Investigation and management of anaemia

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Abstract

Anaemia is not a disease but a manifestation of some other process. Once deficiency of iron, vitamin B_{12} and folic acid have been excluded, other causes, such as infection, inflammation, neoplasia, drug or chemical exposure, or an autoimmune disorder, should be sought. The diagnostic approach should be to obtain details of the patient's personal and family history, ethnic origin, and their dietary and drug history, carry out a clinical examination and request simple laboratory tests. The article presents simple guidelines provided for treating the various abnormalities, once a cause has been established. Defining the type of anaemia means that specific therapy, whether this involves replacing a deficiency or treating a defined abnormality, will usually suffice. Failure to obtain the expected response, provided the patient is complying with treatment, requires review for consideration of an alternative cause.

Keywords anaemia; B_{12}; folate; iron

Anaemia (haemoglobin (Hb) concentration below the reference range for age and sex) is the most common blood disorder, affecting approximately 30% of the world population. Prevalence is high in developing countries, because of dietary deficiencies and/or blood loss through parasitic gut infestations. In the UK, 10% of healthy women have some iron depletion; many are asymptomatic when the anaemia is mild (Hb >100 g/litre), but physical and mental performance may be impaired. Symptoms are apparent in anaemia of sudden onset and when other disorders (myocardial insufficiency, respiratory disease) co-exist. Anaemia due to acute blood loss is not discussed here.

Mechanisms of anaemia

Daily loss of red cells through senescence is usually balanced by production and release of equivalent numbers of new red cells. Anaemia occurs when this equilibrium is disturbed. Once anaemia has been confirmed, two questions have to be addressed. First, what is the pathophysiological basis? Is it due to blood loss? If not, is it the result of impaired red cell production or increased red cell destruction, or a combination of the two? Is there a redistribution of blood with splenic pooling ± increased plasma volume (hypersplenism)? Second, what is the cause? This can often be identified by establishing the type of anaemia (by looking at full blood count indices and reviewing a blood film), and looking for clinical features, but further investigations may be necessary (Table 1).

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Clinical manifestations of anaemia

In general, the symptoms of anaemia are non-specific and may not be present at all if the anaemia is chronic; they include tiredness, fatigue, loss of energy, palpitations, exertional dyspnoea, effort angina, and (in the elderly) intermittent claudication.

Signs to note include pallor of skin, nails and mucous membranes (though these are unreliable), tachycardia, wide pulse pressure, flow murmur, oedema, congestive heart failure (in the elderly), and retinal haemorrhages (in severe anaemia).

Diagnosis and investigation

The cause of anaemia is usually clear from the history and initial simple laboratory tests. Full blood count (FBC) and indices, blood film, reticulocyte count, serum bilirubin, chemical tests of iron status, B_{12} and folate concentrations and bone marrow examination are often sufficient to establish a diagnosis.

Most anaemias have a single cause, but secondary and symptomatic anaemias can be multifactorial and may not fit a specific category. It is helpful to consider anaemias in three groups:

- microcytic, hypochromic (mean corpuscular volume (MCV) <78 fl)
- normocytic, normochromic
- macrocytic (MCV >100 fl).

Microcytic, hypochromic anaemia (Figure 1)

The microcytic, hypochromic anaemias have a low MCV/mean corpuscular haemoglobin (MCH) and involve a disturbance in iron metabolism. The differential diagnosis is:

- iron deficiency (lack of iron)
- anaemia of chronic disease (impaired availability of iron)
- thalassaemia syndromes (defective globin chain synthesis)
- sideroblastic anaemia (defective haem synthesis).

Iron-deficiency anaemia (IDA)

The specific clinical features of IDA result from anaemia and its effect on epithelial tissues. The fingernails are thin, lustreless, brittle with longitudinal ridging and a tendency to split, and may be spoon-shaped (koilonychia). The tongue is smooth (atrophic glossitis), and there may be angular stomatitis. The Plummer–Vinson (Paterson–Kelly) syndrome with dysphagia is uncommon. The causes of iron deficiency are outlined in Figure 1.

The red cells are hypochromic and microcytic; with severe anaemia, anisocytosis (size) and poikilocytosis (shape) are more evident and pencil-shaped cells may be seen. Target cells (few) may be present. The reticulocyte count is low, unless the patient is actively bleeding; white cells and platelets are normal, but a thrombocytosis will occur if the patient is bleeding.

The most valuable confirmatory test is the serum ferritin, but this is an acute phase protein and may be elevated in acute inflammation. Iron studies (serum iron, and transferrin binding capacity, transferrin saturation, serum transferrin receptor) can be more informative.

Bone marrow examination is rarely required to diagnose pure iron deficiency but an iron stain (Perls') will show a complete absence of both storage and erythroblast iron.

Causes of iron deficiency

Increased demand (physiological)	Premature infants, adolescence, pregnancy
Inadequate intake	Socio-economic, food faddism. vegetarian diet
Malabsorption	Coeliac disease, previous gastrointestinal surgery
Blood loss	Gastrointestinal, urogenital menorrhagia
Chronic intravascular haemolysis	

Any adult male or post-menopausal female with an iron-deficiency anaemia should be screened for an occult gastrointestinal malignancy.

Table 1

Anaemia of chronic disease

This is common in chronic infection, inflammation, connective tissue diseases, congestive heart failure and neoplasia. Initially, the anaemia is normocytic and normochromic, but may become microcytic and hypochromic. Other factors (e.g. blood loss, mild haemolysis, folic acid deficiency) may contribute.[1] Changes in iron status are shown in Table 2.

Thalassaemia trait

This is suspected when the MCV is lower than normal with a reduced MCH but serum ferritin is normal or increased. Haemoglobin studies, measuring HbA_2 and HbF, and possibly examining for HbH bodies (α-thalassaemia), may be diagnostic. Diagnosis of β-thalassaemia is relatively easy, whereas α-thalassaemia is usually a diagnosis of exclusion. Family studies provide confirmation, but globin chain analysis or molecular technology may be required. Thalassaemia trait rarely causes anaemia requiring attention except in pregnancy, when the anaemia may be exacerbated by co-existing iron deficiency.

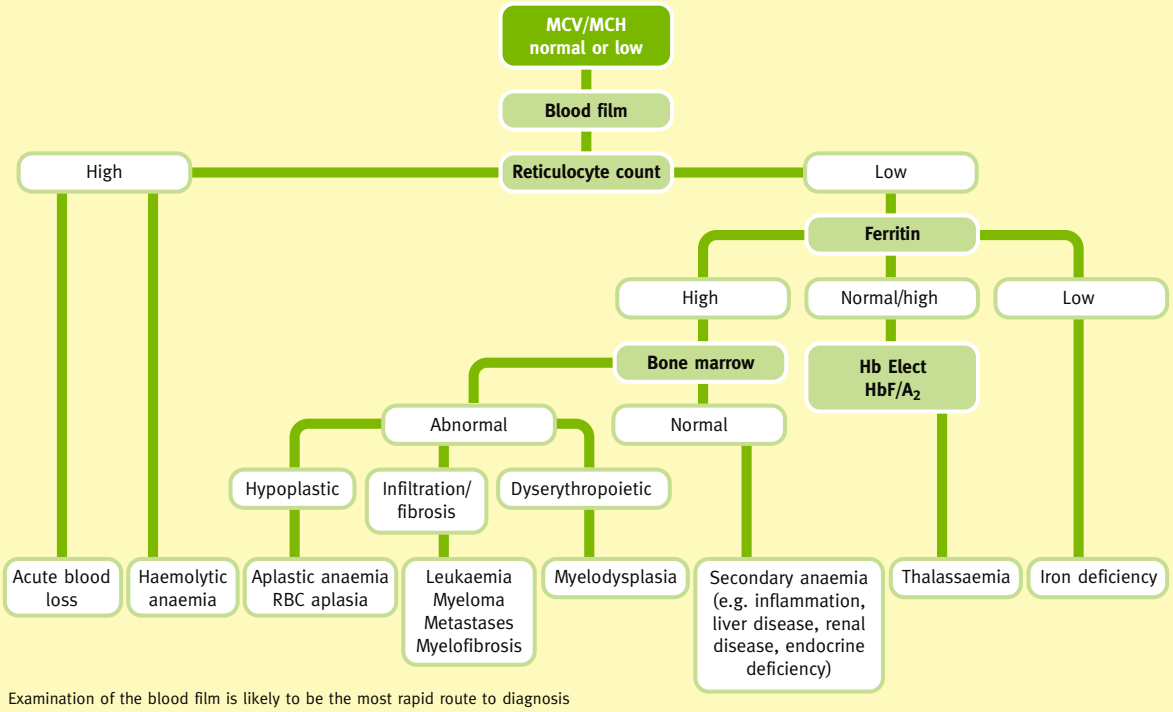
Refractory sideroblastic anaemia:

Many patients have a mild microcytic anaemia and are generally asymptomatic.

Macrocytic anaemia (Figure 2)

Deficiency of B_{12} and folic acid (Table 2) is most likely in vegans and in malnutrition. Pernicious anaemia is the most common cause of clinically significant vitamin B_{12} deficiency in Western populations. An underlying primary haematological disorder may aggravate folic acid deficiency. Consideration of diet, alcohol intake, liver disease, hypothyroidism, gastrointestinal surgery, malabsorption syndrome, drug history (particularly cytotoxic agents), neurological symptoms of B_{12} deficiency and smoking may aid the diagnosis.

Investigation of microcytic, hypochromic and normocytic, normochromic anaemia



Examination of the blood film is likely to be the most rapid route to diagnosis
Hb, haemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; RBC, red blood cell.

Figure 1

Assessment of iron status

Test	Iron-deficiency anaemia	Anaemia of chronic disease	Sideroblastic anaemia	Thalassaemia trait
Hb	Any value	Not usually <90 g/litre	Any value	90–120 g/litre
MCV	↓	N/↓	↑	↓
MCH	↓	N/↓	↑	↓
Serum iron	↓	↓	↑	N/↑
Total serum iron-binding capacity	↑	↓	N	N
% Saturation	↓	↓	↑	N/↑
Transferrin receptor	↑	N[a]	N	N[a]
Ferritin[b]	↓	N/↑	↑	N/↑
Bone marrow Iron stores[c]	Absent	N/↑	↑	N/↑
Sideroblasts	Absent	Absent	'Ring' sideroblasts	Present
Hepcidin[d]	N	↑	N	N
CRP	N	↑	N/A	N/A
ESR	N	↑	N/A	N/A

N/A not applicable. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin.
[a] Increased when iron deficiency complicates anaemia of chronic disease or thalassaemia trait.
[b] May be falsely normal in inflammatory conditions.
[c] The presence of iron excludes iron deficiency.
[d] Not routinely measured.

Table 2

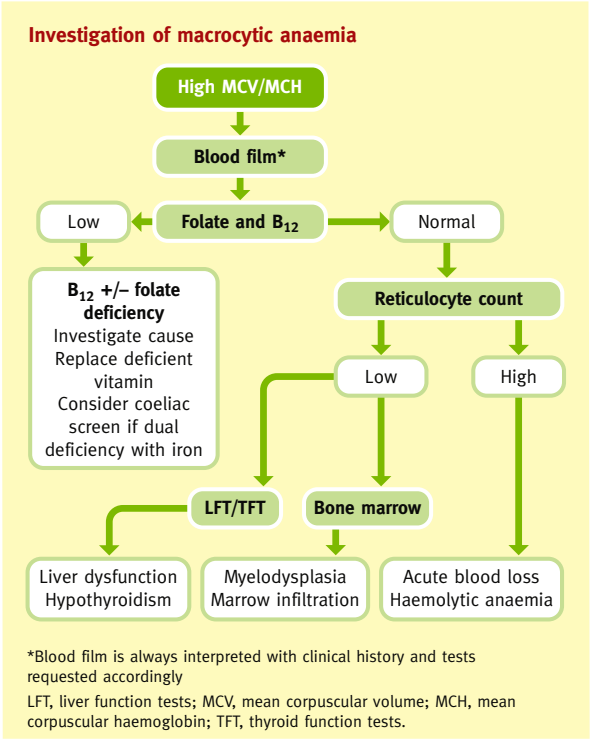


Figure 2

Disorders leading to increased demand, due to physiological changes (e.g. pregnancy) or a pathological cause (e.g. chronic haemolytic anaemias, myelofibrosis) must be excluded. Acute megaloblastic anaemia with marked thrombocytopenia/leucopenia typically presents in patients with marginal folate stores and follows administration of an antifolate drug (e.g. trimethoprim) or, possibly, severe intercurrent infection. A rapid response to folate replacement therapy can be expected.

Diagnosing the cause of persistent mild macrocytosis can be difficult and expensive; in younger individuals, alcohol is most likely, but the doctor should be alert to possible underlying myelodysplasia. Chromosome analysis and a bone marrow trephine biopsy are required for diagnosis.

Vitamin B_{12} deficiency (pernicious anaemia) (Table 3)

There are three classical manifestations of vitamin B_{12} deficiency, which may be present singly or in combination:

- Macrocytic megaloblastic anaemia, with variable leucopenia and thrombocytopenia.
- Glossitis, usually smooth and shiny, but occasionally red, beefy and painful, associated with macrocytosis of all epithelial surfaces and atrophic gastritis (with achlorhydria, loss of intrinsic factor production and features of malabsorption in advanced cases).
- Peripheral neuropathy, which is bilateral (in glove and stocking distribution) and painful, and subacute combined degeneration of the spinal cord due to demyelination of the posterior and lateral tracts. Impaired memory and, rarely, dementia may occur.

Anaemia due to folate deficiency usually manifests with non-specific symptoms of anaemia but needs to be considered in patients with gastrointestinal symptoms.

Causes of vitamin B_{12} deficiency

Inadequate intake
- Vegan diet

Intrinsic factor deficiency
- Pernicious anaemia
- Gastrectomy (total and partial)
- Congenital intrinsic factor deficiency

Small intestinal disease
- Bacterial overgrowth (blind loop syndrome)
- Crohn's disease and resection of terminal ileum
- Selective ileal malabsorption of B_{12} (Imerslund's syndrome)
- Tropical sprue
- Fish tapeworm (*Diphyllobothrium latum*)
- Coeliac disease (folate deficiency more likely)
- Miscellaneous (HIV infection, severe pancreatic disease, drugs — nitrous oxide, colchicine, neomycin)

Causes of folic acid deficiency

Inadequate intake
- Infancy, elderly, poverty, alcoholics, food fads

Malabsorption
- Coeliac disease, dermatitis herpetiformis, tropical sprue

Increased utilization or loss

Physiological: prematurity, pregnancy and lactation

Pathological
- Blood disorders — haemolytic anaemia, myelofibrosis
- Malignancy
- Dialysis
- Severe inflammatory disease (particularly exfoliative skin disorders), Crohn's disease
- Increased urinary loss — acute liver disease, congestive heart failure
- Homocystinuria

Antifolate drugs
- Methotrexate, pyrimethamine, trimethoprim, anticonvulsant drugs

Table 3

Laboratory tests for a macrocytic megaloblastic anaemia must define which deficiency is present and then investigate for the cause. They include the following investigations.

Serum B_{12} and folate assays

Confirm the diagnosis. Red blood cell (RBC) folate reflects body folate status, but some laboratories offer serum folate only. If the assay results are borderline but clinical suspicion is strong, measurement of the metabolites may help; methylmalonic acid is raised in B_{12} deficiency, whereas homocysteine is raised in either B_{12} or folate deficiency.

Blood film

May provide clues to the cause:
- Macrocytosis with a normal red blood cell distribution width (RDW) requires exclusion of alcohol. The blood film shows round macrocytes, often with target cells and/or stomatocytes. A raised serum γ-glutamyltransferase confirms an increased intake of alcohol.
- Oval macrocytes signify a disorder of RBC cell production.
- Hypersegmented neutrophils are strongly suggestive of B_{12}/folate deficiency.

Additional tests to establish the cause of low B_{12} concentration
- Parietal cell and intrinsic factor antibodies: a positive result for intrinsic factor antibodies is diagnostic of pernicious anaemia as this is a more specific assay.
- The Schilling test for B_{12} absorption is no longer available.
- Upper gastrointestinal endoscopy, when upper gastrointestinal symptoms or co-existing iron deficiency are present, chiefly to exclude gastric carcinoma, which occurs in 5% of patients with pernicious anaemia.

Additional tests to establish the cause of folate deficiency

In the absence of an obvious dietary deficiency (common in the elderly), a malabsorption syndrome (e.g. coeliac disease, tropical sprue) should be excluded, particularly in patients with mixed iron and folate deficiency:
- Coeliac screen — estimation of endomysial antibodies (EMA-IgA), and anti-tissue transglutaminase (tTG IgA/IgG) and anti-gliadin (AGA IgA, AGA IgG) antibodies
- If the diagnosis is still in doubt, jejunal biopsy is the gold standard test.

Bone marrow examination

Is rarely necessary in B_{12}/folate deficiency, but should be done if assay values are inconclusive, particularly if the patient is pancytopenic, to exclude aplasia, myelodysplasia or neoplasia. However, it is mandatory in other macrocytic conditions, especially to demonstrate the characteristic dyshaemtopoiesis of a myelodysplastic disorder.

Haemolytic anaemia

A haemolytic process must be suspected in any patient with evidence of RBC damage (e.g. reticulocytosis and raised unconjugated bilirubin). Table 4 highlights the range of investigations that may be needed. Important aspects to note are ethnic origin, family history, medication and exposure to chemicals. Splenomegaly is common. The patient may be jaundiced and have dark urine. Leg ulcers, gallstones and radiological bone changes may be present in chronic severe haemolysis.

The classification of haemolytic anaemia as hereditary or acquired usually parallels the underlying cause, which may be an intrinsic or an extrinsic abnormality, respectively (Tables 5 and 6). Paroxysmal nocturnal haemoglobinuria is an uncommon disorder with an acquired RBC membrane abnormality that causes chronic haemolysis.[2]

Secondary (symptomatic) anaemia

The aim is to exclude a primary haematological disorder. In secondary anaemia, blood (and marrow) changes are a reflection of the disturbance induced by the underlying pathology, which may affect RBCs, white blood cells (WBCs), platelets and the coagulation mechanism.

Laboratory findings reflecting increased RBC destruction

Anaemia

- Spherocytes, sickled cells, fragmented cells ('damaged' RBCs)
- Increased urobilinogen
- Increased unconjugated bilirubin
- Decreased haptoglobin
- Increased serum lactate dehydrogenase
- Haemoglobinaemia[a]
- Haemoglobinuria[a]
- Haemosiderinuria[a]
- Methaemalbuminaemia[a] (Schumm's test)
- Reduced RBC survival

Specific tests are often needed in some haemolytic anaemias, but basic tests may include the following:

- Direct antiglobulin test — for investigating any suspected immunological disorder (particularly warm-type)
- Haemoglobin electrophoresis, HPLC sickle test, HbA_2 and HbF concentrations, H-body preparation, testing for haemoglobin instability, globin chain analysis, DNA studies
- Loss of expression for glycosyl phosphatidylinositol anchor proteins (CD55 and 59) measured by flow cytometry for PNH, Ham's acid haemolysin and sucrose lysis tests are becoming obsolete
- Glucose-6-phosphate dehydrogenase screen/assay, pyruvate kinase assay
- Acidified glycerol lysis test for hereditary spherocytosis, RBC membrane protein analysis, EMA
- Cold agglutinin titre, Donath—Landsteiner test for paroxysmal cold haemoglobinuria

EMA, epithelial membrane antigen; Hb, haemoglobin; HPLC, high-performance liquid chromatography; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cell.
[a] Associated with intravascular haemolysis.

Table 4

Classification of haemolytic anaemia

Intrinsic RBC abnormality (inherited)

Membrane defect

- Hereditary spherocytosis
- Hereditary elliptocytosis

Metabolic defect

- Shunt pathway — glucose-6-phosphate dehydrogenase deficiency
- Embden—Meyerhof pathway — pyruvate kinase deficiency

Haemoglobin defect

- Structural — HbS, HbC, HbE, unstable haemoglobins
- Synthesis — thalassaemia syndromes

Extrinsic RBC abnormality (acquired)

Antibody-mediated

- Blood group incompatibility: blood transfusion reaction, haemolytic disease of the newborn

Autoimmune haemolysis: antibody (warm or cold), drug-induced
Not antibody-mediated

- RBC fragmentation
- Infections
- Chemicals and drug damage
- Paroxysmal nocturnal haemoglobinuria[a]
- March haemoglobinuria[a]

Hb, haemoglobin; RBC, red blood cell.
[a] Typical intravascular haemolysis.

Table 5

Secondary anaemia is usually normocytic and normochromic (Figure 1) with a low reticulocyte count. Examination of the blood film is often more informative than bone marrow examination and gives clues to the nature of the underlying disorder. Biochemical tests for renal, liver or endocrine function may be indicated.

Patients with pancytopenia, RBC, WBC or platelet abnormalities,or leucoerythroblastic changes require bone marrow aspirate and trephine biopsy for the diagnosis of aplastic anaemia, leukaemia, lymphoma, myeloma, metastases, myelofibrosis and myelodysplastic disorders. Cytochemistry, immunohistochemistry, immunophenotyping, chromosome analysis and molecular techniques may also be required. Marrow failure is discussed in *MEDICINE* 2013; **41**(5).

Anaemia in the elderly

Anaemia in the elderly can be difficult to resolve as multiple co-morbid conditions and therapy may complicate the picture.[3, 4] A more painstaking approach is required. Whilst iron deficiency is commonest cause, the anaemia of chronic disease is frequently encountered, with or without renal impairment. Frequently the cause of the anaemia is not readily apparent; red cell indices may not help, and a reticulocyte count should be included. Careful examination of the peripheral blood film is of paramount importance to exclude an underlying haematological malignancy or infiltration.

Management of anaemia

The importance of establishing the cause of anaemia before starting therapy cannot be overemphasized. If there is no response to therapy the diagnosis should be reviewed, compliance questioned, continuing blood loss considered and alternative causes of anaemia sought.

Iron deficiency

Can be frustrating to treat. Non-compliance is common, and such patients are often labelled 'iron-resistant', leading to further expensive, unnecessary investigations. Modern diets (muesli, bran, wholemeal flour) interfere significantly with iron absorption and doctors tend to prescribe too much iron, increasing the likelihood of non-compliance. If the patient is intolerant of ferrous sulphate, ferrous gluconate or parenteral iron may be considered (see *British National Formulary* for dosages). Parenteral iron preparations should be administered only where facilities to deal with anaphylaxis are available.

Vitamin B_{12} deficiency

Hydroxocobalamin, 1 mg intramuscularly (IM) on alternate days for five doses, saturates body stores. The maintenance dose is

Causes of non-immune acquired haemolytic anaemia

Infection	
Bacterial	Meningococcal sepsis Pneumoccoal sepsis Gram-negative organisms Atypical mycobacteria Clostridia
Virus	HIV
Protozoa	Falciparum malaria Babesiosis Bartonella
Chemical/physical	Drugs, such as salazopyrine, dapsone, nitrates (oxidative injury) Industrial/domestic substances Burns Drowning Lead poisoning Liver disease (spur cell anaemia) Copper (Wilson's disease) Snake venom Cardiopulmonary bypass
Fragmentation (mechanical) haemolytic anaemia	
Cardiac haemolysis	Prosthetic heart valves, perivalvular leak
Microangiopathic (MAHA)	Vasculitis, TTP/HUS, DIC, malignant hypertension, disseminated carcinoma, pre-eclampsia/HELLP, ciclosporin, tacrolimus, transplant rejection, catastrophic antiphospholipid syndrome
Giant haemangioma	
March haemoglobinuria	
Acquired membrane disorder	Paroxysmal nocturnal haemoglobinuria (PNH)

DIC, disseminated intravascular coagulation; HELLP, haemolysis with elevated liver function tests and low platelets; HUS, haemolytic-uraemic syndrome; TTP, thrombotic thrombocytopenic purpura.

Table 6

1 mg IM 3-monthly. Following total gastrectomy, prophylactic hydroxocobalamin, 1 mg IM 3-monthly, is required. Further B_{12} measurements are not necessary. Vegans should receive dietary advice; if this is not followed, cyanocobalamin, 50 mg orally daily, is adequate. A trial of hydroxocobalamin in the elderly with a raised MCV and borderline serum B_{12} is worthwhile.

Folic acid deficiency

It is essential to exclude B_{12} deficiency before treating folate deficiency. Folic acid, 5 mg orally daily is sufficient. The duration of treatment depends on the cause; long-term treatment is required in inherited haemolytic anaemia and myelofibrosis.

Treatment of specific disorders

Refractory sideroblastic anaemia

Folic acid, 5 mg orally daily, is recommended to counter the increased but ineffective erythropoiesis. Pyridoxine, 200—400 mg orally daily, can be used but is rarely effective. Erythropoietin may benefit some patients. Determine at what haemoglobin concentration the symptoms of anaemia occur in the individual patient, and institute regular transfusions of packed RBC to maintain it above this level.[5] In transfusion-dependent patients, iron chelation therapy may be required, especially the younger ones; plan to keep serum ferritin below 1000 μg/litre. More aggressive therapy is rarely justified in low-risk MDS[6] (see *MEDICINE* 2013; **41**(5)).

Haemolytic anaemia

Patients with a compensated haemolytic process require no treatment. Folic acid, 5 mg daily, is given lifelong in those with symptomatic haemolytic disorders. Complicating iron deficiency is uncommon.

Symptomatic hereditary spherocytosis and elliptocytosis

Some patients can have severe haemolysis, episodes of red cell aplasia or a large spleen, and may benefit from splenectomy.[7] A normal blood count is usually achieved after this procedure.

Warm autoimmune haemolytic anaemia

Warm autoimmune haemolytic anaemia is almost always direct antiglobulin test positive, and often presents acutely. It should be treated with prednisolone, 1 mg/kg daily for 4 weeks or until the haemoglobin has risen above 120 g/litre, followed by gradual reduction. If complete remission is not achieved and the dose of prednisolone is unacceptably high, splenectomy should be considered, with appropriate anti-infection measures.[8] All patients should take folic acid, 5 mg daily. Acute exacerbations may improve with gammaglobulin, 0.4 g/kg intravenously (IV) daily for 5 days. Other immunosuppressive approaches in highly refractory cases include azathioprine, antilymphocytic globulin, ciclosporin, mycophenolate mofetil, and monoclonal antibody therapy, such as rituximab (anti-CD20)[9] and Campath-1H (anti-CD52).

Immune haemolytic anaemia associated with cold antibodies

Immune haemolytic anaemia associated with cold antibodies is usually episodic on exposure to cold, and keeping warm may suffice to prevent it; if transfusion is necessary, blood should be given through an in-line blood warmer. However, some cold haemagglutinin disorders may benefit from chemotherapy (e.g. chlorambucil) to reduce the antibody titre. In patients with underlying lymphoma, specific treatment of the lymphoma may lead to a remission in the haemolytic process. Plasmapheresis or, possibly, immuno-adsorption techniques may be required in refractory cases to reduce the antibody titre. In acute intravascular haemolysis, protection of the kidneys may be the most important consideration.

Microangiopathic haemolytic anaemia

RBC fragmentation in disseminated intravascular coagulation is seldom significant; treatment of the underlying cause resolves haemolysis. In thrombotic thrombocytopenic purpura (see chapter on thrombocytopenia), continued presence of fragmented RBCs following plasma infusion or plasmapheresis signifies that the process is still active. Fragmentation can be dramatic in

patients with an unstable or leaking prosthetic heart valve. Valve replacement is the definitive treatment, together with folic acid, 5 mg daily, and oral iron (to replace iron lost through the kidneys).

Glucose-6-dehydrogenase deficiency

Acute haemolytic episodes (favism) caused by drugs, diet or infection may require blood replacement. The process is self-limiting. Folic acid, 5 mg daily, is prescribed until haemoglobin returns to normal. The Northern European variety requires regular folic acid.

Haemoglobinopathies and thalassaemia

See chapter on Inherited anaemias.

Paroxysmal nocturnal haemoglobinuria

Paroxysmal nocturnal haemoglobinuria (PNH) is an unusual disorder that presents in a variety of ways (e.g. intravascular haemolysis with haemoglobinuria, abdominal pain caused by thrombosis of mesenteric or hepatic veins, aplasia) and is often intermittent. Management is largely symptomatic; blood transfusions and anticoagulant therapy are often required. Allogeneic stem cell transplantation is curative, but carries the risk of death. The management of PNH has been transformed by the introduction of eculizumab, a complement-blockade antibody active against C5, which offers an immediate effect on intravascular haemolysis and protects patients from thrombosis.[10] Transformation to acute leukaemia occurs in some patients. ◆

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