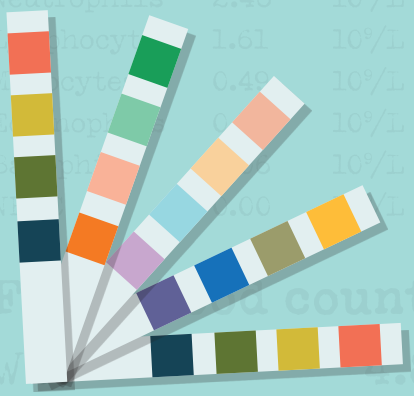
LAB RESULTS MADE EASY

Nazia Hussain

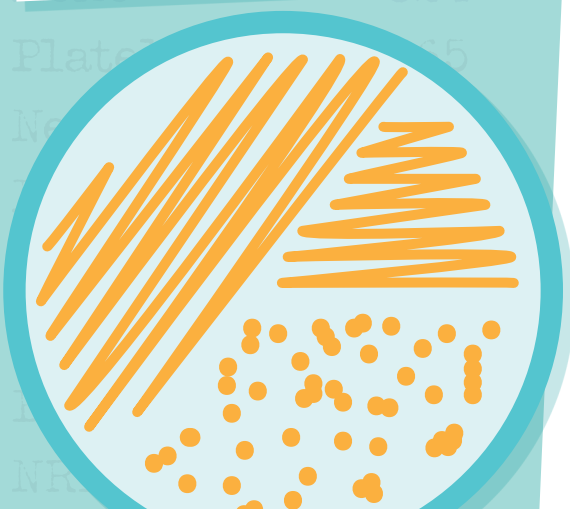


UREA AND ELECTROLYTES

Na	136	mmol/L	(134-145)
K	6.1 H	mmol/L	(3.6-5.0)
Urea	4.2	mmol/L	(1.7-7.1)
Creatinine	101 H	umol/L	(45-84)
eGFR	52	mL/min/1.73m^2	

LIVER FUNCTION TEST

Tot. Bilirubin	10	umol/L	(0-22)
Total Protein	67	g/L	(63-82)
Albumin	40	g/L	(35-50)
Globulin	26	g/L	(21-35)
Alk. Phosph.	76	U/L	(38-126)
ALT	71 H	U/L	(0-50)



Full blood count:

Wbc	4.8	10^9/L	(4.0-10.0)
Rbc	5.33 H	10^{12}/L	(3.80-4.80)
Hb	144	g/L	(120-150)
Hct	0.445		(0.360-0.460)
MCV	84	fL	(83-101)
MCH	27.0	pg	(27.0-32.0)
MCHC	324	g/L	(315-345)
Platelets	365	10^9/L	(150-410)
Neutrophils	2.46	10^9/L	(2.00-7.00)
Lymphocytes	1.61	10^9/L	(1.00-3.00)
Monocytes	0.49	10^9/L	(0.20-1.00)
Eosinophils	0.17	10^9/L	(0.02-0.50)
Basophils	0.06	10^9/L	(0.00-0.10)
NRBC	0.00	10^9/L	

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Contents

Chapter 2

Haematology

ABNORMAL RESULTS

TESTS

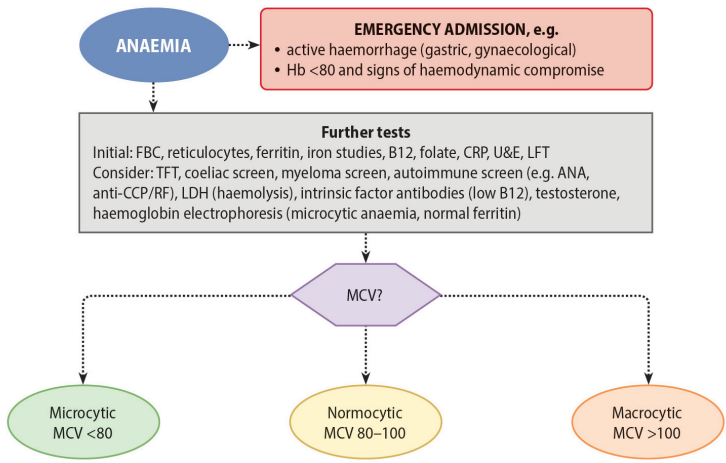
Follow your local reference ranges, clinical pathways, management and referral guidance. This guidance is not a substitute for individual clinical judgement. Reference ranges will vary according to the assay used by laboratories. Those provided are examples and may vary in your locality.

2.1 Full blood count

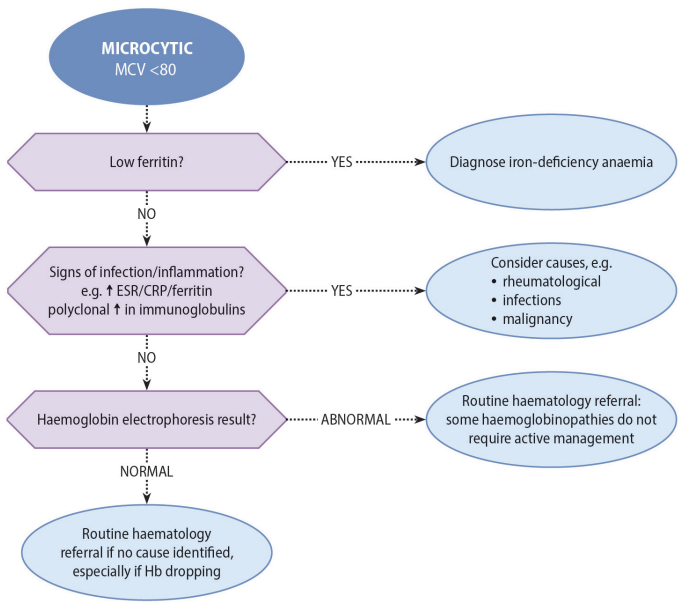
2.1.1 Haemoglobin

Low haemoglobin (anaemia) (♂ Hb <130 g/L; ♀ Hb <115 g/L)

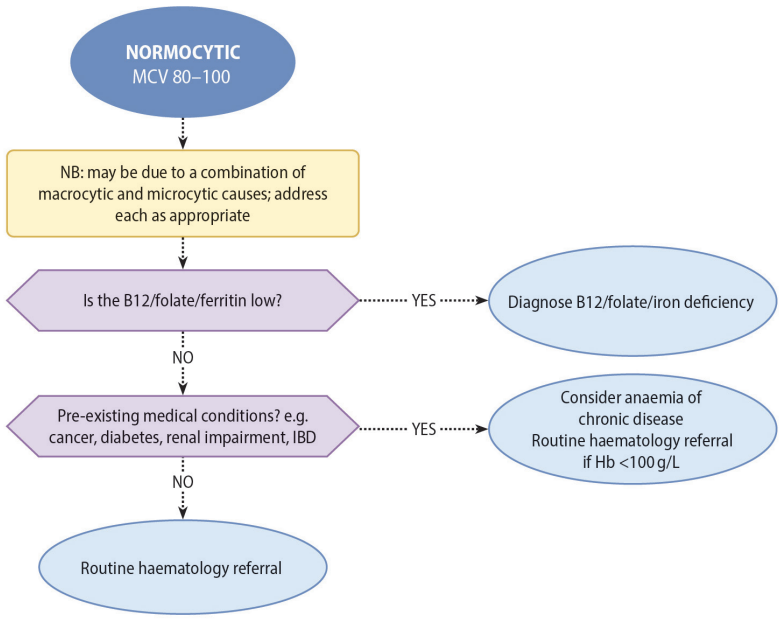
Normal range: ♂ 130–180 g/L; ♀ 115–165 g/L MCV: 80–100 fL



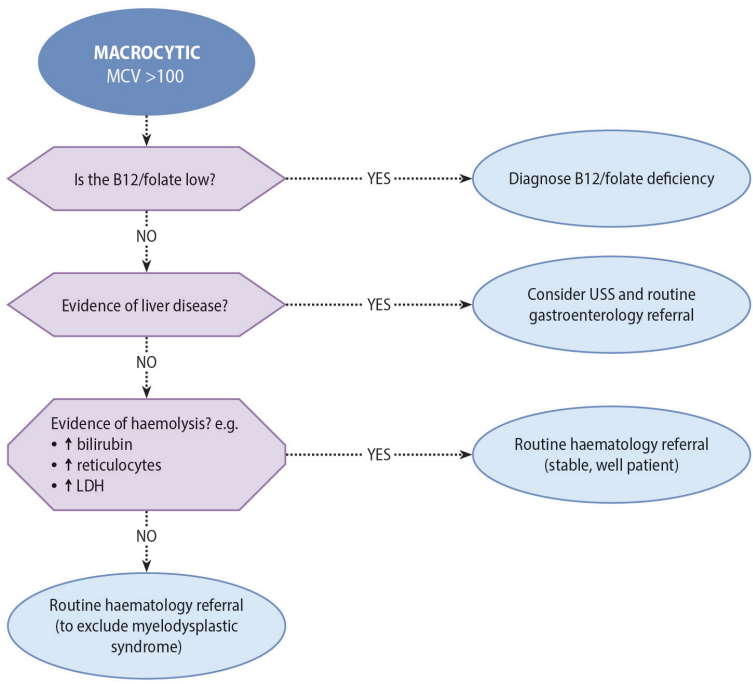
Microcytic anaemia (MCV <80 fL)



Normocytic anaemia (MCV 80–100 fL)



Macrocytic anaemia (MCV >100 fL)



Background

- Anaemia can be multifactorial: note a combination of causes may result in a mixed picture
- The MCV is a useful starting point to guide further investigation

Causes

Microcytic anaemia (MCV <80 fL)

- Iron-deficiency anaemia (IDA)
- Inflammation or infection
- Haemoglobinopathies, e.g. thalassaemia, sickle cell disease

Normocytic anaemia (MCV 80–100 fL)

- Mixed haematinic deficiency, e.g. iron and B12 deficiency
- Anaemia of chronic disease, e.g. renal impairment, diabetes, ↓ testosterone
- Malignancy
- Acute blood loss

Macrocytic anaemia (MCV >100 fL)

- ↓ B12
- ↓ folate
- Alcohol excess
- Liver disease
- Hypothyroidism
- Medication, e.g. hydroxycarbamide, methotrexate
- Pregnancy
- Haemolysis
- Bone marrow disorder, e.g. myelodysplasia

History and examination

- Bleeding history
- Chronic disease history, e.g. renal failure, liver disease, inflammatory bowel disease (IBD)
- Ethnicity
- Family history (FHx), e.g. of bleeding disorder

- Lifestyle review, e.g. diet, alcohol
- Medication, e.g. non-steroidal anti-inflammatory drugs (NSAIDs), steroids
- Significant past medical history e.g. gastritis, fibroids
- Symptoms and signs of anaemia, e.g. shortness of breath, fatigue, dizziness, pallor, jaundice, koilonychia, angular cheilosis, glossitis, alopecia
- Symptoms and signs of recurrent infections, ulcers, recent viral illness, autoimmune or connective tissue disorders
- Symptoms and signs of malignancy, e.g. bowel symptoms, post-menopausal bleeding, haemoptysis, lymphadenopathy and hepatosplenomegaly, 'B symptoms' (fever, drenching night sweats, weight loss >10% in previous 6 months), weight loss

Investigations

- Initial:
  - full blood count (FBC) repeat
  - reticulocytes
  - ferritin, iron studies
  - B12, folate
  - CRP
  - U&E, liver function test (LFT)
- Consider:
  - thyroid function test (TFT)
  - coeliac screen
  - myeloma screen
  - lactate dehydrogenase (LDH) (haemolysis)
  - intrinsic factor antibodies (low B12, if not had previously and no known GI surgery that could cause malabsorption)
  - autoimmune screen, e.g. ANA, anti-CCP/RF (as per local guidance)
  - testosterone
  - haemoglobin electrophoresis (if microcytic anaemia, normal ferritin levels and not previously checked)
  - urine dip (for blood)
  - stool parasites (if relevant travel history and/or eosinophilia)
  - faecal immunochemical test (FIT): offer to all with IDA, or age ≥60 and non-IDA
  - liver ultrasound scan (USS) (liver disease)
  - pelvis USS: women age ≥55 with anaemia and visible haematuria (endometrial cancer)
  - routine oesophagogastroduodenoscopy (OGD): age ≥55 with anaemia and upper abdominal pain (oesophageal or stomach cancer)

Referral

Emergency admission

- Acutely unwell, e.g. active haemorrhage, Hb <80 and haemodynamic compromise
- ↓ B12/folate with neurological symptoms (hypokalaemia can develop during initial replacement of severe B12 deficiency)
- Unexplained progressive symptomatic anaemia
- Sickle cell crisis, e.g. severe pain, acute chest syndrome, stroke, priapism

Urgent suspected cancer

- Suspected malignancy (relevant specialty)
- Suspected haematological malignancy (haematology), e.g.
  - abnormal blood film, e.g. leucoerythroblastic picture (presence of immature white cells and nucleated red blood cells)
  - anaemia with accompanying cytopenia but normal B12, folate and ferritin
  - associated hepatosplenomegaly, lymphadenopathy

Routine outpatient

- Persistent unexplained anaemia with Hb ≤100 g/L (haematology)
- Unresponsive to or unable to tolerate corrective therapy (relevant specialty)
- Anaemia of chronic disease (relevant specialty as needed)
- Renal anaemia (nephrology)
- Persistent unexplained MCV >105 (haematology)
- Interpreting haemoglobin electrophoresis results; not all haemoglobinopathies need active management, e.g. beta thalassaemia trait, sickle cell trait and alpha thalassaemia trait (haematology)
- Suspected haemolysis (haematology)

Advice & Guidance

- Diagnostic uncertainty (relevant specialty)

GP management tips

- Consider interval monitoring of patients who are elderly/frail with a mild, unexplained, asymptomatic anaemia (Hb >100 g/L) following exclusion of reversible causes
- Uncomplicated B12 or folate deficiency does not require referral
- IDA is generally not managed by haematology
- Haemoglobinopathy screening: document testing result clearly (no need for repeat testing)

Iron-deficiency anaemia (IDA)

Background

- Defined as ↓ red blood cell production due to ↓ body iron stores
- Blood findings: ↓ haemoglobin, ↓ MCV, serum ferritin level <30 µg/L, ↓ transferrin saturation
- Blood film: microcytic, hypochromic red cells, pencil cells and thrombocytosis
- Interpreting ferritin levels
  - ferritin is the most specific test for iron deficiency in the absence of inflammation
  - the lower limit of normal for most labs is between 15 and 30 µg/L
    - ferritin <15 µg/L is indicative of absent iron stores (specificity 0.99)
    - ferritin <30 µg/L is indicative of low body iron stores
  - ferritin is an acute phase protein, so apparently normal levels may occur with iron deficiency in the context of an inflammatory disease process
  - a cut-off of 45 µg/L has been suggested as providing the optimal trade-off between sensitivity and specificity for iron deficiency in practice (specificity of 0.92); figures below this may warrant consideration of GI investigation, especially in the context of a chronic inflammatory process with anaemia
  - a value >150 µg/L is unlikely to occur with absolute iron deficiency, even in the presence of inflammation

Causes

- Blood loss, e.g. gastrointestinal, gynaecological or urological, blood donor
- Poor dietary iron intake, e.g. vegetarian
- Malabsorption, e.g. coeliac, gastrectomy
- Increased requirements, e.g. myeloproliferative neoplasms
- Pregnancy
- Medication, e.g. aspirin, NSAIDs, selective serotonin reuptake inhibitors (SSRIs), clopidogrel, corticosteroids, long-term PPI

Investigations

- Initial tests
  - FBC, ferritin, iron studies, B12, folate, coeliac screen, ESR/CRP, reticulocytes
  - FIT
  - urine dip (for blood)
- Consider:
  - stool parasite (if relevant travel history and/or eosinophilia)

Referral

IDA is generally not managed by haematology

Emergency admission

- Acutely unwell, e.g. active haemorrhage, Hb <80 and haemodynamic compromise
- Unexplained progressive symptomatic anaemia

Urgent suspected cancer

- Suspected malignancy (relevant specialty)
  - FIT result of ≥10 µg Hb/g faeces (colorectal)
  - post-menopausal bleeding in women age ≥55 (gynaecology; endometrial cancer)
  - post-menopausal bleeding in women age <55 (consider gynaecology referral; endometrial cancer)

Urgent outpatient (gastroenterology)

NB: check local referral protocols if meets urgent suspected cancer pathway criteria

- Men and post-menopausal women with newly diagnosed IDA unless they have overt non-GI bleeding
  - men with Hb <120 g/L and post-menopausal women with Hb <100 g/L should be investigated more urgently, as lower levels of Hb suggest more serious disease (consider urgent suspected cancer referral)
- All people age ≥50 with marked anaemia, or a significant FHx of colorectal carcinoma, even if coeliac disease is found
- Premenopausal women if they are age <50 and have colonic symptoms, a strong FHx (two affected 1st-degree relatives or just one 1st-degree relative affected before the age of 50) of GI cancer, persistent IDA despite treatment, or if they do not menstruate, e.g. hysterectomy

Routine outpatient

- Unable to tolerate corrective therapy, for possible IV iron therapy (gastroenterology)
- Unresponsive to initial therapy, i.e. Hb increase <20 g/L after 4 weeks, or develops anaemia again without an obvious underlying cause (gastroenterology)
- Positive coeliac screen (gastroenterology)
- Menorrhagia unresponsive to medical management (gynaecology)

GP management tips

- Do not wait for investigations to be carried out before prescribing iron supplements, e.g. one tablet daily of oral ferrous sulfate / fumarate / gluconate, unless colonoscopy imminent
- If not tolerated, reduce the dose to one tablet on alternate days, or consider alternative oral preparations, e.g. oral ferric maltol
- Monitor to ensure adequate response to treatment:
  - recheck FBC in the first 4 weeks of treatment: Hb should rise by about 20 g/L
  - if there is a response, check FBC at 2–4 months to ensure Hb has normalised
  - continue iron treatment for a further 3 months to replenish stores, then stop
  - monitor FBC periodically, e.g. every 6 months
  - if Hb drops below normal, prescribe iron supplements
- Further investigation is only necessary if Hb cannot be maintained this way or if there is any evidence of an active undiagnosed pathology, e.g.
  - ongoing weight loss
  - chronic unexplained diarrhoea

- persistently ↑ inflammatory markers
- persistence or recurrence of IDA

- Consider ongoing prophylactic iron (e.g. 200 mg ferrous sulfate daily), monitoring FBC every 6–12 months, in those at particular risk of IDA, e.g.
  - recurring anaemia in elderly and further tests are not indicated or appropriate
  - plant-based diets
  - malabsorption, e.g. coeliac disease, gastrectomy
  - menorrhagia
- Iron turns the stool black, so melaena may be difficult to report once iron treatment is started
- Advise food sources rich in iron:
  - red meats (beef, lamb and pork) and offal
  - fish and poultry
  - plant-based sources: pulses and legumes (e.g. beans, peas and lentils), dark green vegetables (e.g. spinach, kale and broccoli), nuts and seeds
  - some foods are fortified with iron, e.g. all UK-sold bread (except wholemeal) must be fortified; many breakfast cereals are also fortified
  - absorption is enhanced with animal protein foods and vitamin C, but reduced by bran-containing cereals and tannins in tea and coffee
- Iron deficiency without anaemia
  - before iron-deficiency anaemia develops, there is an initial phase where body iron stores are depleted, resulting in low ferritin levels with a normal Hb concentration
  - the prevalence of significant underlying GI pathology, especially malignancy, is low
  - thus, in the absence of other pointers, GI investigation generally is not warranted in premenopausal women; the cause is likely to be menstrual blood loss and/or recent pregnancy
  - the threshold for investigation of iron deficiency without anaemia should be low in men, postmenopausal women, and those with GI symptoms or a FHx of GI pathology

Vitamin B12 deficiency (<180 ng/L: confirmed deficiency)

Background

- Blood findings: macrocytic anaemia with megaloblastic changes (hyper-segmented neutrophils on blood film)
- There is no gold standard test for measuring vitamin B12 deficiency, but the likelihood of deficiency can be determined by measuring serum cobalamin (total B12)
  - a serum cobalamin of <200 ng/L is sensitive enough to diagnose 97% with vitamin B12 deficiency
- NICE recommends these thresholds to interpret test results (serum cobalamin):
  - <180 ng/L confirmed deficiency
  - 180–350 ng/L possible deficiency
  - >350 ng/L unlikely deficiency

Causes

- Poor absorption, e.g. pernicious anaemia, gastrectomy, IBD
- Medication, e.g. PPI, H_2 receptor antagonists, colchicine, metformin, oral contraceptive pill (OCP), recreational nitrous oxide use
- Dietary, e.g. malnutrition, vegan diet

Investigations

- Initial tests
  - FBC, B12, folate, coeliac screen
  - intrinsic factor antibodies (if not had previously and no known GI surgery that could cause malabsorption)
- Consider:
  - LFT, TFT (non-megaloblastic causes of macrocytosis)
  - ferritin, iron studies (exclude concurrent deficiency)

Referral

Uncomplicated B12 deficiency does not require referral to haematology

Emergency admission

- ↓ B12 with neurological symptoms (treatment can cause hypokalaemia so requires regular monitoring)

Urgent suspected cancer

- Known pernicious anaemia and a suspicion of gastric cancer (gastroenterology)
- Suspected blood malignancy (haematology)

Routine outpatient

- Suspected malabsorption, IBD, positive coeliac screen (gastroenterology)
- Nutritional advice (dietitian)
- Cause of deficiency unclear after investigations, not responding to treatment, MCV >105 (haematology)

Advice & Guidance

- Recreational nitrous oxide use requires different tests: serum methylmalonic acid (MMA) can be used as the initial test, or plasma homocysteine (secondary care tests)

GP management tips

- Medication-induced or nitrous oxide-related B12 deficiency:
  - offer either intramuscular (IM) or oral B12 replacement while using medication
  - review if the medication can be stopped; encourage stopping nitrous oxide use
  - review B12 replacement if stopped and deficiency symptoms have resolved
- Suspected dietary cause:
  - review dietary B12 intake and consider oral B12 replacement. B12 sources:

    - meat, egg and dairy products
    - B12-fortified plant foods: yeast extract, fortified plant-based drinks and alternatives to yogurt and most fortified breakfast cereals
  - review OTC vitamin use
    - oral supplement should contain at least one of the following: cyanocobalamin, methylcobalamin or adenosylcobalamin
  - review concurrent causes of possible B12 deficiency
  - consider IM B12 injections instead of oral if:
    - concurrent condition which may affect quality of life, e.g. ataxia or anaemia
    - concerns about oral treatment concordance, e.g. frailty, cognitive impairment
- Cause unknown:
  - offer B12 replacement, considering oral versus IM replacement and review response
- If hydroxocobalamin injection is necessary, initially administer 1 mg IM three times a week for 2 weeks
- The maintenance dose depends on whether the deficiency is diet-related or not
  - if not thought to be diet-related:
    - give hydroxocobalamin 1 mg IM every 2–3 months for life
    - alternatively, consider daily large oral doses (500–1000 µg)
  - if thought to be diet-related
    - oral cyanocobalamin tablets 50–150 µg OD between meals
    - alternatively twice-yearly hydroxocobalamin 1 mg IM
    - in vegans, treatment may need to be lifelong, whereas in other people with dietary deficiency replacement, treatment can be stopped once the B12 levels have corrected and diet has improved
- Monitoring response; check FBC and reticulocytes:
  - within 7–10 days of starting treatment
    - a ↑ in Hb and ↑ in reticulocyte count above the normal range indicates treatment is working
  - after 8 weeks of treatment (FBC, reticulocytes)
    - blood counts and MCV should have normalised
    - measure ferritin/iron studies and folate to ensure other deficiencies not masked
- Measuring cobalamin levels is unhelpful as levels increase with treatment regardless of how effective it is, and retesting is not usually required; however, cobalamin can be:
  - measured 1–2 months after starting treatment if there is no response
  - rechecked if a lack of treatment compliance is suspected, anaemia recurs, or neurological symptoms do not improve or progress
- Neurological recovery may take time: improvement begins within 1 week and complete resolution usually occurs between 6 and 12 weeks

Folate deficiency (<3 µg/L)

Background

- Blood findings: macrocytic anaemia, megaloblastic changes (hyper-segmented neutrophils)
- There is no clear consensus on the level of serum folate that indicates deficiency. Conventionally, a serum folate <3 µg/L is used as a guideline, as the risk of megaloblastic anaemia greatly increases below this level

Causes

- Malabsorption, e.g. coeliac disease, surgery, IBD
- Dietary, e.g. malnutrition, vegan diet, excess alcohol
- Medication, e.g. nitrofurantoin, trimethoprim, anticonvulsants, sulfasalazine, methotrexate
- Increased requirements
  - pregnancy
  - malignancy
  - blood disorders, e.g. haemolytic anaemia, sickle cell anaemia
  - inflammatory diseases, e.g. TB
  - exfoliative skin diseases
- Excessive urinary excretion, e.g. heart failure, liver disease, renal disease

Investigations

- Initial tests
  - FBC, B12, folate, coeliac screen
- Consider:
  - LFT, TFT (non-megaloblastic causes of macrocytosis)
  - ferritin, iron studies (exclude concurrent deficiency)

Referral

Uncomplicated folate deficiency does not require referral to haematology

Emergency admission

- ↓ folate with neurological symptoms

Urgent suspected cancer

- Suspected blood malignancy (haematology)

Routine outpatient

- Suspected malabsorption, IBD, positive coeliac screen (gastroenterology)
- Nutritional advice (dietitian)
- Cause of deficiency unclear after investigations, not responding to treatment, MCV >105 (haematology)

GP management tips

- Ensure B12 levels are normal or replaced **before** treating to avoid development of sub-acute combined degeneration of the cord
- Dietary sources: asparagus, broccoli, brown rice, brussels sprouts, chickpeas, peas
- Prescribe oral folic acid 5 mg daily for 4 months; may be required for longer (even for life) if the underlying cause of deficiency is persistent
- Monitoring response; check FBC and reticulocytes:
  - within 7–10 days of starting treatment
    - a ↑ in Hb and ↑ in reticulocyte count above the normal range indicates treatment is working
  - after 8 weeks of treatment (FBC, reticulocytes)
    - blood counts and MCV should have normalised
  - on completion of folic acid treatment to confirm response

Raised haematocrit (erythrocytosis)

Normal ranges: ♂ 0.40–0.52 L/L (40–52%); ♀ 0.37–0.48 L/L (37–48%)

Background

- Raised haematocrit can be due to ↑ haemoglobin (true erythrocytosis) or ↓ plasma volume (apparent erythrocytosis)
- The term 'polycythaemia' should be reserved for overproduction of red cells due to a bone marrow problem, e.g. polycythaemia rubra vera

Causes

- Primary erythrocytosis
  - polycythaemia rubra vera (97% have *JAK2* gene mutation)
- Secondary erythrocytosis
  - congenital (rare)
  - acquired
    - hypoxia from respiratory or cardiac disease
    - medication, e.g. testosterone, anabolic steroids
    - lifestyle, e.g. obesity, alcohol excess, smoking, hypertension
  - abnormal erythropoietin production
    - renal issues
    - tumour, e.g. fibroids, hepatocellular and renal cell carcinoma
- Apparent erythrocytosis
  - dehydration
  - medication, e.g. diuretics

History and examination

- Aquagenic pruritus (itching after getting body wet)

- Symptoms of hyperviscosity, e.g. headaches, visual disturbances, neurological symptoms, weakness
- Examination: oxygen saturations, blood pressure, BMI

Investigations

- Initial:
  - full blood count (FBC) (uncuffed sample, minimum interval 1 week, non-fasted)
  - blood film
  - U&E, LFT, bone profile
  - HbA1c
  - ferritin/iron studies (iron deficiency can mask the degree of erythrocytosis)
  - urine dip (exclude renal issues, e.g. proteinuria, haematuria)
- Consider:
  - chest X-ray (CXR), spirometry (suspected respiratory cause)
  - USS abdomen

Referral

Emergency admission

- ↑ haematocrit (♂ >0.52, ♀ >0.48) and symptoms of hyperviscosity

Urgent outpatient

- New extreme ↑ haematocrit (♂ >0.60, ♀ >0.56) in the absence of congenital cyanotic heart disease (haematology)
- ↑ haematocrit (♂ >0.52, ♀ >0.48) in association with recent (last 3 months) arterial or venous thrombosis (including DVT/PE, CVA/TIA, MI/unstable angina, PVD) (haematology)

Routine outpatient

- Persistent unexplained ↑ haematocrit (♂ >0.52, ♀ >0.48) (two tests >6 weeks apart) (haematology)
- ↑ haematocrit, but ↓ MCV or ferritin: could be iron-deficient polycythaemia vera; do not give iron therapy in this situation as it will worsen the erythrocytosis (haematology)
- Suspected hypoxic respiratory disease (respiratory)
- Suspected heart failure (cardiology)

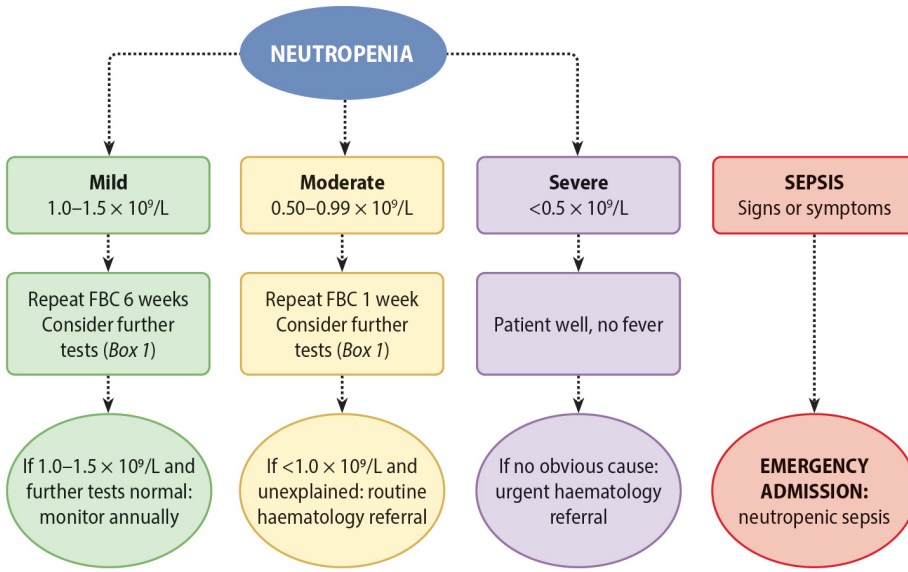
GP management tips

- Cardiovascular risk factors (including hyperlipidaemia, smoking, hypertension and diabetes) should be managed in all with erythrocytosis of any cause

2.1.2 White cell count

Low neutrophils (neutropenia) (neutrophils <1.5 × 10⁹/L)

Normal range: 1.5–8.0 × 10⁹/L



Box 1 Further tests
Initial: Blood film, LFT, TFT, B12, folate
Consider: Autoimmune screen (e.g. ANA, anti-CCP/RF), myeloma screen, HIV, hepatitis B & C

Background

- Neutropenia secondary to chemotherapy should be referred for acute oncology review: neutropenic sepsis is a medical emergency
- There is ↑ risk of more serious infection when <1.0 × 10⁹/L, and especially when <0.5 × 10⁹/L

Causes

- Medication, e.g. carbimazole, clozapine, clotrimazole, chemotherapy, phenytoin
- Viral infections, e.g. Epstein–Barr virus (EBV), hepatitis B and C, HIV (may take weeks to resolve)
- Sepsis
- Autoimmune disease, e.g. rheumatoid arthritis (RA), systemic lupus erythematosus (SLE)
- ↓ B12 or ↓ folate

- Ethnic variations, e.g. people of African or Middle Eastern descent frequently have a constitutional neutropenia, usually >1.0 × 10^9/L, that is of no clinical consequence. This is a diagnosis of exclusion after ruling out other causes and seeing a persistent ↓ count without increased risk of infection
- Hypersplenism
- Thyroid dysfunction
- Nutritional deficiencies, e.g. anorexia nervosa
- Bone marrow issues, e.g. myelodysplasia, aplastic anaemia, acute leukaemia, myeloma

History and examination

- Having chemotherapy or causative medications?
- Baseline observations, including temperature (sepsis signs)
  - NB: temperature may be low or affected by concurrent medication, e.g. steroids

Investigations

- Initial:
  - blood film
  - B12, folate
  - LFT, TFT
- Consider:
  - autoimmune screen, e.g. ANA, anti-CCP/RF (as per local guidance)
  - myeloma screen
  - HIV, hepatitis B and C

Referral

Emergency admission

- Neutrophil <0.5 × 10^9/L and sepsis
- Unwell patient with **any** severity of neutropenia

Urgent suspected cancer

- Suspected blood malignancy, e.g. associated cytopenia, hepatosplenomegaly, lymphadenopathy (haematology)

Urgent outpatient

- Neutrophil <0.5 × 10^9/L, but systemically well (significant risk of infection) (haematology)

Routine outpatient

- Persistently unexplained neutropenia <1.0 × 10^9/L (two tests >6 weeks apart) (haematology)

Low lymphocytes (lymphopenia) (lymphocyte count $<1.5 \times 10^9$/L)

Normal range: $1.5–5.0 \times 10^9$/L

Background

- Grading of severity:
  - mild: $1.0–1.5 \times 10^9$/L
  - moderate: $0.50–0.99 \times 10^9$/L
  - severe: $<0.5 \times 10^9$/L
- Lymphopenia is a common, non-specific and often transient finding which increases in frequency with older age and comorbidities
- It is more often of no pathological significance: however, HIV infection is commonly associated with lymphopenia
- Rarely associated with haematological conditions, but can be observed in lymphoproliferative disorders

Causes

- Increasing age
- Infection, e.g. acute or chronic (HIV, hepatitis B and C, TB)
- Medication, e.g. steroids, immunosuppressants, chemotherapy, methotrexate, azathioprine
- Systemic disorders, e.g. autoimmune disease, IBD, sarcoidosis
- Malignancy, e.g. lymphoproliferative disorders, solid organ malignancies
- Stress, e.g. exercise, malnutrition, alcohol, surgery, radiotherapy
- Chronic disease, e.g. cardiac failure, renal failure
- Primary immunodeficiency

History and examination

- Examine for lymphadenopathy and hepatosplenomegaly
- Ask about B symptoms
- Symptoms and signs of recurrent infections, ulcers, recent viral illness, autoimmune or connective tissue disorders

Investigations

- Initial:
  - blood film
  - B12, folate
  - U&E, LFT
- Consider:
  - myeloma screen
  - autoimmune screen, e.g. ANA, anti-CCP/RF (as per local guidance)
  - HIV, hepatitis B and C

Referral

Urgent suspected cancer

- Suspected malignancy (relevant specialty)

Urgent outpatient

- Severe lymphopenia ($<0.5 \times 10^9$/L), as may predispose to opportunistic infections, e.g. *Pneumocystis* pneumonia, oesophageal candidiasis, herpes zoster (haematology)

Routine outpatient

- Diagnostic uncertainty with persistent moderate lymphopenia >6 months (haematology)
- Lymphopenia with recurrent infections and HIV negative, consider immunodeficiency issue and checking immunoglobulins (immunology)
- Suspected autoimmune disease (rheumatology)

GP management tips

- Mild lymphopenia ($1.0–1.5 \times 10^9$/L), well patient: no further action
- Well patient, age >70 and lymphocytes $>0.5 \times 10^9$/L: no further action
- Moderate lymphopenia ($0.50–0.99 \times 10^9$/L), well patient:
  - consider further investigations
  - if no cause identified, repeat FBC at 6 months
    - if no change in count and patient remains well, no need to investigate further
    - consider routine haematology referral if there are any changes/concerns

High white cell count (leucocytosis) (white cell count $>11 \times 10^9$/L)

Normal range: $3.6–11.0 \times 10^9$/L

Background

- The differential is wide-ranging, from a normal reaction to infection to haematological malignancies

Causes

- Infection (especially bacterial)
- Inflammation
- Stress events, e.g. trauma, MI
- Malignancy, e.g. haematological or solid tumour
- Autoimmune disease
- Smoking (minor non-specific leucocytosis or neutrophilia is often seen)

History and examination

- Examine for lymphadenopathy and hepatosplenomegaly
- Ask about B symptoms
- Symptoms and signs of infection, autoimmune or connective tissue disorders

Investigations

- Initial:
  - assess white cell count (WCC) differential (if lymphocytosis and neutrophilia present, reactive cause is more likely)
  - blood film
  - ESR/CRP
- Consider:
  - autoimmune screen, e.g. ANA, anti-CCP/RF (as per local guidance)
  - HIV, hepatitis B and C

Referral

Emergency admission

- New suspected acute leukaemia (likely to be contacted by lab about the result)
- New suspected chronic myeloid leukaemia (CML) with WCC >100 × 10^9/L or hyperviscosity symptoms (likely to be contacted by lab about the result)
- Acutely unwell patient, e.g. with severe infection / sepsis

Urgent suspected cancer

- New CML without emergency admission criteria (haematology)
- Age ≥60 and ↑ WCC with unexplained non-visible haematuria (bladder cancer, urology)
- Suspected malignancy (relevant specialty)

Urgent outpatient

- Unexplained leucocytosis with WCC >50 × 10^9/L (haematology)

Routine outpatient

- Unexplained persistent raised levels (two tests >6 weeks apart) (haematology)
  - WCC: >20 × 10^9/L
  - neutrophilia: >15 × 10^9/L
  - lymphocytes: >5 × 10^9/L
  - eosinophilia: >1.5 × 10^9/L
  - monocytosis: >1 × 10^9/L
  - basophilia: >0.2 × 10^9/L

High neutrophils (neutrophilia) (neutrophils >8 × 10^9/L)

Normal range: 1.5–8.0 × 10^9/L

Background

- Usually a reactive phenomenon
- It is unusual for a reactive neutrophilia to be above 100×10^9/L

Causes

- Infection (especially bacterial)
- Inflammation
- Stress events, e.g. trauma, myocardial infarction (MI)
- Medication, e.g. steroids, lithium
- Pregnancy
- Smoking (minor non-specific leucocytosis or neutrophilia is often seen)
- Hyposplenism
- Autoimmune disease
- Malignancy, e.g. haematological or solid tumour

History and examination

- Examine for lymphadenopathy and hepatosplenomegaly
- Ask about B symptoms
- Symptoms and signs of infection, autoimmune or connective tissue disorders
- Travel history

Investigations

- Initial:
  - blood film
  - CRP/ESR
  - U&E, LFT
- Consider:
  - autoimmune screen, e.g. ANA, anti-CCP/RF (as per local guidance)
  - prostate-specific antigen (PSA)

Referral

Emergency admission

- Acutely unwell patient, e.g. with severe infection/sepsis
- New suspected CML with WCC >100×10^9/L or hyperviscosity symptoms (likely to be contacted by lab about the result)

Urgent suspected cancer

- Suspected haematological malignancy, e.g. abnormal blood film, splenomegaly (haematology)
- Suspected malignancy (relevant specialty)

Urgent outpatient

- Unexplained inflammatory process (relevant specialty)

Routine outpatient

- Unexplained persistent neutrophilia >15 × 10^9/L (two tests >6 weeks apart) (haematology)

High lymphocytes (lymphocytosis) (lymphocytes >5 × 10^9/L)

Normal range: 1.5–5.0 × 10^9/L

Background

- Usually a reactive phenomenon, but it is important to check a blood film

Causes

- Infection, especially viral, e.g. EBV; bacterial, e.g. tuberculosis (TB) (common)
- Chronic lymphocytic leukaemia (CLL): characterised by chronic lymphocytosis, often asymptomatic in its early stages
- Smoking
- Post-splenectomy
- Autoimmune, e.g. RA

History and examination

- Examine for lymphadenopathy and hepatosplenomegaly
- Ask about B symptoms
- Symptoms and signs of infection, autoimmune or connective tissue disorders
- Travel history

Investigations

- Initial:
  - blood film
  - FBC repeat 6 weeks if suspected viral cause (likely to be transient)
- Consider:
  - glandular fever screen
  - autoimmune screen, e.g. ANA, anti-CCP/RF (as per local guidance)

Referral

Emergency admission

- Acutely unwell patient, e.g. with severe infection / sepsis

Urgent suspected cancer

- Suspected haematological malignancy, e.g. abnormal blood film, splenomegaly (haematology)
- Progressive lymphadenopathy (relevant specialty depending upon location)

Urgent outpatient

- Lymphocytosis >30 × 10^9/L (haematology)

Routine outpatient

- Persistent unexplained lymphocytes >5 × 10^9/L (two tests >6 weeks apart), otherwise well (haematology)

High basophils (basophilia) (>0.2 × 10^9/L)

Normal range: 0.0–0.2 × 10^9/L

Background

- Reactive causes are rare: if persistent, particularly >0.4 × 10^9/L, this strongly suggests a myeloproliferative neoplasm

Causes

- Myeloproliferative neoplasms, e.g. CML, myelofibrosis
- Autoimmune, e.g. IBD, hypothyroidism
- Acute illness
- Allergy
- Hyposplenism

History and examination

- Examine for lymphadenopathy and hepatosplenomegaly
- Ask about B symptoms
- Symptoms and signs of infection, autoimmune or connective tissue disorders

Investigations

- Initial:
  - blood film
  - ESR/CRP
  - TFT

Referral

Urgent suspected cancer

- Suspected haematological malignancy, e.g. abnormal blood film, splenomegaly (haematology)

Routine outpatient

- Unexplained persistent basophilia >0.2 × 10^9/L (two tests >6 weeks apart) (haematology)

High eosinophils (eosinophilia) (>0.5 × 10^9/L)

Normal range: 0.04–0.50 × 10^9/L

Background

- Eosinophils play a part in allergic, parasitic and malignant disease processes, as well as tissue repair and remodelling
- Hypereosinophilia:
  - defined as eosinophils >1.5 × 10^9/L persisting for >6 months with no obvious cause
  - associated with signs of organ dysfunction:
    - cardiovascular: chest pain, heart failure, venous thromboembolism (VTE)
    - respiratory: dyspnoea, cough and wheeze
    - neurological: cerebrovascular accident (CVA), peripheral neuropathy
    - gastrointestinal: dysphagia, treatment-refractory gastro-oesophageal reflux disease (GORD)

Causes

- Atopy, allergy, e.g. asthma, eczema, rhinitis
- Infections, e.g. parasites, fungal, HIV
- Medication, e.g. angiotensin-converting enzyme inhibitors (ACEi), penicillin, anti-epileptics, proton pump inhibitors (PPIs)
- Gastrointestinal, e.g. chronic pancreatitis, IBD, coeliac
- Respiratory, e.g. asthma, sarcoidosis
- Malignancy, e.g. solid tumours, Hodgkin lymphoma, T-cell non-Hodgkin lymphoma, CML
- Hyposplenism
- Autoimmune, e.g. SLE, RA
- Dermatological, e.g. pemphigoid
- Adrenal insufficiency

History and examination

- Examine for lymphadenopathy and hepatosplenomegaly
- Ask about B symptoms
- Symptoms and signs of infection, autoimmune or connective tissue disorders
- Travel history

Investigations

- Initial:
  - FBC, blood film
  - ESR/CRP
  - vitamin B12 (↑ may point to a myeloid disorder)
  - U&E, LFT, bone profile
  - coeliac screen

- Consider:
  - for those with systemic symptoms or persistent eosinophilia >1.5 × 10^9/L, test for causes and evaluate organ damage:
    - autoimmune screen, e.g. ANA, anti-CCP/RF (as per local guidance)
    - parasite investigations, e.g. stool ova cysts, appropriate serology tests
    - CXR: if respiratory symptoms
    - amylase: pancreatic issues
    - hepatitis B and C, HIV

Referral

Emergency admission

- Acutely unwell patient, e.g. with severe infection, or end organ damage

Urgent suspected cancer

- Suspected haematological malignancy, e.g. abnormal blood film, splenomegaly (haematology)
- Suspected malignancy (relevant specialty)

Urgent outpatient

- Eosinophils >5 × 10^9/L without obvious secondary cause (haematology)
- Eosinophils >1.5 × 10^9/L with suspected end organ damage (haematology)

Routine outpatient

- Unexplained persistent eosinophilia >1.5 × 10^9/L (two tests >6 weeks apart), otherwise well (haematology)
- Diagnostic uncertainty (relevant specialty)
- Significant travel history and unsure about appropriate testing (microbiology / infectious diseases)

GP management tips

- For well patients with eosinophilia 0.5–1.5 × 10^9/L, further testing may not be indicated
- Unprovoked DVT/PE may be a manifestation of end organ damage

High monocytes (monocytosis)

Normal range: 0.2–1.0 × 10^9/L

Background

- This is frequently transient
- Persistent count >1.0 × 10^9/L for >12 months may represent a myeloproliferative disorder (chronic myelomonocytic leukaemia – CMML)

Causes

- Smoking (common cause of mild monocytosis)
- Infections, e.g. TB, malaria
- Autoimmune and inflammatory diseases, e.g. sarcoidosis, RA
- Stress response, e.g. post MI
- Hyposplenism
- CMML (chronic, incurable disorder of varying severity)
- Malignancy

History and examination

- Examine for lymphadenopathy and hepatosplenomegaly
- Ask about B symptoms
- Symptoms and signs of infection, autoimmune or connective tissue disorders

Investigations

- Initial:
  - blood film
  - ESR/CRP
  - U&E, LFT, bone profile
- Consider:
  - autoimmune screen, e.g. ANA, anti-CCP/RF (as per local guidance)

Referral

Urgent suspected cancer

- Suspected haematological malignancy, e.g. abnormal blood film, splenomegaly (haematology)

Urgent outpatient

- Persistent monocytosis >5 × 10^9/L (two tests >6 weeks apart) (haematology)
- Monocytosis (1.0–5.0 × 10^9/L) with other cytopenia (haematology)

Routine outpatient

- Persistent monocytosis (1.0–5.0 × 10^9/L) (two tests >6 weeks apart), otherwise well (haematology)

2.1.3 Platelets

Low platelets (thrombocytopenia) (platelets <150 × 10^9/L)

Normal range: 150–450 × 10^9/L

Chapter 5

Clinical scenarios

Abnormal LFT (liver screen)

Initial

- Hepatitis B and C
- Liver autoantibodies (anti-mitochondrial antibody, anti-smooth muscle antibody, antinuclear antibody)
- Immunoglobulins
- Ferritin and transferrin saturation (iron studies)
- USS liver

Consider

- FBC
- Coagulation
- U&E
- TFT
- HbA1c, lipids
- Coeliac screen
- Acute hepatitis: hep A, hep E, CMV, EBV
- HIV
- CK
- Serum caeruloplasmin (checking for Wilson's disease if age <40)
- Alpha-1-antitrypsin deficiency (if there is a positive FHx or associated respiratory symptoms)
- Fibrosis risk assessment if non-alcoholic fatty liver disease (NAFLD) confirmed on USS (check local protocols)

Anaemia

Initial

- FBC
- Reticulocytes
- Ferritin, iron studies
- B12, folate
- CRP
- U&E, LFT

Consider

- TFT
- Coeliac screen
- Myeloma screen
- LDH (haemolysis)
- Intrinsic factor antibodies (low B12, if not had previously and no known GI surgery that could cause malabsorption)

- Autoimmune screen, e.g. ANA, anti-CCP / RF (as per local guidance)
- Testosterone
- Haemoglobin electrophoresis (if microcytic anaemia, normal ferritin levels and not previously checked)
- Urine dipstick (haematuria)
- Stool parasites (if relevant travel history and/or eosinophilia)
- FIT: offer to all with IDA, or age ≥60 and non-IDA (colorectal cancer)
- Liver USS (liver disease)
- Pelvis USS: women age ≥55 with anaemia and visible haematuria (endometrial cancer)
- Routine OGD: age ≥55 with anaemia and upper abdominal pain (oesophageal or stomach cancer)

See also Pernicious anaemia

Antiphospholipid syndrome

Antiphospholipid syndrome is diagnosed in a patient with venous and/or arterial thrombosis and/or defined pregnancy morbidity who has persistent antiphospholipid antibodies.

- **Not** a primary care diagnosis: secondary care will likely initiate specialist review when seeing patients with thrombotic complications
- Seek specialist review if suspected, e.g.
  - VTE in the absence of major provoking factors
  - arterial thrombosis in patients aged <50 without clear risk factors
  - history of SLE or other autoimmune disease developing thrombosis or pregnancy complications
  - recurrent miscarriage (>3)

Cardiovascular disease: PAD, angina, MI, stroke

Initial

- FBC
- U&E, LFT
- HbA1c, lipids

Coeliac disease

Initial

- Coeliac serology:
  - 1st-line: total IgA and IgA tissue transglutaminase (tTG)
  - 2nd-line: IgA endomysial antibodies (EMA) if IgA tTGA testing is unavailable or IgA tTG is weakly positive
  - if IgA deficient (total IgA <0.07 g/L): IgG EMA, IgG deamidated gliadin peptide (DGP) or IgG tTG can be checked

Chapter 6

Signs and symptoms

Follow your local reference ranges, clinical pathways, management and referral guidance. This guidance is not a substitute for individual clinical judgement. Reference ranges will vary according to the assay used by laboratories. Those provided are examples and may vary in your locality.

Abdominal pain

Initial

- FBC
- CRP
- U&E, LFT, bone profile
- HbA1c/glucose

Consider

- CA125
- PSA
- Urine pregnancy test
- Urine dipstick ± MCS
- STI screen
- Stool MCS
- FIT
- Faecal calprotectin
- *H. pylori* testing

Acute confusion (delirium)

Consider

- FBC
- ESR, CRP
- Folate, B12
- U&E, LFT, bone profile
- TFT
- HbA1c/glucose
- Urine dipstick ± MCS

Allergy

This is primarily a clinical diagnosis: tests are used to help confirm or refute a diagnosis. Follow appropriate local testing and referral procedures. Note, there are no tests for food intolerance.

Consider

- Specific IgE testing: to support clinical diagnosis in suspected IgE-mediated allergies
- Check total IgE when testing specific IgE

Alopecia

Consider

- FBC
- Ferritin
- TFT
- Skin scrapings and hair samples for fungal MCS

Altered bowel habit

Initial

- FBC
- U&E, LFT, bone profile
- ESR/CRP
- Coeliac screen

Consider

- TFT
- CA125
- Faecal calprotectin
- Stool MCS, including *C. difficile* toxin
- FIT

Amenorrhoea (primary)

Initial (likely to be investigated by secondary care)

- Urine pregnancy test
- Prolactin
- TFT
- FSH, LH
- Oestradiol
- Total testosterone
- Coeliac screen
- USS pelvis

Amenorrhoea (secondary)

Initial

- Urine pregnancy test
- Prolactin
- TFT