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section 22 Haematological disorders 5402 Taher AT, et al. (2012). Deferasirox reduces iron overload significantly in nontransfusion-dependent thalassemia: 1-year results from a prospective, randomized, double-blind, placebo-controlled study. *Blood*, 120, 970–7. Tanner MA, et al. (2007). A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. *Circulation*, 115, 1876–84. Vlachodimitropoulou Koumoutsea E, Garbowski M, Porter J (2015). Synergistic intracellular iron chelation combinations: mechanisms and conditions for optimizing iron mobilization. *Br J Haematol*, 170, 874–83. Woywodt A, Kiss A (2002).

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J R Soc Med, 95, 143–6. Zhang DL, et al. (2018). Erythrocytic ferroportin reduces intracellular iron accumulation, hemolysis, and malaria risk. *Science*, 359, 1520–3. 22.6.5 Anaemia of inflammation Sant-Rayn Pasricha and Hal Drakesmith ESSENTIALS The anaemia of inflammation is one of the commonest causes of anaemia, particularly in the elderly and in those with extensive comorbidities. Dysregulation of the hepcidin axis is central to its pathophysiology, with upregulation of hepcidin both limiting iron absorption from the gut and preventing effective mobilization of iron stores for erythropoiesis. However, hepcidin-independent mechanisms of the anaemia of chronic disease exist and must be considered in assessing the underlying aetiology of

otherwise unexplained anaemia. Interactions between the anaemia of chronic disease and other forms of anaemia are common. The management of the anaemia of inflammation rests in large part on the treatment of the underlying disease(s) where possible. In cases where anaemia-specific treatment is required, iron supplementation—particularly intravenous iron—may have a role. There is limited evidence for the use of erythropoiesis-stimulating agents in certain circumstances.

Introduction Anaemia of inflammation (synonymous with anaemia of chronic disease) is the most common cause of anaemia among hospitalized patients and in patients with acute and chronic medical conditions. In patients with complex morbidities, anaemia of inflammation can be superimposed upon or complicated by other causes of anaemia. In particular, there is an important overlap between mechanisms involved with anaemia of inflammation and anaemia observed in patients with renal impairment. Although generally mild in severity, anaemia of inflammation may be symptomatic and delay convalescence in clinical conditions. Anaemia is associated with increased mortality in a range of diseases. Diagnosis of anaemia of inflammation depends on a high degree of clinical suspicion and exclusion of other causes of anaemia, and can usually be suggested by a simple panel of investigations that typically reveal a normocytic normochromic anaemia associated with reduced serum iron and normal transferrin levels, along with evidence of inflammation. In selected cases, more invasive tests such as bone marrow examination may be necessary. Decisions to treat anaemia of inflammation require clinical judgement, as resolution of the underlying condition should result in improvement to the anaemia, and specific interventions directed at ameliorating the anaemia may only be temporarily effective. However, improved understanding of the molecular pathogenesis of this condition has led to the development of directed therapies that could improve treatments in the future.

Aetiology Anaemia is a common complication of a range of autoimmune, infectious, malignant, and other medical and surgical processes which cause systemic inflammation. Any condition resulting in systemic inflammation sufficient to produce elevation of hepcidin expression (see 'Pathogenesis/pathology' for details on the role of hepcidin) can produce anaemia of inflammation. Box 22.6.5.1 presents a list of conditions that are associated with anaemia of inflammation. In many of these conditions, complex systemic illness results in multiple mechanisms contributing to anaemia simultaneously; in particular, renal

Box 22.6.5.1 Medical conditions associated with anaemia of inflammation

- Infection • Bacterial (localized, e.g. osteomyelitis, wound infections); disseminated (e.g. endocarditis, septicaemia) • Parasitic (e.g. malaria) • Fungal, especially if disseminated
- Malignancy • Solid tumours • Haematological diseases (e.g. lymphoma)
- Autoimmune diseases • Active rheumatoid arthritis • Systemic lupus erythematosus • Polymyalgia rheumatica • Inflammatory bowel disease • Vasculitis
- Renal • Chronic kidney disease or acute kidney injury
- Cardiac • Congestive heart failure
- Sterile inflammation and tissue necrosis • Sterile abscess • Wound healing • Trauma • Post surgery (e.g. cardiac surgery) • Head injury

22.6.5 Anaemia of inflammation Impairment may diminish the erythropoietin response, exacerbating the insufficient bone marrow response. Iron deficiency may coexist with anaemia of inflammation, especially in hospitalized patients who have undergone recent blood loss or even repeated blood sampling. Anaemia of inflammation and anaemia of chronic disease are synonymous conditions, while functional iron deficiency is an overlapping concept that refers to a state in which, despite the presence of stainable iron in the bone marrow and a ferritin level above the lower threshold of normal, iron incorporation into the erythroblast is inadequate; this situation is also seen, for example, in patients with chronic renal impairment.

Epidemiology Anaemia is common among patients with comorbid inflammatory conditions, especially among hospitalized

patients and the elderly. It is probably the most common cause of anaemia among hospitalized patients. However, the specific proportion attributable to anaemia of inflammation compared with other causes of anaemia in these patients has not always been carefully quantified. The prevalence and severity of anaemia tend to increase with the severity of the underlying condition and the age of the patient group, and hence estimates of prevalence vary widely. For example, estimates of the prevalence of anaemia in patients with acute or chronic inflammation range from 18 to 95%; in patients with cancer from 30 to 77%; and in patients with autoimmune conditions from 8 to 71%. Anaemia of inflammation is considered the second most common cause of anaemia in the world after iron deficiency anaemia. Thus, overall, inadequate iron supply to the erythroblast either due to absolute iron deficiency or inadequate availability accounts for the vast majority of cases of anaemia worldwide.

Pathogenesis/pathology Anaemia of inflammation is mediated via both direct (hepcidin-independent) and indirect (hepcidin-dependent) effects of inflammation on erythropoiesis (Fig. 22.6.5.1). Hepcidin is the master regulator of systemic iron homeostasis. It is chiefly expressed by the liver and acts to inhibit iron export from cells (especially duodenal enterocytes and splenic red pulp macrophages). Therefore, low hepcidin levels promote increased plasma iron levels and availability of iron for erythropoiesis by facilitating iron export from intestinal cells and macrophages, and thus cytokines cytokines Erythropoiesis inflammation Other tissues flow of iron effects of inflammation iron-loaded Transferrin FPN Macrophage HEPICIDIN FPN

Fig. 22.6.5.1 Pathogenesis of anaemia of inflammation. Normally about 1 to 2 mg of iron is absorbed from the diet every day, and is taken through the circulation bound to the dedicated iron-carrying protein transferrin. Most iron is delivered to the erythron for incorporation into the haem of developing erythrocytes. The lifespan of human red blood cells is about 120 days, after which senescent cells are phagocytosed by macrophages that degrade their contents, digest haem, and recycle liberated iron into plasma. About 25 mg Fe is recycled per day. The transfer of iron from duodenal enterocytes into the circulation and the recycling of iron by macrophages into circulation are both achieved by the unique iron exporter protein ferroportin ('FPN'). Hepcidin inhibits ferroportin, thus controlling iron homeostasis. Inflammation is associated with release of cytokines, some of which (especially IL-6) induce production of hepcidin by the liver. Chronic inflammation leads to persistently high levels of hepcidin that over time decrease the amount of iron available for erythropoiesis. Other inflammatory cytokines impair erythropoietin (EPO) production by the kidney and the bone marrow response to EPO. Together these hepcidin-dependent and hepcidin-independent effects lead to the anaemia of inflammation.

section 22 Haematological disorders 5404 enhanced iron absorption from the diet and recycling of iron liberated from senescent phagocytosed red cells. Conversely, elevated hepcidin levels prevent iron export from enterocytes into serum, impairing dietary iron absorption, and inhibit iron export from macrophages, preventing iron recycling. Notably, most (>95%) iron requirements for erythropoiesis are met by recycled iron from erythroblasts recycled from macrophages, and hence prevention of macrophage iron release rapidly results in iron-restricted erythropoiesis. Hepcidin levels are directly regulated by liver iron and levels of circulating transferrin-bound iron; increased iron elevates hepcidin while iron deficiency suppresses it, achieving homeostatic regulation of iron. Hepcidin is also suppressed by increased erythropoiesis (e.g. stress erythropoiesis, administration of erythropoietin, post-phlebotomy, hypoxia, or in conditions such as thalassaemia). Importantly, hepcidin expression is directly increased by inflammation, mediated especially by interleukin (IL)-6 and also by other cytokines including IL-22 and type I interferon (Fig. 22.6.5.1). Thus, any condition that produces an acute phase response may raise hepcidin levels, resulting in

restriction of iron recycling, with reductions in serum iron and availability of iron for erythropoiesis. Inflammation-induced elevations in hepcidin thus also explain the hypoferraemia (low plasma iron levels) of infection. Anaemia of inflammation may also be mediated via hepcidin-independent mechanisms. The erythropoietin response to anaemia may be blunted in patients with anaemia of inflammation; this may be mediated directly by inflammatory cytokines or by impaired kidney function. Inflammation may also directly impair erythropoiesis, and cytokines such as IL-6, tumour necrosis factor- α , and even hepcidin itself have been shown to directly impair erythropoiesis, independently of local or systemic effects on iron handling. Clinical features Anaemia of inflammation typically presents with a mild to moderate anaemia (haemoglobin concentration >80–90 g/litre) although in some cases it may be more severe, especially if exacerbated by other causes of anaemia. Patients have existing or recently diagnosed additional medical conditions. It presents with the usual symptoms of anaemia (e.g. fatigue, lethargy, and exertional dyspnoea) and pallor. As it complicates existing comorbid medical conditions or hospital admissions, it may present with a deterioration in well-being, functional performance, or clinical recovery in an already complex patient with other reasons for reduced performance status. For example, patients may experience an exacerbation in fatigue, symptoms of heart failure such as exertional dyspnoea, and hospitalized patients may become less able to participate in rehabilitation and physiotherapy. As such, isolation of the clinical effects of the anaemia from the underlying condition is difficult and requires judgement and clinical monitoring. Indeed, even a deterioration in a patient's clinical status associated with worsening anaemia may not be exclusively due to the anaemia itself if the underlying condition has simultaneously deteriorated, making the patient feel more unwell. A trial of attempted specific therapy for the anaemia (as discussed later) may be the only way to distinguish between the effects of anaemia and the effects of the underlying condition, and to develop a rationale for anaemia-specific therapy. Differential diagnosis In patients with complex medical conditions, anaemia of inflammation may coexist with, masquerade as, or be masked by a range of other causes of anaemia. As many of these conditions have specific therapies available, or portend serious deteriorations in the underlying condition that must be recognized, the clinician must consider all relevant causes of anaemia (discussed in the following sections) in each case and exclude these where necessary (Box 22.6.5.2). Iron deficiency anaemia Reduced iron stores may complicate cases where iron stores have become depleted over time, for example, in patients with inflammatory bowel disease with systemic inflammation but chronic gastrointestinal bleeding, or in patients undergoing recurrent blood sampling for laboratory tests or blood losses following medical procedures (e.g. intensive care inpatients). Patients may have a more microcytic blood picture, or have a ferritin level disproportionately low for the degree of inflammation. Renal failure Impaired renal function may accompany systemic inflammation in patients with any systemic illness; alternatively, acute kidney

Box 22.6.5.2 Important causes of anaemia in the unwell patient

Reduced red cell production • Anaemia of inflammation • Iron deficiency • Medications:

— Bone marrow failure • Renal failure:

— Acute kidney injury

— Chronic renal failure • Bone marrow failure:

— Replacement by carcinoma, infection

- Acute leukaemia
- Aplastic anaemia, paroxysmal nocturnal haemoglobinuria
- Myelofibrosis • Aplastic sickle cell crisis Impaired red cell survival • Acute blood loss • Haemolysis:
- Idiopathic
- Associated with medication
- Associated with infection
- Delayed transfusion reaction • Microangiopathic anaemia:
- Haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura
- Drugs • Sickle cell crisis:
- Haemolytic
- Sequestration

22.6.5 Anaemia of inflammation 5405 injury and chronic renal failure may occur due to a range of noninflammatory conditions. Erythropoietin deficiency is a consistent feature of renal impairment, decreasing the differentiation of haematopoietic stem cells towards the erythroid lineage and hence suppressing the synthesis of new erythrocytes. Renal failure may also exacerbate anaemia of inflammation through accumulation of hepcidin due to impaired renal excretion. Furthermore, erythropoietin deficiency and its sequela of reduced erythropoiesis may both independently reduce the production of bone marrow-derived hormones that suppress hepcidin, particularly erythroferrone, resulting in inappropriately elevated hepcidin levels. These processes all result in functional iron deficiency due to impaired mobilization of macrophage-sequestered or liver-stored iron for erythropoiesis. Microangiopathic anaemia Microangiopathic anaemias may develop de novo (e.g. in thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome) and inadequate clinical evaluation and misdiagnosis as anaemia of inflammation will result in an adverse outcome for the patient. Patients with these conditions are systemically unwell, with anaemia and renal impairment. Clinical and biochemical evidence of haemolysis, thrombocytopenia, and identification of red cell fragmentation on the blood film will suggest the correct diagnosis. Microangiopathic anaemia must be considered in every patient with anaemia and thrombocytopenia. Patients with medical (e.g. malignancy, sepsis) or surgical disease (e.g. trauma, leaking mechanical cardiac valves, dysfunctional arteriovenous fistulae) and obstetric complications (e.g. pre-eclampsia) may also develop microangiopathic anaemia, most severely disseminated intravascular coagulation. These conditions are discussed in greater detail in Chapter 22.7.5. Bone marrow failure Bone marrow failure may complicate metastatic malignancy or disseminated infection; patients may have pancytopenia. Drugs Various medications used to treat the underlying conditions associated with anaemia of inflammation may also directly cause anaemia through a range of mechanisms. For example, antibiotics to treat infection can also cause haemolytic anaemia (e.g. β -lactams,

methyldopa) or bone marrow suppression (e.g. isoniazid), while drugs used to treat autoimmune conditions (e.g. methotrexate), and chemotherapy to treat malignancy, may also suppress erythropoiesis. Clinical investigations Investigations to diagnose anaemia of inflammation must be interpreted in the broader clinical context. Anaemia of inflammation can usually be diagnosed with a limited panel of simple tests but may occasionally require additional investigations. Newer investigations may soon assist in the diagnosis. Findings characteristic of anaemia of inflammation are summarized in Box 22.6.5.3. Laboratory investigations The underlying condition responsible for the inflammation should be investigated as appropriate. Tests specific to determining the presence of anaemia of inflammation are described in the following sections.

Haematology A full blood count and blood film examination will reveal a mild to moderate anaemia (typically, haemoglobin concentration exceeding 80 g/litre), which is normochromic and normocytic; in some cases, mild hypochromia or microcytosis may be seen. Evidence of infection and inflammation may also be present: for example, granulocytosis with a left shift (evidence of immature granulocytes such as band forms) and evidence of toxic changes. On selected automated analysers, measurement of the reticulocyte haemoglobin (CHr) or percentage of hypochromic red blood cells (%Hypo) may provide information about recent and medium-term iron supply to the bone marrow respectively. Patients with reduced CHr have impaired incorporation of iron into erythroblasts, indicating functional or absolute iron deficiency. Elevated %Hypo indicates that iron stores, erythropoietic stimulation, and/or inflammation are impairing functional iron availability for erythropoiesis. The erythrocyte sedimentation rate is elevated.

Clinical chemistry Inflammatory markers such as C-reactive protein and α_1 glycoprotein are usually elevated. Iron indices usually demonstrate withholding of iron from the plasma—serum iron and transferrin saturation are low, with a normal transferrin level. Serum ferritin levels are likely to be elevated due to its behaviour as an acute phase protein. The soluble transferrin receptor (sTfR) is likely to be in the normal range. Coexistent iron deficiency can be difficult to identify in individuals with anaemia of inflammation, but should be suspected in patients with coexistent inflammation and ferritin concentrations below 100 to 200 μ g/litre, although clinical judgement is required. Iron deficiency may also be suggested by elevation of the sTfR or the sTfR/log₁₀ (ferritin) ratio. In selected cases (especially those where treatment with erythropoietin is being considered), measurement of serum erythropoietin levels may identify an inadequate response to the degree of anaemia, especially in patients with coexisting renal failure. Measurement of serum hepcidin is now readily available in research settings and may soon be accessible.

Box 22.6.5.3 Results of investigations for anaemia of inflammation

Haematology • Mild anaemia • Blood film: mild normocytic (or mildly microcytic) red cells. Toxic changes in granulocytes • Erythrocyte sedimentation rate: elevated

Biochemistry • Inflammatory markers (e.g. C-reactive protein): elevated • Iron indices:

— Ferritin: elevated

— Serum iron: reduced

— Transferrin saturation: reduced

— Soluble transferrin receptor: normal • Erythropoietin: elevated or normal (suggesting inadequate response to anaemia) • Hepcidin: elevated

section 22 Haematological disorders 5406 in the clinic; patients with anaemia of inflammation have elevated serum hepcidin concentrations. Bone marrow aspiration In selected complex cases,

especially where multiple causes of anaemia may be present, examination of the bone marrow should be considered. In particular, using Perls' stain enables definitive detection of iron deficiency, while assessment of erythropoiesis enables identification of erythroid hypoplasia and bone marrow failure. Treatment Control of the underlying disease remains the most important strategy for treatment of anaemia of inflammation. Resolution of inflammation and recovery of red cell production can result in a transient, erythropoiesis-mediated suppression of hepcidin, facilitating iron recycling and supporting recovery of anaemia. The decision to implement specific treatment directed at anaemia of inflammation requires clinical judgement. In the majority of cases where the anaemia is mild and unlikely to be independently affecting the patient's clinical condition or well-being, specific therapy for the anaemia itself is unnecessary. It is therefore imperative to consider whether the anaemia is likely to be significantly affecting the performance and quality of life of the patient, exacerbating other underlying medical conditions (e.g. producing angina in patients with underlying cardiovascular disease), or impairing recovery and capacity to participate in rehabilitation. This may be difficult to ascertain in complex clinical situations. National and international clinical guidelines exist for management of anaemia associated with chronic renal failure, cancer-related anaemia, and to advise on transfusion practice; however, evidence-based guidelines for treatment of anaemia of inflammation per se are lacking. Although anaemia is correlated with impaired survival in many conditions (cancer, acute cardiovascular events and chronic heart failure, and renal failure), correction of anaemia has not been shown to reverse mortality risk, and thus the primary rationale for alleviation of anaemia is improvement of morbidity. The therapeutic goal is to achieve the minimum haemoglobin concentration at which the symptoms of anaemia are ameliorated. A trial of anaemia-specific therapy to assess the value of increased haemoglobin on patient health in difficult cases may be warranted. Treatment is more likely to be warranted in older patients, patients with cardiovascular or respiratory disease, or patients with an acute deterioration in their haemoglobin concentration. Transfusion Blood transfusions are generally safe and are widely used when correction of anaemia is relatively urgent. Patient blood management guidelines recommend that the decision to transfuse should not be solely based on a patient's haemoglobin concentration, but should also take account of the clinical condition. These guidelines suggest that transfusions are appropriate in patients with haemoglobin concentrations less than 70 g/litre, although well-compensated patients can be treated conservatively; in patients with haemoglobin concentrations of 70 to 100 g/litre, the decision should be based on clinical features, especially the need to urgently resolve signs and symptoms of anaemia. There is no evidence transfusion improves mortality in patients in this group. Guidelines do not identify evidence supporting a need for a different approach among the elderly or in patients with respiratory or cerebrovascular disease. Patients with haemoglobin concentrations exceeding 100 g/litre do not generally require and in some cases (e.g. cases of acute coronary syndrome) may be harmed by transfusion. Iron therapy Patients with anaemia of inflammation have functional iron deficiency (i.e. iron stores are sufficient but iron cannot be mobilized to reach developing red blood cells). However, they may also have concomitant absolute iron deficiency (e.g. due to prolonged impairment of intestinal iron absorption), or iron losses due to acute (including surgery and upper gastrointestinal stress ulceration) or chronic bleeding (including frequent blood sampling). Oral iron supplementation is infrequently recommended for iron therapy in anaemia of inflammation. Elevated hepcidin levels impair the efficiency of iron absorption. Gastrointestinal side effects (especially in patients with intestinal diseases) can also limit acceptability and adherence. However, oral iron is cheap and can be useful in selected cases with motivated patients. Increased understanding of the pathophysiology of anaemia of inflammation, coupled with the recent arrival in the pharmacy of a new generation of

intravenous iron formulations, has led to renewed interest in the use of parenteral iron. New products largely overcome the limitations of previous parenteral high molecular weight iron dextran formulations (especially risk of anaphylaxis), and enable high doses of iron to be administered in single treatments. For example, ferric carboxymaltose can be administered in high doses (up to 1000 mg) over 15 min, and carries a very low risk of allergic reaction, and as such, premedication with antihistamines or steroids is unnecessary. Intravenous iron is widely used in chronic renal failure to overcome functional iron deficiency to facilitate erythropoiesis; it is also used in patients with inflammatory bowel disease in whom iron losses may be high due to gastrointestinal bleeding, and avoidance of the oral route is preferred due to concerns about exacerbation of intestinal pathology. Intravenous iron has been shown to improve symptoms in patients with congestive cardiac failure. Systematic reviews indicate that hospital patients receiving intravenous iron have an increased haemoglobin concentration and reduced requirement for transfusion compared with those receiving either no iron or oral iron. Key concerns about the safety of intravenous iron include, in patients receiving formulations comprising iron in a carbohydrate shell (e.g. iron sucrose, polymaltose, and carboxymaltose), hypophosphataemia; this is mediated by elevations in intact fibroblast growth factor-23 causing renal phosphate wasting, which has been associated with osteomalacia in cases of recurrent use. Monitoring of serum phosphate, parathyroid hormone, and vitamin D levels in patients receiving frequent dosing may therefore be advisable. Several studies and one systematic review have indicated an increased risk of infection in patients receiving parenteral iron. Although data are conflicting, intravenous iron should probably not be administered to patients with confirmed or suspected sepsis until the infection has been addressed. Erythropoiesis-stimulating agents As well as controlling anaemia through direct stimulation of erythropoiesis, erythropoiesis-stimulating agents (ESAs) may indirectly benefit red cell production by improving access to iron, through suppression of hepcidin levels. Amelioration of elevated hepcidin in

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