# Geriatric medicine

Edited by Graham Mulley DM FRCP, Developmental Professor of Elderly Medicine, St James's University Hospital, Leeds and
Peter Crome MD PhD FRCP FFPM, Professor of Geriatric Medicine, Keele University School of Medicine, University Hospital of North Staffordshire, Stoke-on-Trent

## Anaemia in elderly patients

**Lesley McCormick** BSc MBChB MRCP(UK), Senior House Officer in Geiatric Medicine

**David J Stott** MBChB MD FRCP(Glas) FRCP(Edin), David Cargill Professor of Geriatric Medicine

*Academic Section of Geriatric Medicine, Glasgow Royal infirmary*

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Anaemia is defined by the World Health Organization (WHO) as a haemoglobin concentration below 12 g/dl in women and 13 g/dl in men.[1] The prevalence of anaemia in elderly subjects varies widely in different populations because of the heterogeneity of study populations, results varying according to race, health status and setting.

Anaemia is more common in hospitalised and nursing home residents than in old people living at home. Large epidemiological cohorts have reported anaemia in around 6–12% of community dwelling older people.[2]

The symptoms usually associated with anaemia include breathlessness, palpitations, tiredness and lethargy. However, in older people anaemia is also associated with increased falls, impaired cognition, reduced muscle strength and physical function, and impaired quality of life.[3,4]

A reduction in haemoglobin is not a normal physiological part of the ageing process nor is it clinically benign – reduced haemoglobin is independently associated with increased mortality in elderly people, even at levels currently considered to be within the lower end of normal.[5]

### Key Points

- **Anaemia is independently associated with mortality and loss of physical function in elderly subjects, even with haemoglobin levels currently considered to be within the lower end of the normal range**
- **Chronic disease and iron deficiency anaemia are the most common causes of anaemia in older people**
- **A ferritin level below 45 µg/l should be used as a cut-off for diagnosing iron deficiency in elderly people, but should be considered as a possibility with ferritin levels up to 100 µg/l**
- **Patients with iron deficiency anaemia should be investigated for chronic gastrointestinal blood loss by endoscopy and colonoscopy regardless of faecal occult blood test results**
- **Coeliac disease should be considered in elderly patients with unexplained anaemia due to iron or folate deficiency**

**KEY WORDS: aged, anaemia, anaemia of chronic disease, folic acid, iron deficiency, vitamin B12**

### Causes of anaemia in older people

Most older people with anaemia have an identifiable pathological cause. Although intrinsic ageing can contribute to a low haemoglobin, it should not be accepted as the primary cause even in very elderly subjects. Multiple causes of anaemia may coexist in the same patient. The most common causes in older people are the anaemia of chronic disease followed closely by iron deficiency (Table 1).

### Anaemia of chronic disease

Anaemia of chronic disease is typically normocytic and normochromic but it can occasionally be microcytic. It is associated with chronic inflammatory disorders, renal impairment, chronic infections and malignancy.[7] There is reduced release of iron from bone marrow despite adequate iron stores and an inadequate erythropoietin (EPO) response to anaemia, resulting in reduced erythropoiesis and shortened red cell survival.

The main differential diagnosis of the anaemia of chronic disease is iron deficiency. The single most helpful blood test to discriminate between these is serum ferritin.[6] In the anaemia of chronic disease, serum ferritin is typically elevated; iron deficiency is unlikely if levels are over 100 µg/l.

Anaemia of chronic disease should be suspected if there is evidence of a chronic inflammatory process. Clinically, this could include:

- a pressure sore or skin ulceration

**Table 1. Prevalence of types of anaemia in older people**. Reprinted with permission from Elsevier.[6]

| Type of anaemia | Prevalence (%) |
|---|---|
| Anaemia of chronic disease | 44 |
| Iron deficiency | 36 |
| Megaloblastic | 8 |
| Myeloma | 2 |
| Sideroblastic | 1 |
| Myelodysplasia | 1 |
| Other | 8 |

- limb girdle stiffness consistent with polymyalgia rheumatica
- enlarged lymph nodes
- abdominal masses suggestive of tumour.

A basic investigative screen is essential. Abnormal results that may point towards an underlying cause of anaemia of chronic disease include:

- elevated serum urea and creatinine
- increased erythrocyte sedimentation rate (ESR)
- abnormal liver function tests
- low serum albumin
- tumour on chest X-ray.

The treatment of anaemia of chronic disease in the older patient is primarily directed at the underlying disorder. For example, successful healing of a pressure sore, drainage of an abscess or resolution of polymyalgia rheumatica with steroids may all result in a rise in haemoglobin. EPO treatment should be considered for severe anaemia due to renal failure.

## Iron deficiency anaemia

### *Laboratory investigations*

Iron deficiency anaemia (IDA) is typically associated with a microcytic, hypochromic blood film, with poikilocytosis, anisocytosis and target cells. However, these findings are insensitive and some patients are normochromic and normocytic.[8]

*Serum ferritin.* The single most useful investigation in establishing iron deficiency is measurement of serum ferritin. However, ferritin rises both with ageing and with chronic inflammation; cut-off levels for diagnosis of likely iron deficiency in older people are higher than those used by many laboratories.

The WHO recommends a ferritin below 12 μg/l as the cut-off for diagnosis of iron deficiency. This has a high specificity but low sensitivity and most elderly patients with IDA have a serum ferritin above this level. In older people a serum ferritin level below 45 μg/l has a sensitivity of 85% and a specificity of 92% for diagnosing bone marrow iron deficiency.[9] The possibility of iron deficiency should be considered with ferritin levels up to 100 μg/l; iron deficiency is unlikely with ferritin above this level, even in the presence of coexistent chronic inflammatory disease.[7]

Iron deficiency is typically associated with a low serum iron and an elevated total iron-binding capacity, but this rise is attenuated in older people and in the presence of coexistent chronic inflammation. In practice, measurement of transferrin saturation adds little to the interpretation of serum ferritin.

*Serum transferrin receptor.* A useful additional blood test may be serum transferrin receptor (sTfR). sTfR is expressed on most cells and has a major role in internalisation of iron. It is overexpressed on the cell membrane when iron stores are deficient, so levels of sTfR are inversely correlated with tissue iron stores. It is not an acute-phase reactant and can be an alternative method for assessment of iron status; it may be particularly useful in differentiating between IDA and the anaemia of chronic disease.

The ratio of sTfR to the log serum ferritin level is known as the sTfR index. This may be sensitive and specific in detection of iron deficiency and can be a valuable tool in differentiating between IDA and anaemia of chronic disease. However, the diagnostic utility of the sTfR has yet to be proven in older people.

*Oral iron replacement.* In cases where serum ferritin is equivocal (45–100 μg/l), a therapeutic trial of oral iron replacement can help confirm the diagnosis. With correction of iron deficiency (confirmed by a rise in ferritin) there will be an early reticulocytosis and rise in red cell distribution width, followed by a rise in mean cell volume and haemoglobin.

*Stainable bone marrow iron.* The definitive test for diagnosis of IDA is absence of stainable bone marrow iron. Bone marrow aspiration is an invasive test that can be associated with significant discomfort. In general, it is performed only when there is doubt about the diagnosis after all non-invasive options have been explored.

## Assessment for source of chronic blood loss

In a patient with IDA it is highly likely that there will be underlying chronic blood loss, particularly from the gastrointestinal (GI) tract.[10,11] Dietary insufficiency is an uncommon cause, and in older populations there is no association between iron intake and anaemia. Therefore, even when the diet appears poor, this cannot be assumed to be the cause of anaemia.

The first step in determining possible chronic blood loss is the history. The use of non-steroidal anti-inflammatory drugs (perhaps bought over the counter) and antiplatelet agents should be established. Enquiry should also be made about blood in vomit, stool or urine, or black stool colour.

However, non-specific symptoms such as dyspepsia or change in bowel habit do not associate strongly with an underlying source of chronic blood loss. Even in the absence of symptoms, up to 44% of adults with iron deficiency will have a GI lesion capable of causing blood loss. Similarly faecal occult blood (FOB) testing is not helpful.

Patients with a series of negative results can still have an important treatable cause of GI blood loss, so the results

**Table 2. Causes of iron deficiency anaemia (IDA) in elderly patients (n=96), revealed at upper gastrointestinal endoscopy and colonoscopy**. Reprinted with permission from S Karger AG, Basel.[9]

| Cause of IDA | %* |
|---|---|
| Gastric or duodenal ulcer | 26 |
| Gastric erosions/oesophagitis | 24 |
| Gastric or oesophageal cancer | 7 |
| Gastric polyp | 3 |
| Colon cancer | 8 |
| Colonic adenoma/polyp | 6 |
| Diverticula | 3 |
| Vascular malformation | 2 |
| Colitis | 2 |
| Haemorrhoids | 6 |
| No lesion found | 16 |

*Percentages total more than 100 as some patients had more than one lesion.

of FOB testing should not influence the decision to investigate further.

## Investigation of the gastrointestinal tract in iron deficiency anaemia

Investigation of both the upper and lower GI tract will often be required. When a benign lesion is found at one end of the bowel it should not be assumed that this is the only cause of the anaemia, so investigation should include both upper and lower GI tract.

### *Endoscopy and colonoscopy*

Endoscopy is the mainstay of investigation for IDA. It is usually preferred to radiological imaging; it has higher diagnostic sensitivity and the opportunity for tissue diagnosis if a lesion is seen. Upper GI endoscopy is better tolerated than barium meal in older patients.

The yield from upper GI endoscopy plus colonoscopy is substantial, with benign lesions in up to 60% and malignancies, polyps or adenomas (premalignancies) in around 25% (Table 2).

If colonoscopy is not available, barium enema is a reasonable alternative, detecting around 95% of the lesions found at colonoscopy. Both colonoscopy and barium enema require good bowel preparation, with pretreatment with laxatives to empty the bowel. Neither of these tests is practicable in frail immobile patients.

### *Computed tomographic colonography*

A newer radiological technique, less invasive than colonoscopy and better tolerated by patients, is computed tomographic (CT) colonography. It does not require sedation, though necessitates full bowel preparation and air insufflation. A meta-analysis of published studies concluded that CT colonography is less accurate than colonoscopy for detection of polyps or other small lesions.[12] CT colonography may be more accurate than air contrast barium enema.

Minimal preparation CT avoids the need for bowel preparation or intravenous contrast and is non-invasive. It is therefore an option in investigation of the GI tract in frail elderly patients. Evidence is limited; results to date show limited sensitivity for detection of clinically significant colonic tumours.[13] Other developing techniques such as magnetic resonance colonography cannot be recommended for routine use at present.

## Coeliac disease

The prevalence of coeliac disease in the UK is high (about 1 in 100). Typical malabsorption symptoms including diarrhoea are uncommon; chronic iron or folate deficiency with anaemia may be the only presenting feature.

Serology using human recombinant tissue transglutaminase antibody has high sensitivity and specificity (93% and >98%, respectively) and is a useful screening tool for coeliac disease.[14] Histological changes on distal duodenal biopsy remain the standard for diagnosis; in patients undergoing endoscopy for IDA, duodenal biopsies should be taken if no other cause for anaemia is found.

## Anaemia due to vitamin B12 deficiency

Vitamin B12 deficiency is common in elderly patients.[15] In the Framingham study,[16] 12% of community dwelling older people had evidence of B12 deficiency, while studies in institutional care have shown a prevalence of up to 40%.

A low serum vitamin B12 level is usually associated with altered erythropoiesis. Typically, severe B12 deficiency causes macrocytosis with a megaloblastic bone marrow, but abnormalities may be subtle with a modest rise in mean cell volume within the accepted reference range.[17] Macrocytosis can also be masked by concomitant iron deficiency. It is therefore important to screen all anaemic elderly patients for both B12 and iron deficiency with measurement of serum vitamin B12 and ferritin levels.

### *Causes of vitamin B12 deficiency*

The most common cause of vitamin B12 deficiency in older people (60–70%) is inability to cleave the vitamin from dietary protein to allow absorption.[18] This food-cobalamin malabsorption is primarily caused by atrophic gastritis and hypochlorhydria. The problem is therefore inability to release B12 from food, despite adequate intake and the ability to absorb free B12.

Pernicious anaemia is often assumed to be the cause for B12 deficiency, but accounts for only 15–20% of cases in older people. Pernicious anaemia is an autoimmune disorder. Parietal cell antibodies, present in the serum of about 90% of patients with pernicious anaemia, are also found in many elderly patients with gastric atrophy; specificity is therefore low. Intrinsic factor antibodies have a higher specificity but sensitivity is low (about 50%).

Other causes of B12 deficiency are relatively rare. Occasional patients have primary dietary deficiency. Surgical removal of the terminal ileum will inevitably result in B12 deficiency if replacement is not given. Metformin can cause B12 deficiency.

### *Schilling test for absorption of vitamin B12*

The Schilling test can be used to measure B12 absorption. The standard test involves first assessing absorption of radiolabelled vitamin B12. If excretion in the urine is low, the patient then proceeds to the second part of the test in which absorption of radiolabelled vitamin B12 is assessed when given with intrinsic factor. In pernicious anaemia, the expected result is reduced B12 absorption when given alone in part 1, corrected by the addition of intrinsic factor in part 2 of the test.

However, this test is of no value in detecting food-cobalamin malabsorption. In addition, a falsely low result may occur if the 24-hour urine collection is incomplete or renal function is impaired – often the case in elderly patients. The treatment of food-cobalamin malabsorption and pernicious anaemia is the same, with replenishment of vitamin B12.

The result of the Schilling test does not affect clinical management, so it is not

recommended in routine clinical practice for older patients with B12 deficiency and anaemia.

## Anaemia due to folate deficiency

The predominant cause of folate deficiency is poor dietary intake. It may also occur with malabsorption, use of certain drugs or in medical conditions associated with increased cell proliferation. Serum and red cell folate assays are readily available. Red cell folate is a better measure as it is more stable and not affected by day-to-day changes in dietary folic acid intake.

The cause in most elderly patients is nutritional and no further investigation is necessary. Malabsorption should be considered if there is unexplained weight loss, steatorrhoea, low albumin or multiple deficiencies of other vitamins and minerals including iron, calcium and vitamins B12 and D.

## Other causes of anaemia

Other causes of anaemia in the older patient are relatively rare. Myeloma typically causes a high ESR. Further investigation includes plasma protein electrophoresis and urine Bence-Jones protein. Myelodysplasia causes an elevated mean cell volume and should be considered if B12 or folate deficiency are excluded. These rare causes of anaemia are likely to require specialist assessment which may involve bone marrow examination.

## Conclusions

Anaemia is common in older people. Making an accurate diagnosis requires careful interpretation of laboratory data including serum ferritin, vitamin B12 and red cell folate. The most common forms of anaemia in older people are the anaemia of chronic disease and iron deficiency.

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