Peninsula Cancer Alliance

Haematology Site Specific Group

Advice and Guidance for non-Haematological Clinicians

V.1.2 August 2025
Date of review: August 2027

VERSION CONTROL

THIS IS A CONTROLLED DOCUMENT - PLEASE ARCHIVE ALL PREVIOUS VERSIONS ON RECEIPT OF THE CURRENT VERSION.

Please check the Peninsula Cancer Alliance (PCA) website for the latest available version:

https://peninsulacanceralliance.nhs.uk/site-specific-groups/haemato-oncology-ssg/

The Haematology Site-Specific Group (SSG) will evaluate and update these guidelines on an annual basis, via the PCA SSG meetings, considering advancements and/or changes to relevant healthcare policies/clinical guidelines and evidence-based research.

These guidelines have been approved by a representative from each provider within the Peninsula Cancer Alliance and by the Peninsula Cancer Alliance Clinical Lead for primary care.

VERSION	DATE ISSUED	SUMMARY OF CHANGE	OWNER
1.0	OCTOBER 2024	FINAL AGREED	PCA Haematology SSG
1.1	JANUARY 2025	EDITS TO PBM	BK
1.2	AUGUST 2025	EDITS FOLLOWING PPEG REVIEW	PCA Haematology SSG

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1. EOSINOPHILIA

1.1 SCOPE

The **common causes** of eosinophilia are allergy (asthma, eczema, seasonal allergies) and medication (sometimes self-administered).

A more extensive list of causes is found here:

http://onlinelibrary.wiley.com/doi/10.1111/bjh.14488/full

Consider intestinal/other parasites if travel/environmental/occupational history, even long ago.

Persistently raised eosinophils may be toxic especially at levels above $1.5x10^9$/l.

If there are associated new onset cardiac or pulmonary problems seek early advice.

1.2 HISTORY

- Allergic disorders
- Skin rashes
- Medication including accurate start dates, and time correlation with blood counts
- Travel history
- Thrombotic history
- Cardiorespiratory
- Gastrointestinal
- Constitutional
- Red flag malignancy symptoms (night sweats, unintentional weight loss, pruritus)

1.3 EXAMINATION

- Signs of allergy
- Skin rash
- Cardiac and respiratory systems
- Lymph nodes/Hepatosplenomegaly

1.4 INVESTIGATIONS

1.4.1 Blood tests

- FBC and blood film
- U+E, LFT, bone, LDH, CRP, vitamin B12 assay

In patients who are otherwise well with mild to moderate eosinophilia between 0·5 and $1·5x10^9$/l, further testing may not be indicated, especially if history of atopy or allergy.

Patients with systemic symptoms or those with persistent eosinophilia (at least $1·5 \times 10^9$/l), with or without suspected organ damage, should be investigated for possible secondary causes.

Further investigations in primary care can include stool culture for parasites and chest x-ray.

1.5 REFERRAL

If:

- Eosinophil count is sustained (> eight weeks) >1.5x 10^9/l
- Systemic symptoms
- Evidence of end organ damage

Refer to Haematology if no detectable secondary cause <u>OR</u> refer to secondary care, specialty according to clinical impression and site of pathology

2. HAEMOGLOBINOPATHY

Sickle Cell Crisis is a medical emergency.

Unwell patients with known or suspected sickle cell disease should be discussed with the Haematology Registrar or Consultant Haematologist on-call and admitted through the Emergency Department if necessary.

2.1 SCREENING

https://www.gov.uk/guidance/sickle-cell-and-thalassaemia-screening-programme-overview

There is a national UK antenatal screening service offered for all pregnancies.

Cornwall and Devon are low prevalence areas and whether to test is based on a Family Origin Questionnaire.

Screening should occur by 10 weeks of pregnancy to allow prenatal diagnosis by 12 weeks + 6 days

The haematology department are responsible for processing the tests. Responsibility for follow up lies with the obstetric and genetic services.

Haemoglobinopathy screening is also included in the newborn blood spot tests.

The main purpose is to identify sickle cell disease early – identification and management improves outcomes – but the majority of haemoglobinopathies will be detected.

2.2 DETECTION:

The majority of adult patients will be aware if they have a significant haemoglobinopathy and will be under the care of a haematologist. However, those with heterozygous ('trait') or mild homozygous disease may be detected incidentally though screening or through an abnormal FBC performed for other reasons.

Variant haemoglobins are also commonly detected incidentally when HbA1C is requested. - Letters are generally sent out to GPs together with patient information leaflets where appropriate for potentially clinically significant findings.
Consider testing for those who have moved into the area, for children who did not undergo antenatal screening, and for family tracing.

Diagnosis is by capillary electrophoresis and confirmatory gel electrophoresis. Additional genetic testing may be required.

Haematology review is seldom necessary for these patients, but knowledge is essential when affected people are considering having children, with the possibility of partner testing.

Patient friendly information leaflets available for various different carrier states (beta thalassaemia carriers, delta beta thalassaemia carriers, Hb OArab carriers, Hb C carriers, Hb D carriers, Hb E carriers, Hb Lepore carriers, Sickle cell carriers) at:

https://www.nhs.uk/conditions/thalassaemia/carriers/

2.3 PRE-OPERATIVE SCREENING

Patients who are of African or Afro-Caribbean heritage, or who have a family history of sickle cell trait or disease, should be offered diagnosis by haemoglobin electrophoresis before any general anaesthetic or elective procedure.

In an emergency a Sickledex test may be performed which detects both heterozygous (trait) and homozygous disease, with haemoglobin electrophoresis required to distinguish the two.

2.4 SICKLE CELL TRAIT

Explain to the person with sickle cell traits and/or their family/carers that:

- They should very rarely have symptoms. However, they are at risk of a vaso-occlusive episode if they become oxygen deprived. They should therefore:
- Avoid extreme exertion
- Avoid high altitudes, such as travelling in an unpressurized aircraft.
- Inform the anaesthetist that they are sickle cell carriers if they are going to have an anaesthetic.
- They have 1 in 2 chance of passing the sickle haemoglobin gene to their child. If the other parent is also a carrier, there is a 1 in 4 chance that their child will have sickle cell disease.
- It is important to have malaria prophylaxis if they will be visiting an area where malaria is endemic. See the CKS topic on Malaria prophylaxis for more information**.**

2.5 REFERRAL

Refer children and adults with **SICKE CELL DISEASE/TRAIT & haematuria to HAEMATOLOGY**

Refer children and adults **URGENTLY** if they present with symptoms suggestive of renal medullary cancer — haematuria, weight loss, loin pain, fever, and abdominal pain **TO HAEMATOLOGY.**

3. HYPOGAMMAGLOBULINEMIA

3.1 SCOPE

Hypogammaglobulinemia may be:

Primary:

- Usually diagnosed in infancy and managed by Paediatrics/ Immunologists but increasingly common to be picked up in adults.

Secondary:

- Excessive loss of immunoglobulin e.g. protein losing enteropathy, nephrotic syndrome, severe burns
- Drug induced e.g. chemotherapy, corticosteroids, immunosuppressants
- Malignancy e.g. lymphoproliferative disorders, myeloma, lymphoma, Good's syndrome
- Autoimmune disease

Patients usually present with recurrent infections (especially upper and lower respiratory tract infections & GI infections) but also autoimmune or connective tissue disease.

3.2 INVESTIGATIONS

3.2.1 Initial investigations on finding low immunoglobulins

FBC, U&Es, Bone profile, Protein Electrophoresis, Serum Free Light Chains (SFLC) or Urinary Bence Jones Protein (BJP) if SFLC is Unavailable.

If paraprotein, abnormal SFLC ratio or positive BJP present, please refer to Paraprotein guideline.

If lymphocytosis present, please refer to Lymphocytosis guideline.

If cytopenias present, consider routine referral to Haematology. (NB. If patient has weight loss, night sweats or bulky lymph nodes this should be a two week wait referral to exclude lymphoma).

3.3 REFERRAL

If hypogammaglobulinemia and recurrent infections, review clinical immunology guidance below:

UHP Clinical Immunology Referral Guidance

4. INFLAMMATORY MARKERS

CRP should be your first line inflammatory marker test of choice

There are not many situations where good clinical correlation with (or without) the CRP cannot guide patient management. If a second line inflammatory marker is required, we will send plasma

viscosity (PV) to University Hospital Plymouth. This test will carry an expected 2-4-day turnaround time.

PV should not be requested automatically for routine situations where the ESR was used previously. We will be consciously discouraging unnecessary PV requests.

We will be monitoring our test volumes alongside any specific concerns that have been flagged by our users.

ICE will be set up to allow specification of PV request rationale:

- If temporal arteritis (TA)/giant cell arteritis (GCA) or hyperviscosity syndrome is suspected then PV, although not necessary, may be requested. Appropriate management of these indications should not be delayed while results are pending.
- If a systemic inflammatory illness such as rheumatoid arthritis or systemic lupus erythematosus is suspected and CRP is normal, then PV may be appropriate to establish a baseline for monitoring. This should only be done under guidance of rheumatology or another speciality.
- If CRP has been shown to inadequately reflect disease activity in a patient with established chronic inflammatory illness (such as rheumatoid arthritis or systemic lupus erythematosus) then monitoring with PV may be appropriate. This should only be done under guidance of rheumatology or another speciality.
  - PV is currently a referral criterion for Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome.
  - There is room to select 'Other' as the rationale for your PV request if it does not fall within these criteria. These will be vetted on a case-by-case basis. We aim not to be obstructive, but if clinical details are inadequate, we will store the sample pending further information.

5. LYMPHADENOPATHY

5.1 SCOPE

Lymphadenopathy occurs in a range of infective, inflammatory, and neoplastic conditions.

5.2 INVESTIGATIONS

HIV testing should be offered for any unexplained lymphadenopathy

5.3 REFERRAL

Referral should be prompted by one or more of the following:

- generalised or progressive lymphadenopathy greater than 1cm persistent for more than 6 weeks
- hepatosplenomegaly
- accompanying 'B' symptoms (>10% weight loss in 6 months, unexplained fevers)

If full blood count is normal, the only diagnostic test is a biopsy; direct referral to the anatomical site of the possible node should be considered

Neck nodes -> ENT

Axillary -> Breast
Groin -> Haematology (in the absence of direct access US)

6. LYMPHOCYTOSIS

6.1 SCOPE

Lymphocytosis is a common finding.

Transient increases in the lymphocyte count (lymphocytosis) are usually due to acute infections e.g., viral infections, pertussis.

6.2 ASSESSMENT

6.2.1 Viral

Usually causes a modest and temporary (< 2 months) rise in lymphocytes.

If the patient is unwell, request a blood film and consider testing for EBV, CMV, HIV.

NB. The EBV screen (Monospot or Paul Bunnell) gives both false positive and false negative results and requesting serology for IgG and IgM antibody is preferable and specific.

6.2.2 Other causes

Smoking is a common cause of low level and persistent lymphocytosis.

Some bacterial (e.g. pertussis) and protozoal (e.g. toxoplasmosis) infections also cause a lymphocytosis.

Less common causes of lymphocytosis include auto-immune disease, medication, and stress (extreme exercise, cardiac or trauma, previous splenectomy, and obesity)

6.2.3 Malignant

Lymphocytes may rise most commonly with chronic lymphocytic leukaemia (CLL) and similar low-grade lymphoproliferative disorders (LPD).

A variety of lymphomas may also 'spill' into the peripheral blood, but this is rare.

Acute lymphoblastic leukaemia (ALL) is rare, and the patient would likely be unwell with other blood abnormalities – usually with bone marrow failure (anaemia, thrombocytopenia, and neutropenia. The blood film would show blast cells.

Refer acute lymphoblastic leukaemia immediately via medical admissions for impatient care.

6.2.3 CLL

The most common cause of malignant lymphocytosis.

Asymptomatic CLL does **not** benefit from early treatment. Lymphocytosis **without symptoms** can reasonably be monitored in the community with a second FBC after 2 months and then annually.

6.3 INVESTIGATIONS

Repeat FBC in 2-3 months if first time lymphocytosis detected.

If persistent lymphocytosis, examine for lymphadenopathy and splenomegaly
Seek reactive causes

6.4 REFERRAL CRITERIA

Refer to routine Haematology if lymphocytosis &:

- Significant and persistent (> 4 weeks) lymphadenopathy in the absence of a secondary cause
- Splenomegaly
- Systemic symptoms
- Unexplained anaemia (Hb <100g/L) or thrombocytopenia (Platelets < 100)
- Progressive lymphocytosis with an increase of ≥50% over a 3-month period or lymphocyte doubling time of <6 months (patients with a lymphocyte count < 30 may require a longer observation period to determine doubling time).

CLL is not usually an indication for an urgent suspected cancer referral but seek haematology advice is the patient is significantly unwell.

If known CLL being monitored in the community already then referral or discussion with haematology is indicated if:

- the lymphocyte count is rising rapidly (e.g. An increase of ≥50% over a 2-month period or lymphocyte doubling time of <6 months (NB. patients with a lymphocyte count < 30 may require a longer observation period to determine doubling time).
- the patient is systemically unwell (involuntary weight loss, night sweats)
- clinically significant and persistent lymphadenopathy
- clinically palpable splenomegaly
- other components of the blood count are abnormal (anaemia, thrombocytopenia)

6.5 PATIENT RESOURCES

http://bloodwise.org.uk/info-support/chronic-lymphocytic-leukaemia/
http://www.macmillan.org.uk/information-and-support/leukaemia/chronic-lymphocytic

7. LYMPHOPENIA

Lymphopenia is common, described in an array of conditions, is common in old age, and carries no particular clinical significance of its own accord. It requires no further action nor monitoring. The patient's medical history and examination should determine if any further action is required. Haematology review is not indicated.

There should be a low threshold for HIV testing.

If lymphopenia is accompanied by severe, recurrent, or unusual infections, review Clinical Immunology referral guidance: UHP Clinical Immunology Referral Guidance

8. MACROCYTOSIS (MCV>98fL)

8.1 SCOPE

Isolated macrocytosis is a quite common FBC abnormality. In the absence of anaemia there are usually **no clinical implications**.

It is often a spurious finding due to sample storage time (particularly a long warm courier journey)

8.2 ASSESSMENT

It is however important to consider and exclude potentially reversible causes:

- Liver disease
- Alcohol misuse
- Vitamin B12 or folate deficiency
- Drug effect
- Hypothyroidism
- Pregnancy
- Rare: haemolysis, myeloma, myelodysplasia
-

8.3 INVESTIGATIONS

- Take a good medication and alcohol history
- Consider a panel of blood tests to include: FBC, reticulocytes, LFT, B12, folate, TSH
- If patient not anaemic, and no abnormalities found on initial blood screen:
  We recommend no further investigation or management.

If there are clinical concerns or mild associated blood test abnormalities:

We recommend either **repeat FBC in 6 months** to monitor the trend (if stable no further investigation as above), or a routine request for further advice via advice and guidance.

We **do not recommend** patient referral to our service

9. NEUTROPENIA

9.1 SCOPE

The normal neutrophil range is lower for those of Black, Black British, Caribbean, or African ancestry.

Common causes include:

- Infection

- Most commonly this is seen in viral infections e.g. EBV, but can be seen in infections of any kind
- HIV testing should be offered for any unexplained neutropenia
- Drug induced - E.g. Antimicrobials, immunosuppressants, chemotherapy, anti-convulsants, antipsychotics. Please consult the BNF.
- Autoimmune Disease and Chronic Inflammatory Disease
- Nutritional deficiency - E.g. folate, B12, anorexia
- Bone marrow pathology

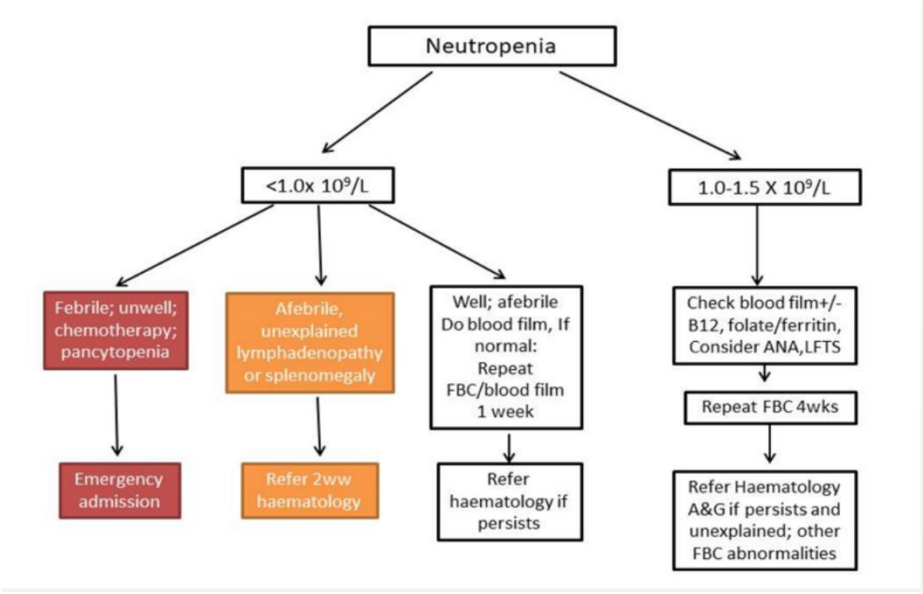
9.2 ASSESSMENT

In a well patient, isolated neutropenia should prompt assessment for the above causes and a repeat

- Mild-moderate neutropenia (>1 x10*9/l) in 4-6 weeks with a blood film
- Severe (≤1 \10*9/l) in 1-2 weeks with a blood film

Febrile neutropenia (neutrophils <1.0 x10*9/l) is a medical emergency and requires urgent MEDICAL admission

9.3 MANAGEMENT



10.NEUTROPHILIA

10.1 SCOPE

Mixed leucocytosis (lymphocytosis and neutrophilia) is almost always reactive and is not suggestive of a haematological disorder.

Neutrophilia is most commonly a reactive phenomenon; it is rare for primary haematological disorders to present with neutrophilia alone.

10.2 ASSESSMENT

Common reactive causes include:

- Infection
- Inflammation
- Smoking
- Obesity
- steroids (inhaled and oral)
- heavy exercise
- anxiety/stress
- recent infarction
- recent surgery

10.3 MANAGEMENT

Reactive neutrophilia does not require monitoring

Consider referral for

- progressive unexplained rise in neutrophils, >15X10*9 for > 6 weeks
- other unexplained blood count abnormalities
- clinically palpable splenomegaly.

Please request a blood film prior to referral

11.NIGHT SWEATS

11.1 SCOPE

There are many causes of night sweats other than lymphoma.

In the absence of any blood or examination findings to suggest lymphoma, whole body imaging is NOT indicated.

Without abnormal blood count or examination findings the likelihood of lymphoma or leukaemia as a cause is extremely low and other causes should be sought.

11.2 ASSESSMENT

Causes:

- Anxiety disorders
- Medications
- Antidepressants especially SSRI
- Hormone blocking drugs
- Alcohol (use and withdrawal)
- Recreational drugs (opioids, cocaine, cannabis, benzodiazepines)
- Endocrine
- Menopause and sex hormone deficiencies
- Hypoglycaemia
- Thyroid disease
- Carcinoid
- Phaechromocytoma
- Infection including HIV, TB, and bacterial endocarditis
- Neurological

- Stroke
- Autonomic neuropathy

11.3 INVESTIGATIONS

- Thorough history especially of therapeutic or recreational drug use
- FBC and blood film, electrolytes, liver function, bone screen
- Consider LDH, immunoglobulins, HIV test
- Thyroid function
- Sex hormones (FSH, LH as indicated)
- Consider CXR

11.4 REFERRAL

- Only if there are any indicators of haematological malignancy on the above screening tests e.g. Unexplained cytopenias, lymphocytosis or blood film suggestive of lymphoproliferative disorder
- Involuntary weight loss
- Lymphadenopathy (as 2ww)
- Splenomegaly (as 2ww)

Do not refer isolated night sweats to haematology

12. PARAPROTEINS (MGUS)

12.1 SCOPE

Several disorders are associated with the presence of a monoclonal protein in the blood (paraprotein and/or abnormal serum free light chain ratio) or urine (Bence Jones protein). These include MGUS (monoclonal gammopathy of undetermined significance), myeloma, lymphoma, chronic lymphocytic leukaemia (CLL) and AL amyloidosis.

MGUS is defined by a low level of monoclonal protein and the absence of any symptoms/signs attributable to a plasma cell disorder or lymphoma. It is asymptomatic and quite common, found in 3-5% of people aged over 70 years and up to 10% in people aged over 80 years.

MGUS does not require treatment but there is a potential to progress to symptomatic disease. Patients with intermediate-risk or high-risk MGUS therefore need long term monitoring.

12.2 ASSESSMENT

MGUS is a diagnosis of exclusion. More significant causes of a paraprotein need to be considered and excluded first.

12.2.1 Myeloma

- May present with bone pain, lytic bone lesions, renal impairment, hypercalcaemia, anaemia, recurrent infections, and/or hyperviscosity.
- Arrange urgent admission if there is spinal cord compression, significant hypercalcaemia, or acute renal failure.

12.2.2 Lymphoma / CLL

- May present with lymphadenopathy, hepatosplenomegaly, B symptoms (weight loss, fevers, drenching sweats) and/or cytopenias.
- In addition to the above, CLL is associated with an elevated lymphocyte count (manage according to the lymphocytosis guideline).

12.2.3 AL Amyloidosis

- May present with heart failure (typically a restrictive cardiomyopathy), proteinuria/nephrotic syndrome, unexplained gastrointestinal symptoms, peripheral neuropathy, carpal tunnel syndrome, and macroglossia.

12.3 INVESTIGATIONS

12.3.1 Bloods

FBC, U&E, creat, bone profile, immunoglobulins, protein electrophoresis, serum free light chains (SFLC) or Urinary Bence Jones Protein if SFLC unavailable.

12.3.2 Urine

Urinary Bence Jones Protein (BJP)*, Albumin (or Protein) Creatinine ratio.

* NB. If a serum free light chain profile has been sent, then urine for BJP is no longer necessary except if investigating for AL amyloidosis.

12.3.3 Tips for interpretation of immunoglobulins/paraproteins

(where result is available/ visible to GP):

- The paraprotein level refers to the size of the paraprotein (i.e. the protein electrophoresis result) not the total IgG/IgM/IgA level.
- **IgM paraproteins are usually associated with lymphoma whereas IgG/IgA paraproteins are usually associated with myeloma, but there is cross over. IgM myeloma is extremely rare.**
- A polyclonal hypergammaglobulinemia (i.e. global increase in IgG/IgM/IgA) with no paraprotein on protein electrophoresis is **not** a sign of myeloma. It is a non-specific finding in infective/inflammatory/reactive conditions and **does not need** haematology referral.

12.3.2 Tips for interpretation of serum free light chains:

SFLC (serum free light chains) are only significant if there is a monoclonal increase in **either** kappa or lambda resulting in an abnormal ratio. A normal ratio is 0.26-1.65 if eGFR >60.

- An increase in both kappa and lambda with a normal ratio carries similar significance to a polyclonal hypergammaglobulinaemia and **does not need** haematology referral
- A ratio of 1.65-3.10 when eGFR <60 could be normal for renal dysfunction. Repeat in 3 months. Consider a haematology advice & guidance request if upward trend.
- If ratio is moderately abnormal:
    - 0.1-0.26

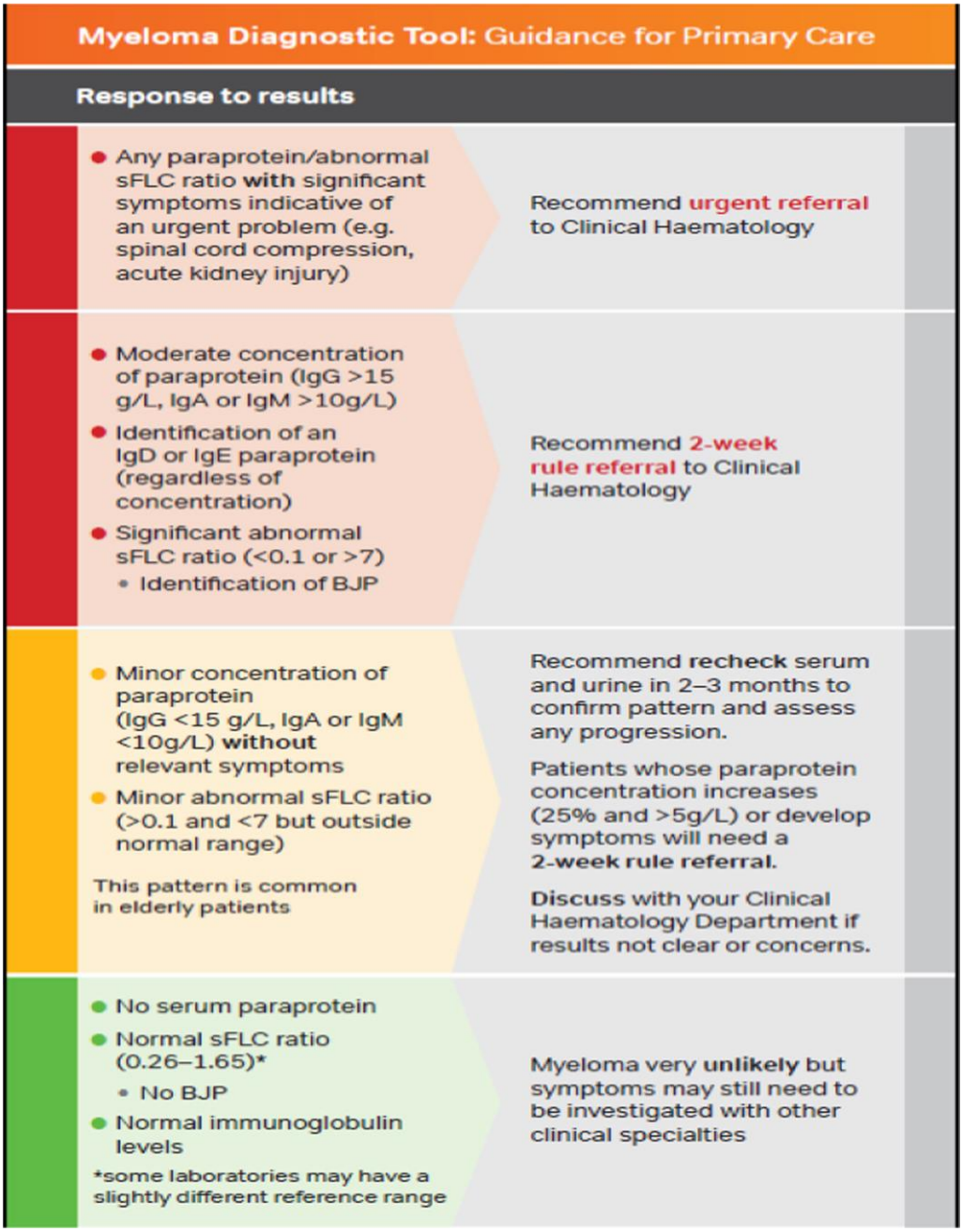
    - 1.65-7.0 with no background CKD
    - 3.1-7.0 with background CKD
- Consider a haematology advice and guidance request for oversight of onward management.
- Consider 2 week wait referral if clinical symptoms or other results strongly suggest myeloma.
- If ratio is <0.1 or >7.0 in an asymptomatic patient with otherwise normal/stable blood results, send a haematology advice & guidance request for oversight of onward management.
- If ratio is <0.1 or >7.0 in a patient with symptoms or abnormal blood results suggestive of myeloma, send a haematology 2 week wait referral.

12.4 REFERRAL CRITERIA

See table below for guidance

NB. A paraprotein >15 and/or light chain ratio <0.1 or >7.0 is not diagnostic of myeloma. If this is the only blood abnormality in an otherwise asymptomatic patient, then please seek advice and guidance from haematology in preference to a 2 week wait referral.

Investigation and management of monoclonal gammopathy of undetermined significance. A British Society for Haematology Good Practice Paper – Stern et al Br J Haematol. wileyonlinelibrary.com/journal/bjh 2023; 202:734-744



12.5

MANAGEMENT OF MGUS

All patients with MGUS can be risk-stratified according to 3 risk factors:

- Paraprotein level >15g/l
- Abnormal serum free light chain ratio (<0.26 or >1.65)
- Non-IgG paraprotein

Number of risk factors present	Risk category	Risk of progression at 20 years

0	Low	5%
1	Low-Intermediate	21%
2	High-Intermediate	37%
3	High	58%

All patients should be given information and educated in what symptoms to report e.g.

https://www.myeloma.org.uk/wp-content/uploads/2023/04/Myeloma-UK-MGUS-Infosheet.pdf

12.5.1 Low / Low-Intermediate risk MGUS

Newly diagnosed patient with low or low-intermediate risk MGUS do not require secondary care referral unless they meet the criteria above. They do not require bone marrow biopsy or imaging.

Monitoring will be dependent on your local Trust policy, with some hospitals offering haematology-led remote tracker clinics whilst others rely on primary care monitoring.

12.5.2 Suggested monitoring for low / low-intermediate risk MGUS

Newly diagnosed MGUS patients should have FBC, creatinine, calcium, paraprotein and serum free light chain levels performed 6 months after diagnosis with annual follow-up thereafter, although the interval can be longer for low-risk MGUS and further investigations reduced if life expectancy is short.

Consider discussion with haematology if:

Paraprotein (not the total immunoglobulin subtype value) increases by 25% between monitoring bloods

An increase in paraprotein of 5g/l or involved light chain by 100mg/l between monitoring bloods

Development of symptoms of myeloma/lymphoma/amyloid, or development of otherwise unexplained hypercalcaemia, renal impairment, or anaemia

Results meet any of the original 2 week wait referral criteria above

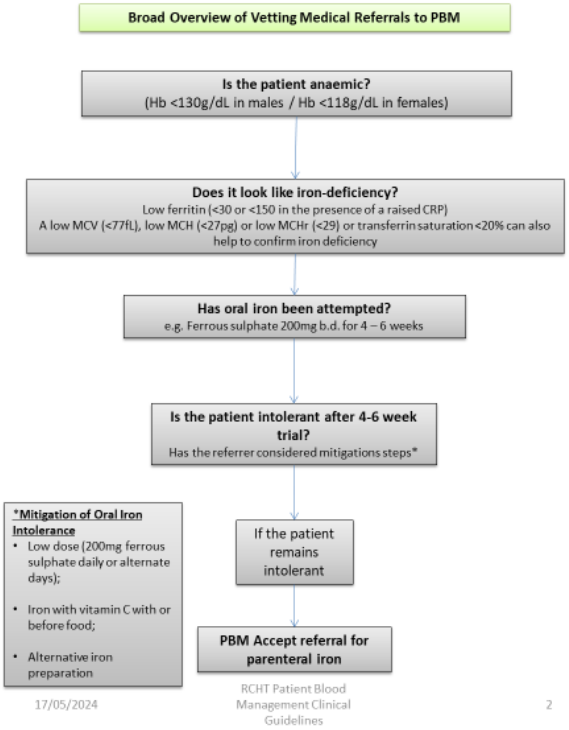
12.5.3 High-intermediate / High risk MGUS

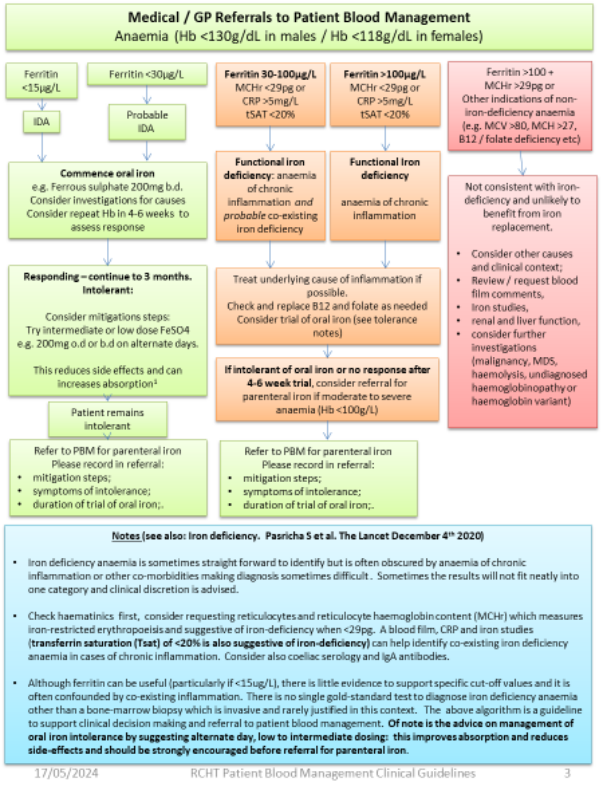
The current recommendations are that high-intermediate and high risk MGUS should undergo secondary care investigations and work-up with high risk MGUS having ongoing secondary care monitoring. However, this should be clearly individualised. It is therefore suggested that all high-intermediate / high risk MGUS not meeting the above referral criteria are, in the first instance, referred for haematology advice and guidance.

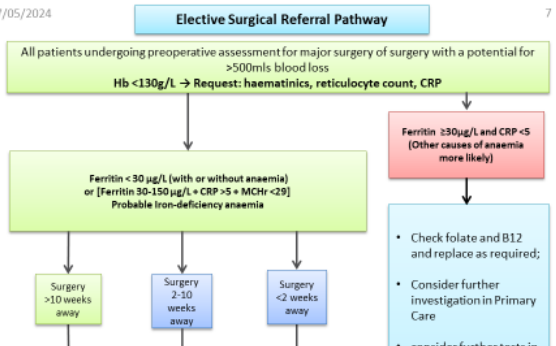
If referred back to primary care for ongoing monitoring, then suggested monitoring frequency is as above.

13. Patient Blood Management (PBM)

13.1 REFERRAL PATHWAYS







13.2 NOTES TO PRIMARY CARE

Side effects of oral iron are common. It is therefore important to prescribe in a way that minimises these and avoids the need for referral for parenteral iron which is more invasive and costlier. Clinicians are advised to consider the following measures to optimise tolerance of oral iron:

- intermediate or low dose ferrous sulphate e.g. 200mg o.d: this is proven to reduce side effects and increases absorption.
- we also recommend iron is taken 30 minutes before a meal.
- Advice to the patient on dietary improvement to optimise dietary iron intake.
- An alternative preparation such as ferrous gluconate or ferrous fumarate should be tried before abandoning oral iron.

NB: There is no benefit to enteric coated or modified release iron capsules.

Some clinicians recommend giving oral iron with a source of ascorbic acid (vitamin C), either by taking it with orange juice or with a 500mg ascorbic acid tablet. This is based on the hypothesis that ascorbic acid may increase iron absorption. However, some recently published studies show no major impact of lowering the pH on iron absorption and we are not aware of any high-quality data to support this practice.

Therefore, we cannot make a strong recommendation on the addition of vitamin C to improve oral iron absorption. If oral iron is ineffective in improving Hb, then referral to PBM remains appropriate.

13.3 IRON DEFICIENCY IN THE ABSENCE OF ANAEMIA

The primary purpose of the Patient Blood Management Service is the management of patients suffering from anaemia with iron deficiency (IDA) to reduce patient exposure to blood transfusions and preserve blood stocks.

Whilst it is recognised that symptomatic iron deficiency in the absence of anaemia can benefit from replacement, it is strongly encouraged that every attempt is made to replace iron stores orally and address the cause in these circumstances.

The management of oral iron intolerance can be addressed by using oral iron on alternate days at a low (200mg $FeSO_4$) or intermediate dose – this improves absorption and reduces side-effects and should be tried before referral for parenteral iron.

Where capacity exists, cases of non-anaemic iron deficiency may be considered on a case-by-case basis by PBM, particularly where evidence for replacement is strongest; there is an established regular requirement for replacement (typically patients with inflammatory bowel disease or persistent menorrhagia pending intervention) and capacity within PBM exists.

Where PBM capacity does not allow for this, referrers are encouraged to use alternative facilities for infusional iron, where iron infusions can be safely administered.

13.4 INFORMATION FOR PATIENTS

13.4.1 Iron Replacement

Iron deficiency may be caused by:

- Bleeding (for example from menstruation or in the bowel)
- Diet which is poor in iron
- Pregnancy
- Malabsorption (a bowel abnormality preventing iron being absorbed)

Increasing the amount of iron in your diet will help.

Iron rich foods include:

- Meat, fish, and shellfish
- Eggs
- Green vegetables (for example broccoli, spinach, kale, peas)
- Beans and lentils
- Nuts and seeds
- Brown rice and other wholegrains
- Breakfast cereals with added iron ('fortified')

13.4.2 Iron tablets

If your doctor prescribes iron tablets they should be taken as follows:

One iron tablet taken half an hour before a meal. If this does not cause too many side effects, it can be increased to twice per day if your doctor advises.

Iron tablets can cause a feeling of sickness (nausea), bloating and discomfort in the abdomen (tummy), and either constipation or diarrhoea. They will make your bowel motions (poo) look dark or black.
Taking the tablets as described above should keep side effects to a minimum.
There are several other ways in which the side-effects can be overcome:

- Taking your iron tablet once or twice a day every other day: this is proven to reduce side effects and increases absorption.
- We also recommend iron is taken 30 minutes before a meal.
- An alternative preparation such as ferrous gluconate or ferrous fumarate can also be tried.

NB: There is no benefit to enteric coated or modified release iron capsules.

Some clinicians recommend giving oral iron with a source of ascorbic acid (vitamin C), either by taking it with orange juice or with a 500mg ascorbic acid tablet.

This is based on the hypothesis that ascorbic acid may increase iron absorption. However recently published studies show no major impact of vitamin C on absorption of iron. Therefore, we cannot make a strong recommendation on the addition of vitamin C to improve oral iron absorption.

Iron tablets should be taken for at least 1 month. If your body iron stores are low, then a 3-month course is required.

13.4.3 References

1. Stoffel NU et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice daily split dosing in iron depleted women: two open label randomised controlled trials. Lancet Haematol. 2017; 4: e524-33
2. Iron deficiency. Pasricha S. *et al.* The Lancet December 4th, 2020 https://doi.org/10.1016/s0140-6736(20)32594-0
3. Ponikowski P et al. Beneficial effects of long-term intravenous therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J.* 2015; 36:657-68

14. POLYCYTHAEMIA

14.1 SCOPE

An elevated haemoglobin / haematocrit has a wide differential diagnosis including:

- Primary proliferative polycythaemia, or polycythaemia vera (PV)
- Secondary causes (such as hypoxic lung disease, obesity/obstructive sleep apnoea, erythropoietin-secreting tumours, testosterone supplementation)
- Relative polycythaemia resulting from plasma depletion. (e.g. dehydration, diuretics)

The JAK2 V617F mutation is detectable in over 95% of patients with PV. Where this mutation is absent, it is a reliable indicator that the patient does not have PV and that secondary causes are implicated.

14.2 INDICATIONS FOR TESTING

- Haematocrit* > 0.52 in males
- Haematocrit* > 0.48 in females

**Testing on at least two separate occasions > 3 months apart*

14.2.1 Blood tests to be sent in primary care

- Erythropoietin (clotted sample)
- JAK2 V617F mutation (EDTA sample)

14.3 REFERRAL CRITERIA

- All JAK2 V617F positive cases
- JAK2 V617F negative cases, and
    - Unprovoked thrombosis
    - High/low erythropoietin level AND no secondary cause**

14.4 CRITERIA FOR MANAGEMENT** IN PRIMARY CARE

- JAK2 V617F negative, and
- Normal erythropoietin level
- Secondary cause present irrespective of erythropoietin level

14.5 **MANANGEMENT OF SECONDARY POLYCYTHAEMIA IN PRIMARY CARE

Routine FBC monitoring is not indicated.

Aspirin is not indicated.

Venesection is rarely indicated in secondary polycythaemia, and management should be directed at the underlying cause. In select cases it can be considered if symptomatic; seek haematology advice if there is clinical concern.

(This Guidelines have come from the Southwest MPN Group with some slight amendments for the PCA.)

15. RAISED SERUM FERRITIN

15.1 SCOPE

Serum ferritin is derived from intracellular ferritin which is responsible for the dynamic storage of iron within the cell. Ferritin exists in all cells, but highest levels are seen with macrophages of the bone marrow and liver – the predominant storage sites of body iron.

Ferritin within the serum is a subunit of intracellular ferritin. It is actively excreted from cells and has no role in iron transport. In steady state the quantity in the serum is proportional to the quantity in storage cells. This means that serum ferritin is proportional to the body iron

content. However, in the setting of infection and inflammation, more ferritin is lost from cells and serum ferritin is no longer proportional to body iron content.

15.2 ASSESSMENT

A serum ferritin below 15mcg/l is indicative of absolute iron deficiency

A normal serum ferritin does not exclude iron deficiency, particularly where there is infection or inflammation

A raised serum ferritin is identified as follows:

- Above 200mcg/l in women and above 300mcg/l in men

15.3 MANAGEMENT

Most raised ferritins seen in primary care are due to infection or inflammation.

Do not refer for advice for a raised ferritin without the result of transferrin saturation.

Do not refer for isolated raised serum iron without a raised transferrin saturation.

Do not refer isolated raised T sats if ferritin is normal.

- If serum ferritin above 200mcg/l and Tsat% above 40% in Women request HFE gene mutation analysis on an EDTA sample
- If serum ferritin above 300mcg/l and Tsat% above 50% in Men request HFE gene mutation analysis on an EDTA sample
- If HFE gene analysis shows homozygosity for the C282Y mutation, refer to Hepatology for management of Genetic Haemochromatosis in line with published guidance: https://onlinelibrary.wiley.com/doi/pdf/10.1111/bjh.15164
- If the serum ferritin is elevated without elevation of the transferrin saturation this indicates that the cause is NOT iron overload.
- Suggest further investigation and management in line with published guideline: Investigation and management of a raised serum ferritin (wiley.com) https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjh.15166

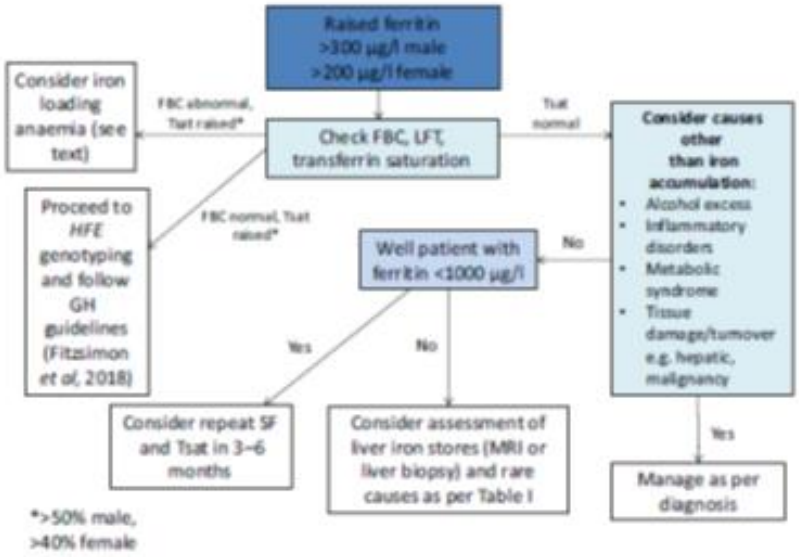


Fig 1. Suggested algorithm for investigation of isolated elevated serum ferritin levels in patients without known secondary iron overload. FBC, full blood count; GH, genetic haemochromatosis; LFT, liver function tests; MRI, magnetic resonance imaging; SF, serum ferritin; Tsat, transferrin saturation.

Table I. Causes of raised serum ferritin.

Increased ferritin synthesis due to iron accumulation	Increase in ferritin synthesis not associated with significant iron accumulation	Increased ferritin as a result of cellular damage
Hereditary (genetic) haemochromatosis	Malignancies	Liver diseases including liver necrosis, chronic viral hepatitis, alcoholic and non-alcoholic steatohepatitis*
Hereditary aceruloplasminaemia	Malignant or reactive histiocytosis	Chronic excess alcohol consumption
Secondary iron overload from blood transfusion or excessive iron intake/administration	Hereditary hyperferritinaemia with and without cataracts	
Ineffective erythropoiesis: sideroblastic anaemia, some myelodysplastic syndromes (e.g. refractory anaemia with ring sideroblasts)	Gaucher disease	
	Acute and chronic infections	
	Chronic inflammatory disorders	
	Autoimmune disorders	
Thalassaemias		
Atransferrinaemia		
Ferroportin disease		

*May also have iron overloading.

16. RAISED VITAMIN B12

Do not measure B12 levels in those on parenteral replacement – it will be high

Causes

- Oral self-administration of supra-physiological doses
- Liver disease, renal failure, autoimmune disease, inflammatory disorders, malignancy, and myeloproliferative neoplasms (MPN)

MPN can effectively be excluded if there is a normal Full Blood Count and Blood Film.

17. SPLENECTOMY/HYPOSPLENISM

17.1CAUSES

- Surgical splenectomy
- Sickle cell disease (not sickle cell trait)
- Coeliac disease

Potentially life-threatening infection is the major long-term risk of hyposplenism. Most commonly pneumococcal infection, H. influenza type B & Neisseria meningitides.
Rarer causes include E. coli, Malaria, Babesiosis, Capnocytophaga canimorsus (dog bites)

Asplenic patients should be strongly advised of the increased risk of severe falciparum malaria, should take all antimalarial precautions/prophylaxis, and ideally avoid holidays in malaria-endemic areas.

17.2 MANAGEMENT

17.2.1 Immunisations

See current Greenbook guidance:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/857279/Greenbook_chapter_7_Immunsing_immunosupressed.pdf

NB:

- All routine vaccines, including live vaccines such as measles, mumps, and rubella (MMR) can be given safely to children or adults with an absent or dysfunctional spleen.
- Asplenia or hyposplenism is not a contra-indication for live vaccinations prior to travel (e.g. yellow fever and live oral typhoid vaccine).

17.2.2 Antibiotic prophylaxis

Lifelong prophylactic antibiotics should be offered to patients considered at continued high risk of pneumococcal infection using oral penicillins or macrolides.

Patients not at high risk should be counselled regarding the risks and benefits of lifelong antibiotics and may choose to discontinue them.

All patients should carry a supply of appropriate antibiotics for emergency use.

Review of guidelines for prevention and treatment of infection in patients with absent or dysfunctional spleen:

British Society of Haematology https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2141.2011.08843.x

17.4 PATIENT INFORMATION

https://www.gov.uk/government/publications/splenectomy-leaflet-and-card

18. SPLENOMEGALY

18.1 MANAGEMENT

Spleen size is proportional to height and weight; larger spleens can be seen in tall patients, those with elevated BMIs or those with hepatic steatosis/fatty liver.

Radiological splenomegaly that is not clinically palpable with normal FBC/film and no lymphadenopathy is extremely unlikely to have a haematological cause.

Refer if lymphadenopathy, B-symptoms, paraprotein on SPEP, unexplained blood count abnormality, or clinically palpable spleen. Consider non-haematological causes of splenomegaly e.g. infection, liver disease, portal hypertension, sarcoidosis, and metastatic carcinoma.

19. THROMBOCYTOSIS (HIGH PLATELETS)

19.1 SCOPE

Thrombocytosis is defined as a platelet count >450 x 10^9/L and is a common incidental finding.

There are broadly two types of thrombocytosis:

Primary haematological disease:

- Essential thrombocythemia
- Other myeloproliferative disorder (e.g. polycythaemia rubra vera, myelofibrosis, chronic myeloid leukaemia)
- Can be asymptomatic but supporting features include splenomegaly, thrombosis, bleeding, polycythaemia (+/- hypochromic indices suggesting iron deficiency), and neutrophilia.

Secondary or reactive (often, but not always, associated with an elevated CRP):

- Infection
- Inflammation
- Bleeding
- Iron deficiency
- Tissue damage (e.g. recent trauma or surgery)
- Malignancy (and rebound after chemotherapy)
- Hyposplenism (e.g. splenectomy, coeliac disease)
- Tissue damage (e.g. recent trauma or surgery)

- Severe prolonged exercise
- Any other causes of an acute phase response

19.2 ASSESSMENT

- History and examination to identify potential secondary causes
- History of thrombosis or bleeding
- Examine for splenomegaly

19.3 INVESTIGATIONS

- FBC and blood film
- CRP
- Ferritin
- Urate and LDH

19.4 MANAGEMENT AND REFERRAL

Secondary thrombocytosis requires management of the underlying disorder.
Correct and investigate iron deficiency.

Beware of giving iron therapy in iron deficient polycythaemia (risk of acute Hb rise and thrombosis).

19.4.1 Urgent Referral

In absence of raised inflammatory markers and no obvious secondary cause:

- Platelets >1000 x 10^9 /l
- Platelets 600-1000 x 10^9/l in association with recent thrombosis or abnormal bleeding

If not meeting urgent referral criteria:

- Repeat FBC in 4-6 weeks
- If persistent thrombocytosis (in absence of raised inflammatory markers and no obvious secondary cause), request JAK2 mutation.
- NB. Other gene mutations will be reflex tested if JAK2 negative. Haematology can help with interpretation when full results are through.

19.4.2 Routine Referral

- Platelets >600 x 10^9/l on at least two occasions, 4-6 weeks apart with normal inflammatory markers and no obvious secondary cause
- Platelets >450 x 10^9/l on at least two occasions, 4-6 weeks apart with normal inflammatory markers and no obvious secondary cause PLUS one of the following:
  i. previous history of thrombosis (within 2 years)
  ii. splenomegaly
  iii. polycythaemia or neutrophilia
  iv. positive molecular test (e.g. JAK2, CALR, MPL)

19.4.3 Seek Advice & Guidance

- Platelets 450-600 with normal inflammatory markers, no obvious secondary cause, and negative molecular test results

20. VACCINATION IN CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)

20.1 SCOPE

Most patients with CLL will develop secondary immune defects including secondary hypogammaglobulinemia. They are prone to invasive pneumococcal chest infections and development of secondary bronchiectasis.

20.2 RECOMENDATIONS

Recommended Vaccination for CLL patients (at diagnosis and independent of immunoglobulin levels):

- All CLL patients should receive the seasonal flu vaccine annually and COVID vaccination as per current JCVI advice for immunocompromised individuals.
- Pneumococcal pneumonia vaccination (regardless of previous vaccination):
    - the pneumococcal conjugate vaccine (PCV13, Prevnar®) followed by
    - the pneumococcal polysaccharide vaccine (PPV23, Pneumovax II®) at least two months later. Ideally, rresponse should be assessed with antibody titres (6 months after the second dose)
- Pneumococcal polysaccharide vaccination should be repeated at five yearly intervals. Patients who have been previously vaccinated with pneumococcal vaccine only (PPV23 Pneumovax II®), should receive a "catch up" dose of the pneumococcal conjugate vaccine (PCV13, Prevnar®)

CLL patients should NOT receive live vaccinations e.g. Zostavax® and yellow fever vaccines

20.2.1 Shingles Prophylaxis:

- In line with the JCVI recommendation Sept 2021 patients with CLL are eligible to receive the non-live Shingrix® vaccine for HSV prophylaxis if they meet other eligibility criteria
- CLL patients who have had shingles should receive lifelong aciclovir 400mg BD as secondary prophylaxis once initial treatment has been successfully completed

END

FOR ANY QUERIES AROUND THIS GUIDANCE PLEASE EMAIL:
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