UH Bristol Haematology
Referral Guidelines for Primary Care

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.

These guidelines are gradually being updated and added to Remedy as individual pages. You will be redirected to the page as appropriate.

Please note the guidance relates to both UHBW and NBT referrals.

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 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

Minimal Information:

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

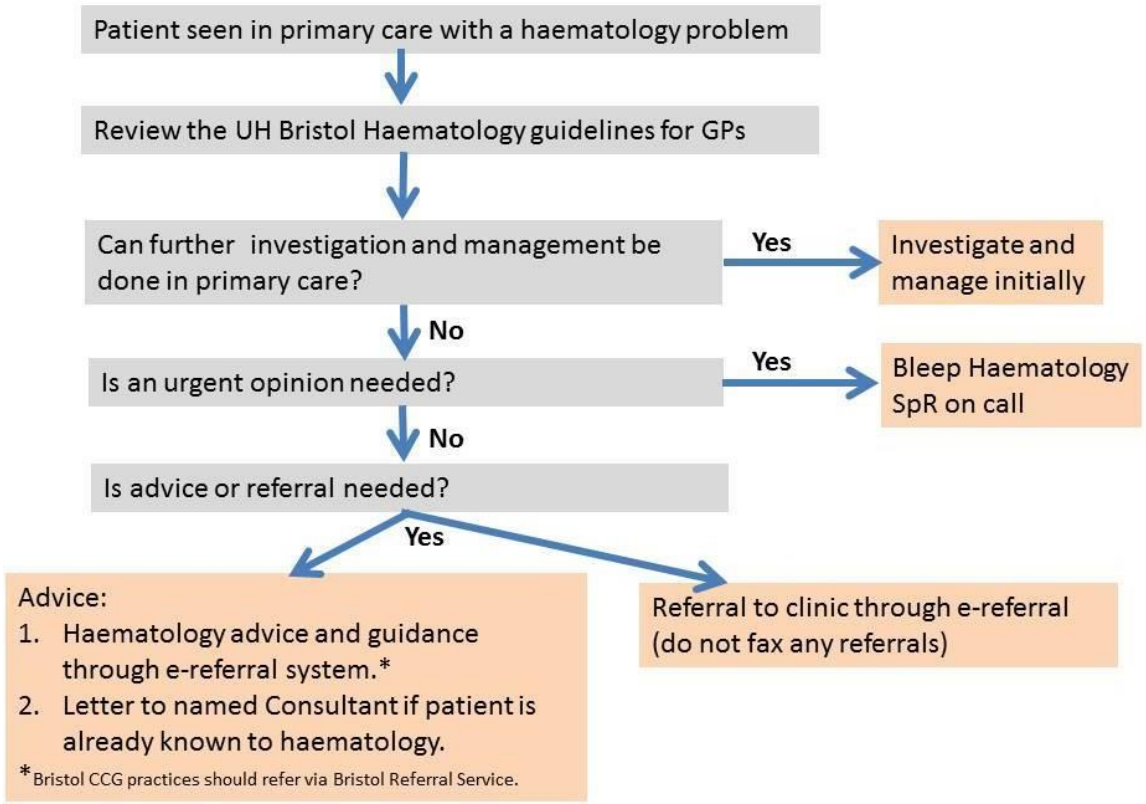
HAEMATOLOGY CLINICS AVAILABLE FOR INITIAL REFERRAL

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, lympocytosis, 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

Please see the Anaemia page of Remedy for the latest information.

HAEMOGLOBINOPATHY:

Please see the Sickle Cell & Thalassaemia page of Remedy for the latest information.

LEUCOCYTOSIS

NEUTROPHILIA

LYMPHOCYTOSIS

Please see the Leucocytosis (including neutrophilia and lymphocytosis) page of Remedy for the latest information.

LYMPHADENOPATHY

Please see the Lymphadenopathy page of Remedy for the latest information.

MACROCYTOSIS

Please see the Macrocytosis page of Remedy for the latest information.

B12 DEFICIENCY

Please see the B12 Deficiency page of Remedy for the latest information.

NEUTROPENIA

Introduction

Mild neutropenia (neutrophil count < 2 x 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 x 10^9/L
- Moderate 0.5-1 x 10^9/L
- Severe < 0.5 x 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 x 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 illlness, 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 x 10^9/L

Haematology referral

- ***Neutrophils < 1 x 109/L and patient unwell/febrile - refer urgently for admission:***

  Patients with neutrophil count < 1 x 10^9/L and fever require urgent, parenteral broad-spectrum antibiotics as infection may progress rapidly to established septic shock.

- ***Neutrophils < 1 x 109/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 109/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 109/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 immunosupressants)
- 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 (<0.5x 10^9/L) may predispose patients to opportunistic infections such as pneumocytisi 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 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.

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

Please see the Polycythaemia page of Remedy for the latest information.

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 genotypying even if ferritin is normal or low.

THROMBOCYTHAEMIA

Thrombocythaemia / thrombocytosis is defined as a platelet count > 450 x 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 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 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 x 10^9/l

THROMBOCYTOPENIA

Thrombocytopenia is defined as a platelet count < 150 x 109/l.
Most patients with counts of > 50 x 109/l are asymptomatic, with the risk of spontaneous haemorrhage increasing significantly below 20 x 109/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 x 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 x 10^9/l confirmed on repeat testing
- Platelet count 50 - 100 x 10^9/l in association with: other cytopenia (Hb < 100g/l, Neutrophils < 1 x 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 x 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 and 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 dugs (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, rivaraoxaban, 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 (1st degree relative) of thrombosis. Acceptable alternatives include progesterone only medication and mirena coil.