohol consumption
- Liver disease
- Reticulocytosis
- Myelodysplastic syndrome (or other bone marrow disorders including Myeloma).
- Pregnancy
- Medications (e.g. Hydroxyurea (hydroxycarbamide), or certain anti-retroviral agents).
- Hypothyroidism

### *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)
- Other primary haematological cause suspected
- MCV > 100fl with accompanying cytopenia (excluding B12 / folate def)
- Persistent *unexplained* MCV > 105fl

In elderly, frail patients with an isolated macrocytosis (absence of cytopenias, haemolysis or myeloma) consider monitoring in the community or discussion with haematology rather than referral.

## B12 DEFICIENCY

### About B12 deficiency:

- Clinical features of B12 deficiency are highly variable.
- Mildly reduced B12 levels are common.
- Less than 10% of such patients show clinical evidence of deficiency.
- Deficiency suggested by:
  - Anaemia and blood film changes
  - Presence of neurology
- Limited correlation between FBC abnormalities and the presence of neurological manifestations:
  - Entirely normal FBC findings in 20-30% of cases presenting with neurological symptoms.

### Assessment

#### History:

- Diet, history of autoimmune disease, features suggestive of malabsorption, drug history (oral contraceptive pill/metformin).

#### Examination:

- Paraesthesia, unsteadiness, peripheral neuropathy, pregnancy, glossitis (may suggest B12 deficiency whilst mouth ulcers may be suggestive of folate deficiency).

### Investigations:

- Serum B12 assay
- **Suggested interpretation of serum B12 assay results:**

B12 level	Action
< 100 ng/l	B12 deficiency very likely - treat as indicated.
100-150ng/l	Probable B12 deficiency Consider treatment, particularly if other evidence of deficiency e.g. neuropathy or macrocytosis.
150-200ng/l	B12 deficiency possible (borderline result), suggest trial of B12 if suggestive features present, e.g. neuropathy or macrocytosis. If no features consider repeat after 1-2 months and low dose oral supplementation if persistent low level (followed by repeat in 4 months).
> 300ng/l	B12 stores normal. Stores adequate for at least 2 years

- Blood film:
  - Hypersegmented neutrophils, macrocytosis or ovalocytes suggestive of B12 deficiency.
- Investigate causes of B12 deficiency:
  - **Anti-intrinsic factor antibodies** should be tested if pernicious anaemia is suspected regardless of B12 level- may be found in up to 35% of cases of pernicious anaemia. Life-long replacement therapy is indicated.
  - Look for other evidence of malabsorption.

- Trial of B12 if clinical suspicion but indeterminate B12 levels:
  - Patient feels better after a couple of days.
  - Increased reticulocyte count at 1 week with a normalizing full blood count at 8 weeks.
  - Neurology improves after 6-12 weeks.

### *Special situations:*

- Pregnancy: Vitamin B12 testing should generally not be performed in pregnancy as results are entirely unreliable (Levels naturally decrease in pregnancy). If clinical suspicion is strong, consider testing but interpret the results with caution. Discussion with haematology may be needed and specialized more reliable tests may be available but are not currently done in Bristol so will need sending away (Holo transcobalamin). An alternative approach would be a short course of therapy if clinical suspicion and recheck post pregnancy.
- Oral contraceptive pill: Only test if strong clinical suspicion as difficult to interpret. Asymptomatic women with mild reduction 145-190ng/l do not need replacement, review diet.
- Metformin: Only test if strong clinical suspicion as difficult to interpret. Trial of oral therapy could be considered and monitor 6 monthly.

### *Management*

- Investigate before treating unless severe neurology.
- IM cobalamin as per BNF
- High dose (1000micrograms daily) oral hydroxycobalamin can be considered as an alternative. 1% is absorbed via gastrointestinal tract and is IF independent.
- A trial of low dose hydroxycobalamin 50 micrograms daily can be considered in borderline cases.

### *Referral:*

- B12 or folate deficiency does not normally require routine referral for haematology outpatient assessment.
- For further information on B12 and folate deficiency:  
<http://onlinelibrary.wiley.com/doi/10.1111/bjh.12959/pdf>



## NEUTROPENIA

### *Introduction*

Mild neutropenia (neutrophil count  $< 2 \times 10^9/L$ ) is one of the commonest reasons for referral to Haematology Clinics, yet it is extremely uncommon in these cases for any significant haematological diagnosis to be made.

### *Classification*

Neutropenia is classified as:

- Mild  $1-1.5 \times 10^9/L$
- Moderate  $0.5-1 \times 10^9/L$
- Severe  $< 0.5 \times 10^9/L$

### *Common causes of neutropenia*

1. Transient
  - Transient neutropenia lasting  $< 2$  weeks is usually related to viral infections and not associated with clinical problems. Occasionally these infections may contribute to mild neutropenia for several months after the illness
2. Persistent
  - Benign ethnic neutropenia (neutrophils counts down to  $0.8 \times 10^9/L$ ) is relatively common in individuals of Afro-caribbean or Middle Eastern descent
  - autoimmune disorders such as SLE, rheumatoid arthritis
  - splenomegaly
  - drug-related
  - haematological disorders (e.g. myelodysplastic syndrome, leukaemias, lymphoma, myeloma, B12/folate deficiency)

### *History:*

- Frequency and severity of infections, mouth ulcers, recent viral illness, exposure to drugs/toxins, and symptoms of malabsorption

### *Drugs:*

- Excluding cancer chemotherapy, the highest risk categories are antithyroid drugs, co-trimoxazole, sulfasalazine, neuropsychotropics, anticonvulsants and high dose omeprazole. Many drugs may cause mild neutropenia - e.g. NSAIDs, sodium valproate.

### *Examination:*

- Mouth ulcers, fever, signs of infection, lymphadenopathy, splenomegaly. N.B. fever may be only sign of infection in patients with severe neutropenia  $< 0.5 \times 10^9/L$

### *Haematology referral*

- *Neutrophils < 1 x 10<sup>9</sup>/L and patient unwell/febrile - refer urgently for admission:*  
Patients with neutrophil count < 1 x 10<sup>9</sup>/L and fever require urgent, parenteral broad-spectrum antibiotics as infection may progress rapidly to established septic shock.
- *Neutrophils < 1 x 10<sup>9</sup>/L and patient well/afebrile without an obvious cause:*  
Review medications and inform the patient to report fever or unwellness promptly, repeat FBC with blood film examination within 48 hours and again in 2 weeks; if neutropenia persists, refer to haematology.
- *Neutrophils 1-1.5 x 10<sup>9</sup>/L and the patient is well with otherwise normal FBC:*  
Repeat with blood film at 6 weeks and refer to haematology if neutropenia is progressive or symptomatic severe or discuss with haematologist if persistent but stable
- *Neutrophils 1-1.5 x 10<sup>9</sup>/L and other blood count abnormality present and persistent on 2 occasions at least 6 weeks apart or patient unwell:*  
Refer to haematology or discuss with haematologist

If ethnic neutropenia suspected (asymptomatic) confirm neutropenia with repeat FBC and confirm normal morphology with blood film - there is no need to refer patients with ethnic neutropenia unless there is diagnostic uncertainty.

If uncertain about whether to refer a patient with neutropenia we would be happy to discuss any patient by e-mail (preferred) or phone.

## LYMPHOPENIA

### *Common causes*

- Normal finding in the elderly
- Infection (including viral (e.g. HIV, flu, hepatitis), bacterial, fungal, protozoal)
- Medications (e.g. steroids and immunosuppressants)
- Excess alcohol
- Systemic autoimmune diseases (e.g. SLE, Rheumatoid arthritis)
- Other systemic illness (e.g. renal, liver, cardiac failure, recent surgery, malignancy, malnutrition)

### *Less common causes*

- Primary immunodeficiency
- Lymphoproliferative disorders

Chronic severe lymphopenia ( $<0.5 \times 10^9/L$ ) may predispose patients to opportunistic infections such as pneumocystis pneumonia, oesophageal candidiasis, herpes zoster, recurrent severe warts, systemic CMV

### *Assessment in primary care*

- Any symptoms suggestive of primary immunodeficiency?
- Any implicated medications or excess alcohol?
- Symptoms or signs of systemic illness (e.g. infection, autoimmune disease, malignancy, malnutrition)?
- Symptoms or signs of a lymphoproliferative disorder?

### *Investigations in primary care*

Elderly, asymptomatic patients with a lymphocyte count  $>0.5$  do not require further investigation

Other patients:

- Repeat FBC and film in 6 weeks to confirm persistence
- Renal and liver function
- Consider HIV, hepatitis B and C serology
- Consider autoantibody screen depending on symptoms
- Serum immunoglobulins

### *Referral*

Infants and children with persistent lymphopenia should be referred to an immunologist for investigation of a primary immune deficiency. Asymptomatic, well patients with an isolated lymphopenia and no abnormalities on the investigations above do not necessarily need referral. Consider repeat FBC and film in 6 months.

Symptomatic patients should be referred to the relevant specialist on the basis of the above investigations (e.g. Infectious diseases if HIV positive, Rheumatology if suspected autoimmune disease, Immunology if no obvious cause or primary immunodeficiency suspected). Only refer to haematology if a lymphoproliferative disorder is suspected.

## PARAPROTEINS

*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.*

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.

### *Haematology referral*

#### **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, splenomegaly or lymphocytosis

*Patients with suspected spinal cord compression should be discussed urgently 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

## POLYCYTHAEMIA

Elevated haemoglobin / haematocrit has a wide differential diagnosis:

- Primary proliferative polycythaemia (polycythaemia vera)
- Secondary causes (such as hypoxic lung disease, smoking, obstructive sleep apnoea and erythropoietin-secreting tumours) Relative polycythaemia resulting from plasma depletion (e.g. diuretics, alcohol).

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.

### *Assessment in primary care:*

- Any history of chronic lung disease, obstructive sleep apnoea, congenital cardiac disease?
- Any history of arterial or venous thrombosis?
- Other arterial risk factors?
- Smoking, alcohol and medications (especially diuretics)
- Any itching or splenomegaly?

### *Investigations in primary care:*

- SaO<sub>2</sub>, blood pressure and urine dipstick
- Repeat FBC uncuffed, renal and liver function, glucose
- Consider CXR or other respiratory investigations according to symptoms

### *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

### *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 and transferrin saturation
- Genetic counselling / screening of first degree relatives of hereditary haemochromatosis cases. First degree relatives should be screened by HFE genotyping even if ferritin is normal or low.

## THROMBOCYTHAEMIA

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

### *Common causes:*

- Infection
- Inflammation
- Iron deficiency
- Surgery, trauma or blood loss

### *Less common:*

- Primary myeloproliferative disorder (e.g. 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).

### *Haematology referral*

#### **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 x 10<sup>9</sup>/l.

Most patients with counts of > 50 x 10<sup>9</sup>/l are asymptomatic, with the risk of spontaneous haemorrhage increasing significantly below 20 x 10<sup>9</sup>/l. Differential diagnosis includes:

Common causes of thrombocytopenia	Examples
Immune	ITP primary or secondary to conditions such as SLE, Lymphoproliferative e.g. chronic lymphocytic leukaemia (CLL), HIV or hepatitis C infection.
Drugs and some vaccines	Alcohol, Heparin, quinine, trimethoprim, thiazides, gold, valproate, phenytoin, carbamazepine,
Acute or chronic infections (bacterial, viral or protozoa)	Streptococcus, TB, mycoplasma, H Pylori, malaria, EBV, VZV, Rubella, HIV, Hepatitis C
Marrow dysfunction	Dysplasia, infiltration (including leukaemia, lymphoma, myeloma and metastases), aplasia, fibrosis
Liver disease	Any cause (with or without cirrhosis and hypersplenism)
Hypersplenism	Any cause of splenomegaly
Haematinic deficiency	B12, folate
Microangiopathic haemolysis (rarer but important)	e.g. Disseminated intravascular coagulopathy (DIC), Thrombotic thrombocytopenic purpura (TTP), Haemolytic uraemic syndrome (HUS)
Pregnancy specific	Gestational, HELLP syndrome (haemolysis, elevated liver function and low platelets) syndrome

### *Assessment in primary care:*

#### *The history:*

- Bruising or bleeding
- Constitutional symptoms- such as fevers, night sweats and weight loss should prompt investigation for lymphoma, infection or malignancy.
- Infection/immune history
- Drug and Alcohol history
- Pregnancy – This broadens the differential diagnosis

#### *Clinical examination:*

- Clinical inspection for petechiae, bruising, mucosal
- Lymphadenopathy or hepatosplenomegaly
- Features of chronic liver disease

#### *Investigations in primary care:*

- Repeat full blood count and ask for a blood film
- Renal, Liver function and LDH
- If bruising or bleeding PT/PTT/fibrinogen
- Consider discontinuation of potentially precipitating medications (discuss with haematologists if needed).



### *Haematology referral:*

**Patients with platelets  $<20 \times 10^9/l$  or active bleeding or red cell fragments or blasts on the film should be discussed with the on call haematology SpR or consultant (urgently by phone) to arrange appropriate direct assessment.**

**The following should be referred promptly for outpatient assessment:**

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

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

- Blood film examination – may exclude platelet clumping artefact
- Repeat FBC in 4-6 weeks including a FBC in citrate to exclude artefact due to EDTA antibodies
- Consider HIV and hepatitis C testing if persistent thrombocytopenia

**Referral for specialist opinion should be considered for:**

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

## RAISED PLASMA VISCOSITY / ESR

These are non-specific tests and results should be interpreted according to clinical context. The standard inflammatory marker should be the CRP. For mainly historical reasons, plasma viscosity was widely used in and around Bristol. This test is no longer offered routinely and, in the majority of indications, this would be replaced by a CRP.

Occasionally an additional inflammatory marker is useful, over and above the CRP. The ESR will be available for such cases. The main indications for an ESR are in suspected polymyalgia rheumatic/giant cell arteritis/temporal arteritis. Additionally, it may on occasion be useful in SLE, vasculitis, inflammatory bowel disease and exclusion of osteomyelitis in diabetic foot ulcers. We would advise against an ESR as a myeloma screen – rather immunoglobulins with serum protein electrophoresis to check for a paraprotein should be performed.

Plasma viscosity will no longer be routinely available. It will be available as a send-away test for the investigation and monitoring of hyperviscosity.

### *Common causes:*

- Infection
- Inflammation (including autoimmune disease such as temporal arteritis)
- Cancers
- Smoking
- Obesity

### *Less common:*

- Connective tissue disease
- Myeloma
- Waldenstroms
- Lymphoma

### *Assessment in primary care:*

History should specifically include constitutional symptoms (weight loss, sweats, fevers, itching), bone pain

### *Investigations in primary care:*

- FBC, CRP, Calcium, renal and liver function
- Immunoglobulins
- Serum protein electrophoresis
- Urine Bence Jones protein

Further tests should be done according to the symptoms and signs (e.g. autoimmune screen)

### *Haematology referral*

Only refer to haematology if a paraprotein is present or lymphoma is suspected. In the absence of specific symptoms, signs or other abnormal blood results, a marginally raised plasma viscosity is usually of doubtful significance.

## ABNORMAL BLEEDING

Patients presenting with abnormal bleeding symptoms are common in primary care. Although in most cases, this does not indicate a serious underlying coagulopathy, bleeding symptoms can sometimes be a feature of an acquired or familial bleeding disorder that requires specialist investigation.

### *Common causes*

- Benign easy bleeding or bruising tendency
- Anticoagulant or anti-platelet drugs
- Underlying comorbidity such as liver disease or renal impairment
- Inherited bleeding disorder

### *Assessment in primary care:*

#### *1. Bleeding history*

All patients should undergo a systematic enquiry to document the anatomical sites of bleeding symptoms, time-course and severity.

The likelihood of a coagulopathy is greater if bleeding occurs at multiple sites and is severe (e.g. prolonged nose bleeds >30 minutes or requiring treatment from an ENT specialist, heavy periods requiring medical or surgical treatment, traumatic bleeding requiring hospital treatment). Bleeding after more than one surgical or dental procedure or persistent bleeding over months or years is suggestive of bleeding disorder.

By contrast, features such as easy bruising, other bleeding symptoms at a single anatomical site and only one episode of abnormal bleeding do not suggest a bleeding disorder. Absent bleeding after multiple surgical or dental procedures suggests that there is not a bleeding disorder.

#### *2. General medical assessment*

To identify co-morbidities associated with bleeding

#### *3. Drug history*

Warfarin, new anticoagulant drugs and anti-platelet drugs (eg aspirin, clopidogrel, prasugrel) may all be associated with abnormal bleeding, particularly if prescribed in combination. Many other drugs (eg non-steroidal anti-inflammatory drugs, serotonin reuptake inhibitors) may reduce platelet function and be associated with mild bleeding.

#### *4. Family history*

An inherited bleeding disorder is more likely if similar bleeding symptoms occur in other close family members.

Investigation in primary care:

- Coagulation screen\* (PT and APTT)
- Platelet count

\*The PT and APTT are likely to be abnormal in patients receiving warfarin and in many patients receiving new oral anticoagulant drugs (eg dabigatran, rivaroxaban, apixiban). In this setting abnormal test results do not necessarily indicate over-anticoagulation.

### *When to consider referral to haematology*

Patients who have moved to the area (e.g. University students) and have a known diagnosis of a bleeding disorder such as haemophilia should be referred to UHBristol Haemophilia

Centre to be registered locally. It is preferable to meet these patients and formulate a plan outside an emergency setting.

Any patient with bleeding that is-

- Severe at a single anatomical site, particularly after a surgical or dental procedure
- Occurs at multiple anatomical sites
- Persistent over time
- Present in other family members
- Any patient with a prolonged PT or APTT that cannot be explained by anticoagulant drugs, irrespective of bleeding symptoms

## THROMBOSIS

We would recommend that patients with an unprovoked proximal DVT or unprovoked PE or VTE at unusual sites are referred to the haemostasis/thrombosis (ADM 21) clinic prior to stopping anticoagulation. It is important to discuss the option of long term anticoagulation with these patients with careful consideration of bleeding risk on anticoagulation versus thrombosis risk off anticoagulation and patient choice. In addition, specific further investigations may be warranted in selected cases.

**Standard investigations for all patients commencing anticoagulation for VTE** (FBC, UE/LFT, Baseline PT/INR and APTT, Pregnancy test for women of child bearing potential)

### Investigation for cancer

Patients over 40 years with an unprovoked VTE should have:

- History including and examination specifically focussed on cancer related symptoms and signs
- calcium
- chest X-ray
- dip-stick urinalysis

AND if not performed in the past year

- mammography
- cervical smear
- PSA

## HEREDITARY THROMBOPHILIA SCREENING

We would actively discourage requesting thrombophilia screens in primary care. Patients actively seeking a thrombophilia screen should be referred to the haemostasis/thrombosis (ADM21) clinic to discuss the implications of testing.

Hereditary Thrombophilia testing should be avoided:

- Asymptomatic family relatives of a patient with VTE
- Patients with a provoked clot
- At the time of the acute VTE event or when on anticoagulation
- Patients continuing long term anticoagulation

Testing will only be considered and requested in secondary care in a minority of selected patients with an unprovoked VTE stopping anticoagulation who are young or have a strong family history.

Acquired thrombophilia screening for antiphospholipid syndrome may be considered in patients with an unprovoked VTE stopping anticoagulation.

Of note, oestrogen containing contraceptives and HRT are relatively contraindicated in patients with either a personal history or a family history (1<sup>st</sup> degree relative) of thrombosis. Acceptable alternatives include progesterone only medication and mirena coil.