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**Investigating anaemia**

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better medicine

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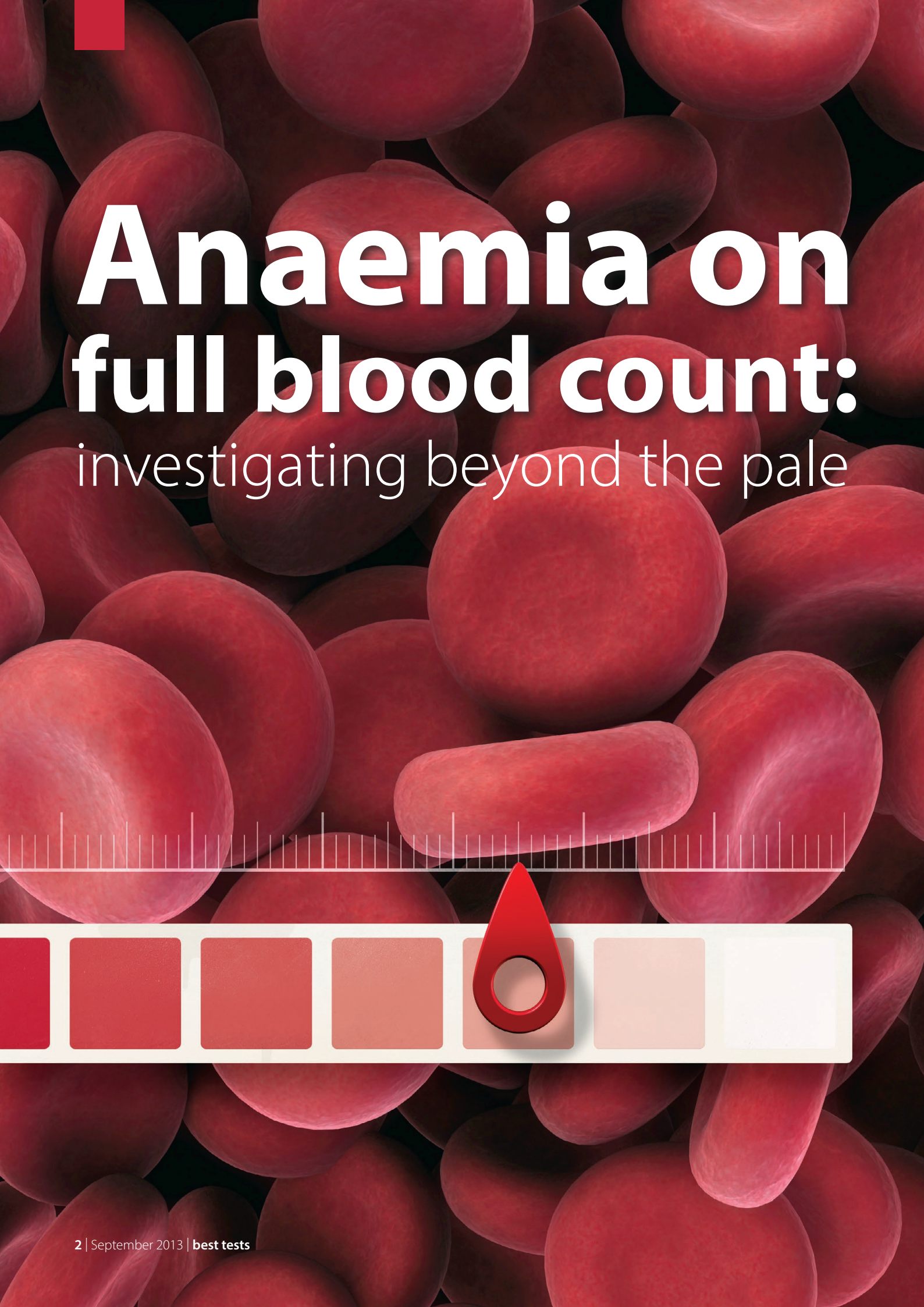# Anaemia on full blood count:
## investigating beyond the pale

A finding of anaemia on a full blood count is only the first step of a series of investigations for most patients. The mean red blood cell volume is used to classify anaemia into microcytic, normocytic or macrocytic, which helps to guide additional investigations. As most people with anaemia are asymptomatic or have non-specific symptoms, clinical examination usually only provides limited information. Clinical judgment, however, is an important part of the work-up as the cause of the anaemia and the likelihood of serious disease may differ between patients. The most frequent causes of anaemia in New Zealand are iron deficiency and anaemia of chronic disease.

## Anaemia is a frequent finding on a common test
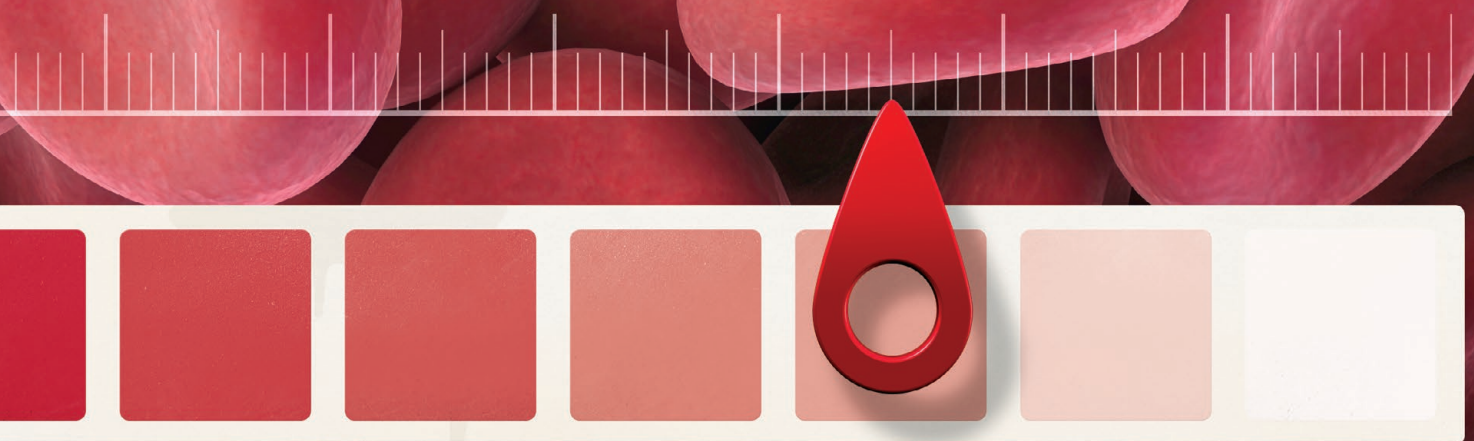
A full blood count (FBC), also known as a complete blood count, is one of the most frequently requested blood tests in primary care. In New Zealand in 2012, over two million FBCs were performed.[1] An incidental finding on a FBC will often be the first sign that a patient has anaemia. Anaemia is defined as a haemoglobin level below that which would be normal for a person's age and sex.[2]

There are many potential causes of anaemia, the most frequent of which among people in New Zealand are iron deficiency due to blood loss and anaemia of chronic disease. Co-morbidities, medicine use and dietary deficiencies also need to be considered.[3] Patients with features suggestive of a more serious underlying cause for anaemia usually require referral to a Clinical Haematologist or a Gastroenterologist for further investigation.

### Identifying patients who are anaemic

Anaemia, unless it is severe, is difficult to diagnose clinically and, apart from tiredness and pallor, there are often few clues in the history and on physical examination. Haemoglobin levels < 130 g/L in males and < 115 g/L in females usually indicate that a person has anaemia.[3] However, the diagnostic range for anaemia varies between guidelines and between laboratories within New Zealand; the range will be included with the laboratory results. In general, the lower the patient's haemoglobin level, the more likely there is to be a serious underlying pathology, and the more urgent the need for investigation.[4]

The symptoms of anaemia depend on how rapidly the condition has developed.[3] Clinical features may include pallor, tiredness, shortness of breath (particularly on exertion), cardiac symptoms (tachycardia, bounding pulses, systolic murmurs), fingernail changes, angular stomatitis and, depending on the underlying cause, jaundice. However, some people with severe anaemia that has developed slowly can adapt to low levels of haemoglobin with relatively few symptoms.[3] Patients who have had an acute bleed are more likely to be symptomatic as they have not had time to compensate for the reduced haemoglobin levels.

### Classification of anaemia

The mean cell volume (MCV), provided as part of FBC results, is used to categorise anaemia and determine which additional investigations are appropriate. The MCV is measured in femtolitres (fL – equal to $10^{-15}$L), and divides anaemia into three categories:[3]

- Microcytic anaemia – MCV < 80 fL
- Normocytic anaemia – MCV 80 – 95 fL
- Macrocytic anaemia – MCV > 95 – 100 fL

The adult reference range for MCV is 80 – 95 fL,[3] although there is some debate about the cut-off for the upper limit of normal. Some references define macrocytic anaemia as > 100 fL.
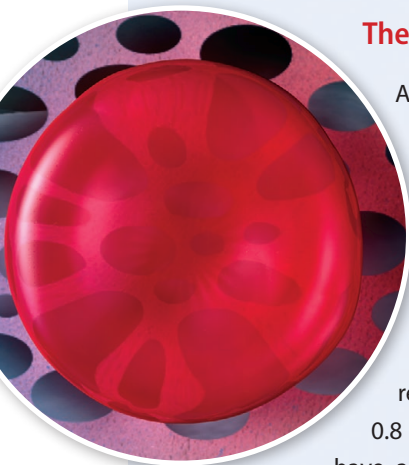
## The short, busy life of a red blood cell

A red blood cell (RBC) is a small, highly deformable cell, without a nucleus. During its production (erythropoiesis) a developing RBC loses its nucleus, maximising the volume of haemoglobin it is able to contain. Erythropoiesis normally results in the daily replacement of 0.8 – 1% of circulating RBCs which have an average lifespan of 100 – 120 days.[5] Erythropoiesis occurs in the bone marrow and is stimulated by the production of the hormone erythropoietin (EPO) which is released by the kidneys in response to reduced oxygen levels in the blood.[5] Normally the process works at equilibrium, creating new cells at the rate of cell loss. However, it is elastic to demand, and erythropoiesis can increase four to five-fold when necessary, if iron levels and nutrition are adequate.[5] If EPO production is deficient, e.g. in some patients with advanced chronic kidney disease (CKD), erythropoiesis stimulating medicines may be required.

Many factors can affect RBC size. For example, immature RBCs, known as reticulocytes, are initially larger than mature RBCs and decrease in size over several days as they mature, following release into circulation.[5] An increased reticulocyte count can therefore cause the MCV to be elevated. In microcytic anaemia, the cell size is decreased due to reduced haemoglobin. This can be due to either less haem (i.e. iron) or an imbalance in globin chain synthesis, as in genetic disorders such as thalassaemia, which alter globin production. Maturation disorders during erythropoiesis can also result in microcytosis if the cell cytoplasm is affected, or macrocytosis if defects of nuclear maturation occur.[5]
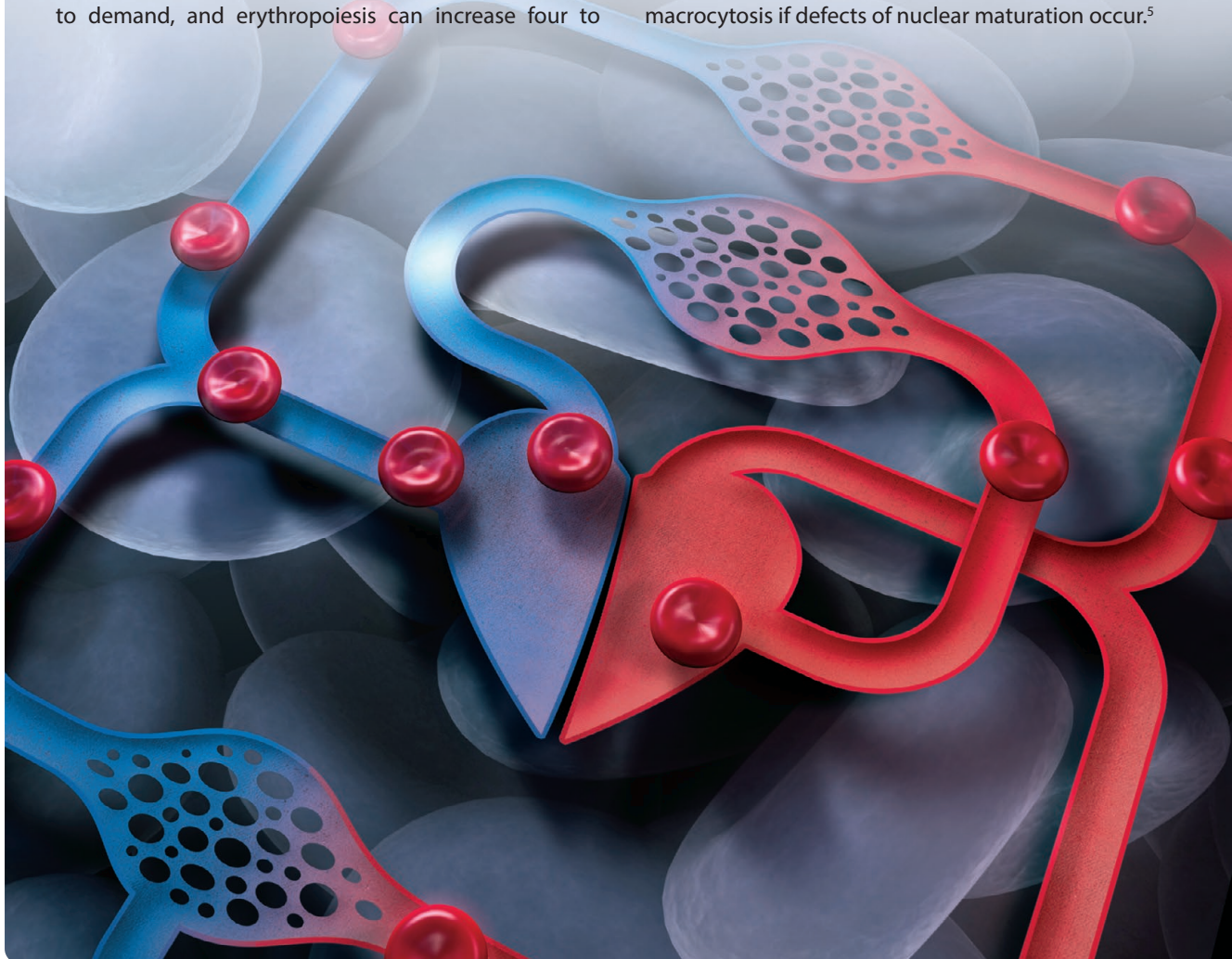
# Microcytic anaemia

**Microcytic anaemia** is defined as a MCV < 80 fL in a person with confirmed anaemia (i.e. low haemoglobin). The main causes of microcytic anaemia are:[2, 3]

- Iron deficiency (relating to blood loss, dietary deficiency and occasionally malabsorption)
- Anaemia of chronic disease (also associated with normocytic anaemia)
- Haemoglobinopathies, e.g. thalassaemia
- Sideroblastic anaemias (rare genetic or acquired disorders)

In a primary care setting in New Zealand, iron deficiency and chronic disease will be the most likely causes of microcytic anaemia.

Anaemia of chronic disease is the second most prevalent form of anaemia, after iron deficiency anaemia.[6] Unlike iron deficiency, anaemia of chronic disease is caused by reduced iron availability due to the body lowering plasma iron levels and increased phagocytosis of RBC by macrophages. Ferritin levels are also raised in anaemia of chronic disease, as it is an acute phase protein, and this is a diagnostically distinguishing feature between the two conditions. Anaemia of chronic disease is variable in presentation, but is typically mild (100 – 110 g/L) and normocytic, however, it may become microcytic in patients as the disease progresses and the anaemia becomes more severe (less than 80 g/L).[6]

Thalassaemias are more common in certain ethnicities, such as in people of South-East Asian, Mediterranean or Pacific origin (Page 9).

## Investigating the cause of microcytic anaemia

**A serum ferritin** test should be requested when microcytic anaemia is identified on FBC. Ferritin is an iron storage protein that keeps iron in a soluble and non-toxic form. Serum ferritin reflects true iron stores in uncomplicated iron deficiency and fluctuates less due to short-term variations than serum iron levels and total iron binding capacity (TIBC).[3] However, ferritin is also an acute phase protein and can be raised by inflammation, infection, chronic disease and malignancy. Ferritin is stored in the liver, so liver disease or inflammation may also result in elevated levels.[3]

### When ferritin is low

A serum ferritin below 15 – 20 micrograms/L in a person with microcytic anaemia confirms iron deficiency anaemia.[3]

In women who are pregnant, where iron demands are high, a ferritin of <30 micrograms/L is suggestive of early iron depletion that is likely to progress unless treated.[7]

**The cause of iron deficiency anaemia always needs to be investigated.**

When taking the patient history, consider the primary causes of iron deficiency, which include:[3, 8]

- Obstetric/gynaecological causes – menorrhagia, normal menstruation combined with a deficient diet, pregnancy. N.B. subjective assessments of menstrual blood loss are highly unreliable; consider the use of a pictorial blood assessment chart/menstrual diary[9]
- Gastrointestinal bleeding – oesophagitis, oesophageal varices, ulcerated hernia, peptic ulcer, inflammatory bowel disease, malignancy, angiodysplasia
- Malabsorption – coeliac disease, atrophic gastritis, *Helicobacter pylori* infection
- Pharmacological – medicines that cause gastric erosions/ulceration, e.g. non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and medicines that interfere with coagulation/platelet function leading to an increased risk of gastrointestinal haemorrhage, e.g. anticoagulants, selective serotonin reuptake inhibitors (SSRIs)
- Increased demand – pregnancy, growth spurts (uncommon)
- Dietary deficiency – vegans, older people, toddlers fed exclusively milk[10]
- Other – blood donation, blood loss from non-gastrointestinal sources, e.g. nosebleeds, trauma, surgery

Ask about weight loss and gastrointestinal symptoms such as altered bowel habits, dyspepsia and visible blood in stool. Also ask about a family history of colorectal cancer, haematological disorders, e.g. thalassaemia, hereditary haemorrhagic telangiectasia and bleeding disorders.

Hookworm infection is the most common cause of iron deficiency in developing nations,[3] so this should be considered in people who have recently immigrated from, or spent time in, a developing country.

**Coeliac serology should be considered for all people with unexplained iron deficiency anaemia.**[8] The prevalence of coeliac disease is estimated to be 10 – 15% in symptomatic

people with iron deficiency anaemia and 3 – 6% in asymptomatic people with iron deficiency anaemia.[11] An IgA tissue transglutaminase antibody (TTG) test is appropriate to test for coeliac disease in primary care. Patients must have consumed a normal diet containing a minimum of four slices of wheat-based bread (or equivalent) per day, for four to six weeks prior to serological testing for coeliac disease.[12]

For further information on testing for coeliac disease see: "The investigation of coeliac disease: a follow up", BPJ 12 (Apr, 2008).

> 🚩 **Red flags in iron deficiency anaemia:**
>
> - Upper and lower GI investigations should be considered in all males and post-menopausal females with iron deficiency anaemia unless there is an obvious alternative cause.[4] N.B. faecal occult blood testing is not beneficial for investigating people with iron deficiency anaemia as it is insensitive and non-specific.[4]
> - Patients with gastrointestinal symptoms and unexplained anaemia, require urgent referral, particularly those aged over 50 years or with a family history of colorectal cancer[8]
> - Males with haemoglobin levels less than 110 g/L and non-menstruating females with haemoglobin levels less than 100 g/L require urgent referral
> - Patients who do not respond to a trial treatment of iron replacement should be referred for further investigation
>
> N.B. In premenopausal females, do not exclude the possibility that iron deficiency may be due to causes other than menstruation.

## When ferritin is normal or raised

A raised or normal ferritin level in patients with microcytic anaemia can be due to two factors:

1. Spuriously elevated as a result of inflammation, infection or liver disease; or
2. Truly raised where there is excess body iron

**Clinical signs of inflammation may indicate that ferritin is spuriously raised**, although this will not always be apparent. During inflammation and infection, serum ferritin levels are increased to bind any free iron and prevent it being accessible

to pathogens. If the patient has an acute inflammatory illness then consider deferring testing serum ferritin or repeat the test once the patient's symptoms have resolved. Normal or raised ferritin levels do not exclude iron deficiency anaemia if an underlying illness is present.[4]

> A diagnosis of anaemia of chronic disease does not rule out iron deficiency anaemia, and the possibility of iron deficiency should always be considered in people with chronic diseases causing anaemia.

**Does the patient have a chronic disease?**

Many long-term conditions associated with inflammation can cause normocytic anaemia, which may progress to microcytic anaemia. These include:

- Situations of chronic inflammation
  - Chronic infections
  - Autoimmune conditions, e.g. rheumatoid arthritis, SLE, inflammatory bowel disease
  - Malignancy
- Chronic heart failure
- Chronic kidney disease

In chronic inflammation, inflammatory cytokines inhibit iron transport by blocking iron from leaving macrophages and other cells important for iron trafficking. This results in a functional iron deficiency where iron is not made available by macrophages to developing RBC. Inflammatory cytokines also act to suppress erythropoietin secretion, compounding the inhibition of erythropoiesis.

The anaemia associated with chronic heart failure is likely to be multi-factorial, with contributing factors including iron deficiency, chronic inflammation, renal disease and use of angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs).[13] ACE inhibitors are renoprotective, although they may contribute to anaemia of chronic kidney disease by blocking angiotensin II production and causing a reduction in circulating erythropoietin.

In chronic kidney disease (CKD) there is inadequate erythropoietin production due to kidney damage and chronic inflammation, and RBC survival is shortened.

For further information on CKD, see: "Managing anaemia of chronic kidney disease", Page 12.

## Iron deficiency without anaemia: latent iron deficiency

Iron deficiency does not always develop into anaemia. Often people have low iron levels and normal haemoglobin levels. Iron deficiency without anaemia is reportedly three times more common than iron deficiency anaemia, and is referred to as latent iron deficiency.[4]

Serum ferritin provides the most useful indirect estimate of a person's iron stores in both latent iron deficiency and iron deficiency with anaemia. Under normal conditions, there is a balance between iron absorption, iron transport and iron storage in the body. When a person's iron stores are lowered or depleted they become iron deficient. Over time, iron deficiency can develop into anaemia if stores fall sufficiently low enough to affect erythropoiesis.

There is a lack of clear guidance on when iron supplementation should be considered for people with latent iron deficiency, and clinical practice varies. In general, consider supplementation for symptomatic patients, e.g. with fatigue, or in patients at higher risk of iron deficiency progressing to anaemia, e.g. low ferritin levels in a woman who is pregnant, or persistent low ferritin levels in a younger female with menstrual losses and low iron intake. In the absence of inflammation or ongoing blood loss, the administration of oral iron will rapidly replenish iron stores.[14] Treatment for three months is generally appropriate for most patients.[4]

Malignancy is rarely detected in patients with iron deficiency without anaemia, however this should be considered in patients aged >50 years. If iron deficiency recurs within 12 months consider coeliac disease and gastrointestinal malignancy and investigate accordingly.[4]

See Page 9 for information on iron supplements, including doses.

**What to do when the picture is not clear**

Differentiating between iron deficiency anaemia and anaemia of chronic disease may be difficult, and the two conditions may co-exist. The likelihood of iron deficiency decreases as serum ferritin increases; iron deficiency is unlikely with ferritin levels over 100 micrograms/L. Iron studies (serum iron, iron binding capacity/serum transferrin and transferrin saturation – see below) may give useful further information if the diagnosis is not clear.

**Serum iron levels** are decreased in patients with iron deficiency anaemia and in conditions where there is acute and chronic inflammation (Table 1).[16] Serum iron may be elevated in patients with thalassaemia and sideroblastic anaemias, as these conditions are associated with abnormal iron processing.[17] Serum iron levels can also be affected by recent diet and the time of day (serum iron levels are diurnal and rise later in the day). Serum iron levels give an idea of dynamic iron transport rather than iron stores, but a more complete picture is given by the iron/transferrin saturation.[16]

**Total iron binding capacity (TIBC)** is a measure of the maximum amount of iron the blood can carry. It is more or less equivalent to serum transferrin. It is normal or increased in people with iron deficiency and, because transferrin is a negative acute phase protein, it is generally decreased with chronic inflammation (Table 1).[16] TIBC will usually be unchanged in people with thalassaemia or sideroblastic anaemia.

**Transferrin saturation** is calculated from the serum iron and the iron binding capacity and gives a measure of iron trafficking and availability for erythropoiesis. It is not a measure of iron stores and will be normal or reduced in people with iron deficiency and acute or chronic inflammation (Table 1).[16] Elevated fasting transferrin saturation may be an indication of iron loading, e.g. as seen in people with hereditary haemochromatosis.

**The other indices of the FBC and blood film are useful when there is uncertainty surrounding a diagnosis** of iron deficiency anaemia. The following features increase the post-test probability of a diagnosis of iron deficiency anaemia being correct: reduced mean cell haemoglobin, hypochromia (decreased haemoglobin concentration in RBC), increased variation in cell size (RDW), irregularly shaped cells (poikilocytosis) and reduced mean cell haemoglobin concentration.[8]

## Other explanations for microcytic anaemia

If iron deficiency and anaemia of chronic disease are ruled out as explanations for microcytic anaemia, a genetic disorder, such as thalassaemia, or more rarely sideroblastic anaemia, should be considered.

**The thalassaemias are a group of genetic disorders** characterised by hypochromic microcytic red cells and ineffective erythropoiesis.[10] They are caused by an imbalance in the synthesis of alpha and beta globin chains.

Alpha thalassaemias are usually due to deletions of alpha globin genes, of which there are four. Deletion of a single gene (silent alpha thalassaemia) results in a mild decrease in MCV, which may still be within the reference range. People with silent alpha thalassaemia are not generally anaemic. Deletion of two genes (alpha thalassaemia trait) causes a more marked microcytosis (MCV 65 – 78) and hypochromia. Any anaemia is usually only mild, although mean haemoglobin levels are approximately 15 – 20 g/L lower than in people with all four

**Table 1:** The differentiation of anaemia in people with a normal or raised ferritin[16]

| | Iron deficiency | Anaemia of chronic disease | Haemoglobinopathies, e.g. thalassaemia, Sideroblastic anaemia |
|---|---|---|---|
| **Serum ferritin** | Decreased | Increased | Increased |
| **Serum iron** | Decreased | Normal or decreased | Normal or increased |
| **TIBC** | Normal or increased | Normal or decreased | Normal |
| **Transferrin saturation** | Decreased | Normal or decreased | Normal or increased |

alpha globin genes. People with deletion of three genes (HbH disease) are almost always anaemic with severe microcytosis and may require intermittent blood transfusions. Deletion of all four alpha globin genes results in fetal hydrops and is generally incompatible with survival. Alpha thalassaemias are common in people from the Indian subcontinent, South-East Asia, North Africa, the Middle East and Pacific Peoples.[18, 19]

Beta thalassaemias are usually due to mutations in the beta globin genes, of which there are two. The severity of the disease depends on the number and nature of the mutations. In general, people with a single mutated gene (beta thalassaemia minor/trait) have mild anaemia with marked hypochromic microcytosis (MCV 60 – 75 fL). Mutation of both genes (beta thalassaemia major) results in a severe transfusion dependent anaemia. Because beta globin synthesis only starts around the time of birth, this will usually become apparent during the first year of life. Beta thalassaemias are found most commonly in people of Mediterranean ethnicities and to a lesser extent in Chinese, other Asians (including from the sub-continent) and African Americans.[10, 16]

If thalassaemia is suspected in a patient with microcytosis with normal ferritin and normal iron stores, a thalassaemia screen can be requested. Thalassaemia screens are relatively insensitive to one and two gene deletion alpha thalassaemias, which may be a diagnosis of exclusion. Identification of the milder forms of thalassaemia is important to avoid unnecessary iron treatment and to allow counselling in regards to future children. Where both parents have potential thalassaemias or other haemoglobin abnormalities, genetic studies may be required for definitive diagnosis and pre-conception counselling.[4]

**Sideroblastic anaemias** are a mixed group of inherited and acquired disorders where the underlying cause is poor iron incorporation into haem.[5] The disorders usually have a characteristic "dimorphic" blood film appearance, with both normocytic normochromic and microcytic hypochromic RBC present. Iron-encrusted mitochondria form a ring round the nucleus of immature erythrocytes causing ineffective erythropoiesis and leading to serum iron accumulation and anaemia.[5, 20] Sideroblastic anaemia is relatively rare and most commonly is due to myelodysplasia. Other causes include excessive alcohol consumption, heavy metal poisoning (lead, zinc), medicines (isoniazid, chloramphenicol) and copper deficiency. Rare congenital forms also exist.[3] Definitive diagnosis requires a bone marrow aspirate to identify "ringed" sideroblasts.[20]

## Managing microcytic anaemia

### Treating iron deficiency anaemia

The first-line management of iron deficiency anaemia is to prevent further blood loss by treating the underlying cause. Treatments that reduce menstrual loss should be considered in premenopausal women, e.g. hormonal contraceptives (including Mirena) or tranexamic acid. Consider stopping or reducing the dose of any medicine that may be contributing to blood loss.

**Review and correct any dietary factors** that may be contributing to the anaemia, e.g. low dietary iron intake in people adhering to a vegan diet.

**Patients diagnosed with coeliac disease should begin a gluten free diet.** Correction of depleted iron and other nutritional deficiencies with supplementary iron, vitamin B12, folate, calcium and vitamin D is often necessary.[12] Referral to a dietitian experienced in managing coeliac disease is recommended to ensure nutritional adequacy and to provide detailed dietary education.

For further information see: "Dietary advice for people with coeliac disease", BPJ SE; Prescription Foods (May, 2011).

**Oral iron supplementation**

Patients with uncomplicated iron deficiency can be given a trial treatment with oral iron supplementation to correct anaemia and replenish physiological stores.[4] A failure to respond to treatment may indicate ongoing iron loss and these patients will generally require gastrointestinal investigation.[10]

The recommended dose of oral iron to treat iron deficiency is 100 – 200 mg elemental iron per day (see Table 2 for elemental iron content of different salt forms).[14] A fully subsidised option is ferrous fumarate, 200 mg tablets (65 mg elemental iron), which would require a dose of two to three tablets daily for an adult with iron deficiency anaemia.[14] If ferrous fumarate is not tolerated, consider oral ferrous sulphate 325 mg tablets (105 mg elemental iron), one to two tablets daily; this is partially subsidised. A 325 mg ferrous sulphate tablet formulated with 350 mg folic acid is also available, partially subsidised.[14]

In the past, it was recommended that vitamin C tablets were prescribed at the same time as oral iron supplements to enhance uptake, however, evidence now suggests that the therapeutic benefit of this is minimal.[14]

**Table 2:** Elemental iron content of different oral iron formulations[14]

| Iron salt | Dose | Elemental iron content |
|---|---|---|
| Ferrous fumarate | 200 mg | 65 mg |
| Ferrous sulfate (tablet) | 325 mg | 105 mg |
| Ferrous sulfate (liquid) | 150 mg (in 5 mL) | 30 mg ( in 5 mL) |

For optimal iron absorption, supplements should be taken on an empty stomach. Gastrointestinal irritation can occur with oral iron, including nausea, epigastric pain and altered bowel function (constipation or diarrhoea).[14] Patients should be advised to continue with their iron supplementation if symptoms arise, but to discuss these symptoms with their General Practitioner or Practice Nurse. If gastric symptoms occur, advise the patient to try taking the supplement with food. Increasing fibre and fluid intake can also be helpful for constipation. Alternate day dosing may be appropriate for some patients to reduce adverse effects.

In patients receiving oral iron supplementation, the haemoglobin concentration should rise by approximately 1 g/L, per day, and should be approximately 20 g/L higher after three to four weeks.[8, 14] Haemoglobin levels (FBC) should be checked periodically to assess response to treatment, particularly in the early stages if the patient has significant anaemia. Once levels return to normal, treatment should be continued for a further three months to replenish iron stores.[14] Ferritin levels should be checked four to six weeks after completing treatment to confirm that iron stores have been replaced.

**Iron transfusion** may be considered for patients who are unable to tolerate oral iron supplementation and patients with malabsorption that prevents the uptake of oral iron (See "Parenteral iron supplementation").[4]

**Blood transfusions** for patients with iron deficiency anaemia are generally only required where there is a risk of cardiovascular instability due to severe anaemia, or if patients have symptomatic anaemia despite iron treatment.[4] The goal of a transfusion is to restore haemoglobin to a safe, but not necessarily normal, level.[4]

### Treating anaemia of chronic disease

Depending on the underlying condition, patients may be treated with blood transfusion, erythropoiesis-stimulating agents or with iron supplementation, occasionally parenteral iron.[6] Erythropoiesis-stimulating agents are funded under Special Authority, and are only available for people with anaemia associated with CKD or with cancer being treated with chemotherapy.

For further information on CKD and erythropoiesis-stimulating agents, see: "Managing anaemia of chronic kidney disease", Page 12.

### Treating thalassaemias and sideroblastic anaemia

**People with thalassaemia major** require regular blood transfusion to reduce the effects of anaemia, and iron chelation treatment to reduce iron toxicity.[2] Folate supplementation and a low iron diet are also often used to manage complications.[2] Recently, allogeneic bone marrow transplantation has been used to successfully treat the condition.[2] Genetic counselling is recommended for all carriers.[2]

**People with sideroblastic anaemia** are usually managed by a Clinical Haematologist. Blood transfusion to correct anaemia may be required.[20]

## Parenteral iron supplementation

Iron infusion may be considered to treat iron deficiency anaemia in adults, if oral iron replacement is not tolerated, has not been effective or is not appropriate. Iron infusion is usually carried out in secondary care, however, some general practice clinics are now offering this treatment. Iron infusion is not recommended for women who are pregnant (especially in the first trimester), as there is no evidence to support its use or safety in pregnant women. Iron infusion should be undertaken with caution in people with an immune/inflammatory condition such as asthma, eczema or rheumatoid arthritis, as they may have a higher risk of allergic reaction.[21] The patient must be closely monitored throughout the infusion to observe for adverse effects, especially allergic reaction. Resuscitation equipment and an anaphylaxis kit should be readily available in the clinic.

Iron polymaltose 318 mg/2 mL (equivalent to 100 mg/2 mL elemental iron) is the recommended treatment, and can be given intravenously or intramuscularly (less commonly).[14] Adverse effects of iron polymaltose include localised pain and swelling, nausea, vomiting, syncope, rash, hypotension and circulatory collapse.[14]

Most DHBs will have a protocol for IV iron infusion which can be adapted for use in a general practice setting. The product datasheet also contains information on dosing and administration. There is evidence that a rapid iron polymaltose infusion protocol is safe, well-tolerated and effective.[22]

For an IV infusion, the total dose of elemental iron should be 1500 mg for most patients. A lower dose (1000 mg) is recommended in elderly or frail people and people with mild anaemia (haemoglobin ≥ 100 g/L). A higher dose (2000 mg) is recommended for younger people, heavier people (≥ 70 kg) or people with more severe anaemia.

Normal saline 250 mL should be used as the infusion fluid, usually at the infusion rate of 125 mL/hour, if tolerated, closely observing for adverse effects. A test dose prior to the infusion is no longer recommended as this is not considered a reliable method to predict the patient's response when the full dose is administered.[21]

The infusion should be slowed if gastrointestinal adverse effects occur, and stopped if symptoms such as dizziness, headache, rash or joint or muscle pain occur. It is recommended that FBC should be tested every three months for one year in patients given parenteral iron supplementation to monitor relapse, and then again at two years post-treatment.[8]

IM injection of iron is less preferred as it is no more effective than IV administration, injections can be painful, and it is associated with a risk of permanent skin staining. A specific technique – the Z technique – should be used for an IM iron injection. For further information, consult the medicine datasheet, available from: **www.medsafe.govt.nz** or **www.nzf.org.nz**

## Managing anaemia of chronic kidney disease

Anaemia which develops in people with chronic kidney disease (CKD) is multi-factorial. The most significant cause is inadequate erythropoietin production. Erythropoietin is produced by peritubular capillary endothelial cells, and their ability to respond to anaemia is blunted in people with renal impairment. Iron deficiency is common in people with CKD, and inflammatory conditions also contribute to the anaemia. There is evidence that RBC survival is also shortened in people with CKD, possibly due to uraemic toxins, and haemoglobin levels may improve with adequate dialysis.

In patients with anaemia and an eGFR of < 60 mL/min/1.73m$^2$ consider whether CKD is a contributing factor to the anaemia.[23] The incidence of anaemia increases with decreasing eGFR.[24] It is estimated that anaemia is present in 50 – 70% of people with an eGFR < 30 mL/min/1.73m$^2$.[24] Conversely, the prevalence of anaemia is low in people with eGFR > 60 mL/min/1.73m$^2$ and, if present, is more likely to reflect causes other than CKD.[24]

Evaluation of anaemia in patients with renal failure is aimed at excluding causes other than erythropoietin deficiency, and should include a full blood count, serum ferritin and transferrin saturation. Reticulocyte haemoglobin content (CHr), which can be measured by most laboratories in New Zealand, is a further helpful parameter, as it gives an indication of iron availability to recently developed RBC and is therefore a measure of dynamic iron status.

Serum ferritin is frequently raised in people with CKD as it is an acute phase protein, therefore the diagnostic threshold for iron deficiency is interpreted differently than for people without CKD.[23] Iron deficiency anaemia can be diagnosed in people with stage 5 CKD with a ferritin level of less than 100 micrograms/L and should be considered in people with stage 3 and 4 CKD if the ferritin level is less than 100 micrograms/L.[23]

The treatment of anaemia of CKD focuses on the management of the underlying condition. Erythropoiesis-stimulating agents are subsidised for the treatment of anaemia associated with severe CKD where no cause for the anaemia is found other than kidney disease. Subsidy is subject to Special Authority approval. Depending on the individual patient and experience of the clinician, treatment may be managed in primary care. However, clinicians who are unsure about the use of erythropoietin and its possible complications should discuss the patient with a Nephrologist.

Epoetin beta is indicated for the treatment of symptomatic anaemia associated with chronic kidney disease, and epoetin alpha is indicated for patients on haemodialysis. Typically, treatment is titrated to achieve a haemoglobin concentration of 100 – 120 g/L.[23] For specific dosing information, refer to the New Zealand Formulary.

Treatment with erythropoiesis-stimulating agents can result in a functional iron deficiency where, although body iron stores are adequate, the demand from the developing RBC exceeds the ability of macrophages to deliver iron to them. Any iron deficiency should be treated prior to use of erythropoiesis-stimulating agents. In people with CKD who have serum ferritin levels greater than 100 micrograms/L iron supplementation should be given prior to treatment with erythropoiesis-stimulating agents if the CHr is ≤ 32 pg (if this test is available) or if the transferrin saturation is less than 20%.[23]

People with CKD should receive iron supplementation during treatment with erythropoiesis-stimulating agents to keep their serum ferritin levels between 200 – 500 micrograms/L.[23] In many cases this will necessitate intravenous iron.[23]

Iron supplementation that increases haemoglobin concentration to greater than 125 g/L may provide an environment more susceptible to bacterial infection and potentially increase the risk of infectious complications and cardiovascular morbidity.[23] In general, this will mean the patient maintains a lower than normal haemoglobin concentration, however, the aim of erythropoietin treatment is to relieve the symptoms of anaemia, and in patients with CKD to avoid the need for blood transfusion.[14]

Supplements of vitamin C, folic acid or carnitine should not be prescribed specifically for the treatment of anaemia of chronic kidney disease as there is no evidence that they provide benefit and they increase the cost of treatment.[23]

# Normocytic anaemia

**Normocytic anaemia** is defined as a normal MCV (approximately 80 – 95 fL) in a person with anaemia. The primary causes of normocytic anaemia are:[25]

- Acute blood loss
- Haemolysis
- Early stage nutrient deficiencies before micro or macrocytic anaemia develops (e.g. iron, folate, vitamin B12)
- Kidney disease
- Chronic disease
- Bone marrow disorders

## Investigating the cause

There are many potential causes of normocytic anaemia and investigation can be more complex than for other types of anaemia. Acute blood loss is almost always obvious and significant haemolysis may cause jaundice and/or discolouration of the urine. Both of these conditions usually require emergency referral. Rarely, they may be present in an asymptomatic patient.

**A reticulocyte count** should be requested to investigate whether the anaemia has arisen from decreased RBC production or increased RBC loss. If the body is unable to produce RBCs at a healthy rate, e.g. in a person with a bone marrow disorder, the reticulocyte count is often lowered, whereas when RBCs are being lost or destroyed, the reticulocyte count is increased.[25] A normal level of reticulocytes as a percentage of all RBCs in a healthy person is 1 – 2% (or $20 - 100 \times 10^9$/L).

**Liver function tests (LFTs), serum creatinine and CRP** should also be requested as they can provide further information to identify an underlying condition that may be suggested by the reticulocyte count.

### When the reticulocyte count is high

**An increased reticulocyte count suggests ongoing blood loss.**[5] Where blood loss has been subclinical, such as a patient with occult gastrointestinal bleeding, features will usually include increased RBC production and normal RBC morphology on blood film. There may be an acute phase response of neutrophilia and thrombocytosis on FBC.[25] N.B. In contrast to ongoing blood loss, acute haemorrhage is associated with a low reticulocyte count (usually < 2.5 times normal).[5]

**A reticulocyte count > 2.5 times the normal level suggests haemolytic anaemia.**[5] Clinical features associated with haemolytic anaemia include scleral jaundice, pallor, discolouration of the urine, splenomegaly and, more rarely, hepatomegaly.[5] Further investigation of haemolytic anaemia is usually carried out in secondary care; serum bilirubin and LDH may be raised and serum haptoglobin levels low. Some types of haemolytic anaemia will be readily apparent on the blood film, such as microangiopathic haemolytic anaemia, which causes narrowed and fragmented RBCs, and the laboratory report will often point to the diagnosis.[25] A direct Coombs test (antiglobulin test) may be considered in asymptomatic patients with elevated reticulocyte counts to investigate the possibility of autoimmune haemolytic anaemia.[26] Where a cause of haemolysis is not readily apparent, the blood film will usually indicate abnormally high numbers of RBCs (polychromasia) and immature, nucleated RBCs.[5]

### When the reticulocyte count is low or normal

The primary causes of anaemia in patients with a low or normal reticulocyte count are normocytic anaemia of chronic inflammation, CKD and bone marrow disorders.

**Chronic diseases are associated with a low or normal reticulocyte count.** In chronic disease, the characteristics and duration of the illness determine the type of anaemia. For example, a patient with recent onset cancer may have normocytic anaemia, however, a patient with long-term active rheumatoid arthritis or a chronic infection is more likely to have microcytic anaemia. Normocytic anaemia is often a reflection of a shorter time in which the patient has been unwell, and anaemia may become microcytic as the disease progresses.[5, 6]

In anaemia of chronic disease, iron studies will generally show ferritin to be elevated while transferrin saturation and other markers of iron stores will be decreased. An increased CRP is also suggestive of anaemia of chronic disease.[25]

Reduced creatinine clearance in a person with normocytic anaemia suggests CKD as an underlying cause (see: "Managing anaemia of chronic kidney disease"),[25] although in older patients multiple myeloma should also be considered as a cause of concomitant anaemia and renal impairment. Iron deficiency, anaemia of chronic disease and anaemia associated with chronic blood loss may all be present concurrently in a patient with severe renal disease.[25]

**Bone marrow disorders are usually associated with a low reticulocyte count.** Bone marrow disorders are distinguishable from other normocytic anaemias by a low reticulocyte count, a reduction in RBCs and associated neutropenia or thrombocytopenia.[25] The patient's blood film may also suggest bone marrow disease, e.g. dysplastic changes, or circulating nucleated red cells, immature myeloid cells or lymphoma cells. Specific bone marrow disorders, and the likely diagnosis, are usually indicated in the laboratory results.

## Managing normocytic anaemia

Patients with normocytic anaemia caused by blood loss or haemolytic anaemia should be referred for further investigation and treatment of the cause.

### Managing anaemia of chronic disease

The first step in managing a patient with normocytic anaemia of chronic disease is to identify and treat the underlying condition, which may resolve the anaemia. Alternatively anaemia may explained as a symptom of a previously identified condition, in which case it should be monitored, and if it worsens, treatment for the anaemia initiated.[25] Depending on the underlying chronic disease/inflammation, this may involve blood transfusion, iron supplementation or erythropoiesis-stimulating agents (in chronic kidney disease).

# Macrocytic anaemia

Macrocytic anaemia is defined as a MCV > 95 – 100 fL in a person with anaemia. Mature RBCs that are larger than normal, i.e. macrocytic, occur due to abnormalities in erythropoiesis, defects in DNA synthesis, changes in the structure of the cell membrane, alterations in cell fluid volume and other mechanisms that are not fully understood.

Macrocytic anaemia can be further classified as megaloblastic or non-megaloblastic depending on the appearance of developing RBC in the bone marrow. Megaloblastic anaemia is characterised by developing RBC that are larger than normal with nuclei that are less mature than their surrounding cytoplasm.[3] This occurs when DNA synthesis is defective and slower than the rate of development of the rest of the cell. Megaloblastic anaemia can also be identified by the presence of neutrophils on blood film with hypersegmented nuclei (six or more lobes).[3] Vitamin B12 or folate deficiency are the usual causes of megaloblastic anaemia. In non-megaloblastic anaemia, DNA synthesis is not affected and the developing RBC in the bone marrow appear normal. Alcohol, liver disease and myelodysplasia are some of the causes of non-megaloblastic anaemia.

## Investigating the cause of macrocytic anaemia

Macrocytic RBC can occur with or without anaemia (see: "Macrocytosis without anaemia". Page 17). Table 3 lists the main causes of macroytosis.

Alcohol misuse should always be considered in patients with macrocytic anaemia.[3] Even relatively moderate quantities of alcohol can cause macrocytosis, e.g. consumption of two gin and tonics, or approximately half a bottle of wine per day, especially in females.[3] The mechanism(s) for this effect is uncertain, however, alcohol consumption is thought to increase lipid deposition into RBC membranes making RBCs larger. Direct toxicity of alcohol on the bone marrow is also likely to contribute.

Vitamin B12 and folate deficiency are the most likely causes of megaloblastic macrocytic anaemia. This is because vitamin B12 (cobalamin) and folate are both co-factors for DNA synthesis.[27] A number of conditions affecting the gastrointestinal tract can result in vitamin B12 and folate deficiency, such as coeliac disease, inflammatory bowel disease and Crohn's disease. Long-term alcoholism

**Table 3:** Examples of conditions associated with macrocytosis (with or without anaemia) and their underlying mechanism(s)[3]

| Underlying mechanism | Condition |
|---|---|
| Abnormalities of DNA synthesis | Vitamin B12 deficiency<br>Folate deficiency<br>Medicines, e.g. methotrexate |
| Increased numbers of immature RBCs | Reticulocytosis<br>Secondary to erythropoietin use |
| Primary bone marrow disorders | Myelodysplastic syndromes<br>Leukaemias |
| Lipid changes in the RBC membrane | Liver disease<br>Hypothyroidism<br>Post-splenectomy |
| Multiple/unknown mechanisms | Multiple myeloma<br>Alcoholism (thought to be related to lipid changes in the RBC membrane, direct toxicity and changes to B12 and folate when alcohol consumption is heavy and prolonged) |
| Carbon dioxide retention resulting in an increase in intracellular volume | COPD |

is also commonly associated with vitamin B12 and folate deficiency.[2, 3] A normal diet will usually provide sufficient vitamin B12 and folate, however, people eating a vegan diet, people who are malnourished or older people may be at risk of dietary deficiency.[3] Other risk factors for vitamin B12 and folate deficiency include low socioeconomic status, previous gastric surgery (although most patients will be taking vitamin B12 and folate supplements) and the use of medicines such as trimethoprim and phenytoin.

**Some medicines can cause macrocytosis,** although usually not macrocytic anaemia, by a variety of mechanisms. They may interfere with DNA synthesis, inhibit absorption of folate or B12 or be directly toxic to cells. Medicines that are known to cause macrocytosis include:

- Methotrexate
- Trimethoprim
- Oral contraceptive medicines
- Phenytoin
- Metformin (by decreasing absorption of vitamin B12)
- Hydrocarbamide (hydroxyurea)

### History and examination can help determine the underlying cause

The patient history should include an assessment of:

- Alcohol consumption
- Diet
- Medicine use
- A history of blood loss or haemolysis
- Symptoms associated with liver disease, hypothyroidism or bone marrow disorders (particularly in older people)

Clinical examination may reveal signs of an underlying condition, e.g. chronic liver disease, hypothyroidism or disease causing malabsorption.

**Patients with vitamin B12 or folate deficiency** may present with pallor, fatigue, gastrointestinal disturbance, weight loss, glossitis (inflammation and discolouration of the tongue) or angular stomatitis. Patients with a severe deficiency can present with peripheral neuropathy, motor disturbances,

visual disturbances and cognitive changes ranging from memory loss to dementia and psychiatric symptoms.[3]

> 🚩 **Red flags in people with macrocytic anaemia** requiring referral to a Clinical Haematologist include:[29]
>
> - MCV > 100 fL with accompanying cytopenia
> - Persistent and unexplained MCV > 104 fL
> - Vitamin B12 deficiency of unknown cause

### Add further laboratory investigations

Laboratory investigations that should be considered after an initial finding of macrocytic anaemia include:

- Serum vitamin B12 and folate
- Liver function tests (LFTs)
- Thyroid stimulating hormone (TSH)
- Serum creatinine
- Blood film

### Investigating vitamin B12 and folate deficiency

**Investigate for coeliac disease** in patients with low vitamin B12 and/or folate levels. Also consider the possibility of other gastrointestinal conditions such as Crohn's disease, especially where relevant symptoms are also present, e.g. recurrent diarrhoea or blood and mucus in stools.[2]

**Investigate for pernicious anaemia** in patients with low serum vitamin B12 levels. This can be tested for by requesting antiparietal cell antibodies or intrinsic factor antibodies.[3] Parietal cell antibodies are present in 90%, and intrinsic factor antibodies in 50%, of people with pernicious anaemia.[3] Pernicious anaemia is associated with the autoimmune destruction of gastric parietal cells that secrete intrinsic factor, which facilitates the uptake of vitamin B12. Pernicious anaemia can be treated in primary care as a vitamin B12 deficiency, but if there is neurological involvement, the patient should be discussed with a Clinical Haematologist.

**Vitamin B12 deficiency** is initially treated with 1 mg hydroxocobalamin intramuscularly, three times per week, for two weeks, then 1 mg every three months.[14] Dietary levels can be increased by consuming foods rich in vitamin B12, e.g. meat, milk, eggs and fortified yeast extracts.[30]

## Macrocytosis without anaemia

Macrocytosis is the term used to describe the presence of macrocytes in the blood. In a primary care setting it has been estimated that 60 – 80% of people with macrocytosis do not have an associated anaemia.[28] The significance of a finding of macrocytosis and the urgency of further investigations can vary greatly, influenced by the degree of macrocytosis and the general health of the patient.[34]

Macrocytosis may be physiological, e.g. during periods of high cell turn-over. Women who are pregnant can have macrocytosis associated with the anaemia of pregnancy and the increased demand for folate. Macrocytosis is also commonly associated with alcoholism (also see Table 3 for other causes).

Macrocytosis may occur spuriously (rarely), and be due to the following factors:

- Cold agglutinins – which cause RBCs to clump and when assessed automatically in the laboratory, appear larger than usual
- Hyperglycaemia – when diluted to allow measurement of MCV, the more concentrated hyperglycaemic blood cells swell causing a false increase in MCV
- Leukocytosis – which can increase the turbidity of a blood sample and automated laboratory machines may overestimate the size of the cells

**Folate deficiency** is treated with 5 mg folic acid, daily, for four months, or until term in pregnant women.[14] Dietary folate levels can be increased by eating green vegetables such as broccoli and Brussels sprouts, citrus fruit, wholemeal bread, legumes and liver.[31] Women who are pregnant or breastfeeding should consume approximately 50% and 25% more folate per day respectively than the average adult.[31]

### Investigating liver dysfunction

Gama glutamyl transferase (GGT) is the liver enzyme most often raised in people who consume excessive amounts of alcohol. Typically this will be elevated in the range of 60 – 200 U/L, but rarely can be as high as 1000 U/L.[32] Aspartate amino transferase (AST) and alanine amino transferase (ALT) may also be elevated (upper reference range 45 U/L).[32] If the AST/ALT ratio is > 2, consider alcoholic hepatitis, especially if there is also raised GGT. Macrocytosis due to alcohol misuse usually resolves with abstinence from alcohol after a period of time.

### Investigating thyroid dysfunction

Hypothyroidism often results in a decrease in RBC mass and normocytic anaemia. However, some patients with hypothyroidism (especially if it is severe) may develop a macrocytosis, with or without anaemia. Hypothyroidism incidence tends to increase with age and may be present in up to 5% of older females.[2] Serum TSH can be used in most situations to investigate suspected hypothyroidism. Additional thyroid tests, such as autoantibodies, can be requested later if required.[33]

⌢ For further information see: "Management of thyroid dysfunction in adults", BPJ 33 (Dec, 2010).

### Consider the possibility of haemolysis

If LFTs, TSH and kidney function are normal and other causes have been eliminated, consider the possibility that the macrocytic anaemia is caused by haemolysis. Haemolysis can be investigated by requesting a reticulocyte count. An increased number of reticulocytes suggests haemorrhage or haemolysis and may explain a mildly elevated MCV.[34] Also see: "Normocytic anaemia", Page 13.

Haemolytic anaemias are relatively uncommon, however, a family history that includes evidence of either sickle cell anaemia, hereditary spherocytosis or glucose-6-phosphate dehydrogenase (G6PD) deficiency should increase suspicion of haemolytic anaemia.[34] G6PD deficiency with a haemolytic response generally only occurs when people take oxidant medicines, e.g. sulphonamides, or consume excessive amounts of broad beans (referred to as favism).[2] People who run long distances may also develop haemolysis induced macrocytosis.[34]

Treatment of haemolytic anaemia depends on the cause and may involve: discontinuation of causative medicines, change in diet, iron supplementation (if haemoglobinuria is significant), splenectomy or blood transfusion in emergency situations. Patients with chronic haemolytic anaemia should be given folic acid to prevent folate deficiency.[3]

N.B. Acute blood loss, e.g. from recent child birth or trauma, can result in a mildly elevated MCV due to more reticulocytes being present in the circulation as lost RBCs are replaced.[3] Reticulocytes are larger than mature RBCs and therefore can cause a transitory elevation in the MCV while the body replaces lost RBC.

### Consider malignant causes

If other investigations have not revealed a possible cause for macrocytic anaemia, then the suspicion of malignancy should be increased, particularly in older patients. There are also a number of rare hereditary conditions causing defects in DNA synthesis that can result in megaloblastic anaemia.[3] These usually present in infancy.

**Myelodysplastic syndromes frequently present as macrocytic anaemia** with normal vitamin B12 and folate levels.[2] These are clonal stem cell disorders characterised by ineffective haematopoiesis, where the bone marrow is very active but cellular maturation is defective. Myelodysplastic syndromes may be accompanied by neutropenia or thrombocytopenia in the peripheral blood, depending on which lineages are affected. A blood marrow aspirate is required to confirm a diagnosis.[29]

Risk factors for myelodysplastic syndromes include age, a history of radiation treatment or chemotherapy, and exposure to pesticides, fertilisers, solvents, e.g. benzene, or heavy metals.[29] Treatment options vary and are dependent upon the age of the patient, the degree of disease progression, the number of cell types that are affected, and the presence of haemorrhage or infection.[29] People with myelodysplastic syndromes often have a poor prognosis, with death occurring due to infection, haemorrhage or transformation to acute leukaemia.[2]

**Paraproteins, e.g. multiple myeloma,** can cause an increase in MCV without macrocytes being present on the blood film.[3] Suspicion of multiple myeloma should be increased in patients aged over 60 years with any bone pain, and fatigue and/or weight loss, renal impairment, with or without hypercalcaemia.[35] A practical approach to investigating the possibility of multiple myeloma is to request serum protein electrophoresis and then to discuss the result with a Haematologist if an increase in immunoglobulins is found. A bone marrow aspirate is generally required to confirm a diagnosis of multiple myeloma.

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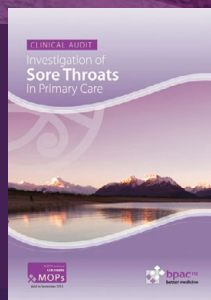
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