

REVIEW ARTICLE

MEDICAL PROGRESS

Anemia of Chronic Disease

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ANEMIA OF CHRONIC DISEASE, THE ANEMIA THAT IS THE SECOND MOST prevalent after anemia caused by iron deficiency, occurs in patients with acute or chronic immune activation.¹⁻⁴ The condition has thus been termed “anemia of inflammation.”¹⁻⁴ The most frequent conditions associated with anemia of chronic disease are listed in Table 1.⁵⁻²²

PATHOPHYSIOLOGICAL FEATURES

Anemia of chronic disease is immune driven; cytokines and cells of the reticuloendothelial system induce changes in iron homeostasis, the proliferation of erythroid progenitor cells, the production of erythropoietin, and the life span of red cells, all of which contribute to the pathogenesis of anemia (Fig. 1). Erythropoiesis can be affected by disease underlying anemia of chronic disease through the infiltration of tumor cells into bone marrow or of microorganisms, as seen in human immunodeficiency virus (HIV) infection, hepatitis C, and malaria.^{23,24} Moreover, tumor cells can produce proinflammatory cytokines and free radicals that damage erythroid progenitor cells.^{3,4,8} Bleeding episodes, vitamin deficiencies (e.g., of cobalamin and folic acid), hypersplenism, autoimmune hemolysis, renal dysfunction, and radio- and chemotherapeutic interventions themselves can also aggravate anemia.^{25,26}

Anemia with chronic kidney disease shares some of the characteristics of anemia of chronic disease, although the decrease in the production of erythropoietin, mediated by renal insufficiency and the antiproliferative effects of accumulating uremic toxins, contribute importantly.²⁷ In addition, in patients with end-stage renal disease, chronic immune activation can arise from contact activation of immune cells by dialysis membranes, from frequent episodes of infection, or from both factors, and such patients present with changes in the homeostasis of body iron that is typical of anemia of chronic disease.²⁷

DYSREGULATION OF IRON HOMEOSTASIS

A hallmark of anemia of chronic disease is the development of disturbances of iron homeostasis, with increased uptake and retention of iron within cells of the reticuloendothelial system. This leads to a diversion of iron from the circulation into storage sites of the reticuloendothelial system, subsequent limitation of the availability of iron for erythroid progenitor cells, and iron-restricted erythropoiesis.

In mice that are injected with the proinflammatory cytokines interleukin-1 and tumor necrosis factor α (TNF- α), both hypoferrremia and anemia develop²⁸; this combination of conditions has been linked to cytokine-inducible synthesis of ferritin, the major protein associated with iron storage, by macrophages and hepatocytes.²⁹ In chronic inflammation, the acquisition of iron by macrophages most prominently takes place through erythrophagocytosis³⁰ and the transmembrane import of ferrous iron by the protein divalent metal transporter 1 (DMT1).³¹

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Table 1. Underlying Causes of Anemia of Chronic Disease.

Associated Diseases	Estimated Prevalence*
	percent
Infections (acute and chronic)	18–95 ⁸⁻¹⁰
Viral infections, including human immunodeficiency virus infection	
Bacterial	
Parasitic	
Fungal	
Cancer†	30–77 ^{9,12-14}
Hematologic	
Solid tumor	
Autoimmune	8–71 ^{5,9,15,16}
Rheumatoid arthritis	
Systemic lupus erythematosus and connective-tissue diseases	
Vasculitis	
Sarcoidosis	
Inflammatory bowel disease	
Chronic rejection after solid-organ transplantation	8–70 ¹⁷⁻¹⁹
Chronic kidney disease and inflammation	23–50 ²⁰⁻²²

* Values shown are ranges. Epidemiologic data are not available for all conditions associated with the anemia of chronic disease. The prevalence and severity of anemia are correlated with the stage of the underlying condition^{5,6} and appear to increase with advanced age.⁷

† The prevalence of anemia in patients with cancer is affected by therapeutic procedures and age. A high prevalence was reported in one study in which 77 percent of elderly men and 68 percent of elderly women with cancer were anemic.¹¹ In another study, anemia was observed in 41 percent of patients with solid tumors before radiotherapy and in 54 percent thereafter.¹²

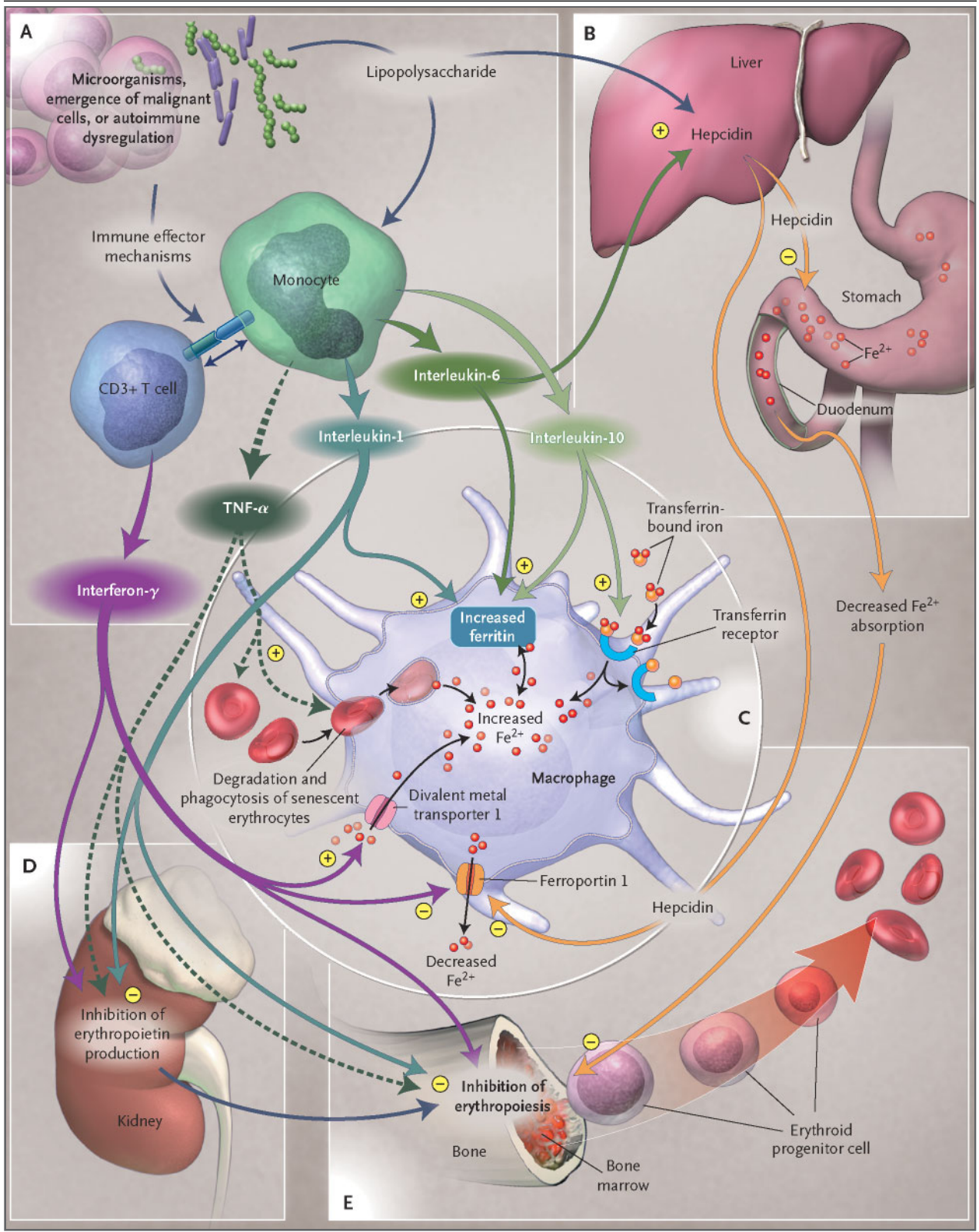
Figure 1 (facing page). Pathophysiological Mechanisms Underlying Anemia of Chronic Disease.

In Panel A, the invasion of microorganisms, the emergence of malignant cells, or autoimmune dysregulation leads to activation of T cells (CD3+) and monocytes. These cells induce immune effector mechanisms, thereby producing cytokines such as interferon- γ (from T cells) and tumor necrosis factor α (TNF- α), interleukin-1, interleukin-6, and interleukin-10 (from monocytes or macrophages). In Panel B, interleukin-6 and lipopolysaccharide stimulate the hepatic expression of the acute-phase protein hepcidin, which inhibits duodenal absorption of iron. In Panel C, interferon- γ , lipopolysaccharide, or both increase the expression of divalent metal transporter 1 on macrophages and stimulate the uptake of ferrous iron (Fe²⁺). The antiinflammatory cytokine interleukin-10 up-regulates transferrin receptor expression and increases transferrin-receptor-mediated uptake of transferrin-bound iron into monocytes. In addition, activated macrophages phagocytose and degrade senescent erythrocytes for the recycling of iron, a process that is further induced by TNF- α through damaging of erythrocyte membranes and stimulation of phagocytosis. Interferon- γ and lipopolysaccharide down-regulate the expression of the macrophage iron transporter ferroportin 1, thus inhibiting iron export from macrophages, a process that is also affected by hepcidin. At the same time, TNF- α , interleukin-1, interleukin-6, and interleukin-10 induce ferritin expression and stimulate the storage and retention of iron within macrophages. In summary, these mechanisms lead to a decreased iron concentration in the circulation and thus to a limited availability of iron for erythroid cells. In Panel D, TNF- α and interferon- γ inhibit the production of erythropoietin in the kidney. In Panel E, TNF- α , interferon- γ , and interleukin-1 directly inhibit the differentiation and proliferation of erythroid progenitor cells. In addition, the limited availability of iron and the decreased biologic activity of erythropoietin lead to inhibition of erythropoiesis and the development of anemia. Plus signs represent stimulation, and minus signs inhibition.

Interferon- γ , lipopolysaccharide, and TNF- α up-regulate the expression of DMT1, with an increased uptake of iron into activated macrophages.³² These proinflammatory stimuli also induce the retention of iron in macrophages by down-regulating the expression of ferroportin, thus blocking the release of iron from these cells.³² Ferroportin is a transmembrane exporter of iron, a process that is believed to be responsible for the transfer of absorbed ferrous iron from duodenal enterocytes to the circulation.³³ Moreover, antiinflammatory cytokines such as interleukin-10 can induce anemia through the stimulation of transferrin-mediated acquisition of iron by

macrophages and by translational stimulation of ferritin expression³⁴ (Fig. 1).

The identification of hepcidin, an iron-regulated acute-phase protein that is composed of 25 amino acids, helped to shed light on the relationship of the immune response to iron homeostasis and anemia of chronic disease. Hepcidin expression is induced by lipopolysaccharide and interleukin-6 and is inhibited by TNF- α .³⁵ Transgenic or constitutive overexpression of hepcidin results in severe iron-deficiency anemia in mice.³⁶ Inflammation in mice that are hepcidin-deficient did not lead to hypoferrremia, a finding that suggests that hepcidin may be central-



ly involved in the diversion of iron traffic through decreased duodenal absorption of iron and the blocking of iron release from macrophages that occurs in anemia of chronic disease (Fig. 1).^{35,37} The induction of hypoferrremia by interleukin-6 and hepcidin occurs within a few hours and is not observed in interleukin-6–knockout mice that are treated with turpentine as a model of inflammation, a finding that suggests that hepcidin may be central to anemia of chronic disease.³⁸ A recently identified gene, hemojuvelin, may act in concert with hepcidin in inducing these changes.³⁹ Accordingly, the disturbance of iron homeostasis with subsequent limitation of the availability of iron for erythroid progenitor cells appears to impair the proliferation of these cells by negatively affecting heme biosynthesis (Table 2).

IMPAIRED PROLIFERATION OF ERYTHROID PROGENITOR CELLS

In patients with anemia of chronic disease, the proliferation and differentiation of erythroid precursors — erythroid burst-forming units and erythroid colony-forming units — are impaired⁴ and are linked to the inhibitory effects of interferon- α , - β , and - γ , TNF- α , and interleukin-1, which influence the growth of erythroid burst-forming units and erythroid colony-forming units.⁴ Interferon- γ appears to be the most potent inhibitor,⁴⁰ as reflected by its inverse correlation with hemoglobin concentrations and reticulocyte counts.⁶ The underlying mechanisms may involve cytokine-mediated induction of apoptosis, which appears, in part, related to the formation of ceramide, the down-regulation of the expression of erythropoietin receptors on progenitor cells, impaired formation and activity of erythropoietin, and a reduced expression of other prohematopoietic factors, such as stem-cell factor.^{4,40,41} Moreover, cytokines exert direct toxic effects on progenitor cells by inducing the formation of labile free radicals such as nitric oxide or superoxide anion by neighboring macrophage-like cells (Table 2).⁴²

BLUNTED ERYTHROPOIETIN RESPONSE

Erythropoietin regulates erythroid-cell proliferation centrally. Erythropoietin expression is inversely related to tissue oxygenation and hemoglobin levels, and there is a semilogarithmic relation between the erythropoietin response (log) and the degree of anemia (linear). Erythropoietin responses in anemia of

chronic disease are inadequate for the degree of anemia in most, but not all, conditions.^{43,44} The cytokines interleukin-1 and TNF- α directly inhibit erythropoietin expression *in vitro*⁴⁵ — a finding that is probably due, at least in part, to cytokine-mediated formation of reactive oxygen species, which in turn affects the binding affinities of erythropoietin-inducing transcription factors and also damages erythropoietin-producing cells. Although convincing data from human studies are lacking, the injection of lipopolysaccharide into mice results in reduced expression of erythropoietin mRNA in kidneys and decreased levels of circulating erythropoietin.⁴⁵

The responsiveness of erythroid progenitor cells to erythropoietin appears to be inversely related to the severity of the underlying chronic disease and the amount of circulating cytokines, since in the presence of high concentrations of interferon- γ or TNF- α , much higher amounts of erythropoietin are required to restore the formation of erythroid colony-forming units.⁴⁶ After binding to its receptor, erythropoietin stimulates members of the signal transduction pathways and subsequently activates mitogen and tyrosine kinase phosphorylation, processes affected by the inflammatory cytokines and the negative-feedback regulation they induce.^{45,47}

The response to erythropoietin is further reduced by the inhibitory effects of proinflammatory cytokines toward the proliferation of erythroid progenitor cells, the parallel down-regulation of erythropoietin receptors, and the limited availability of iron to contribute to cell proliferation and hemoglobin synthesis. Finally, increased erythrophagocytosis during inflammation leads to a decreased erythrocyte half-life, along with anticipated damage to erythrocytes that is mediated by cytokines and free radicals (Table 2).^{48,49}

LABORATORY EVALUATION

IRON STATUS

Anemia of chronic disease is a normochromic, normocytic anemia that is characteristically mild (hemoglobin level, 9.5 g per deciliter) to moderate (hemoglobin level, 8 g per deciliter). Patients with the condition have a low reticulocyte count, which indicates underproduction of red cells. A definitive diagnosis may be hampered by coexisting blood loss, the effects of medications, or inborn errors of hemoglobin synthesis such as thalassemia. The

Table 2. Pathophysiological Factors in Anemia of Chronic Disease.*

Feature	Key Factors	Mechanisms	Cellular Pathway	Systemic Effects
Pathologic iron homeostasis	TNF- α or interleukin-1	Induces ferritin transcription Leads to a decreased erythrocyte half-life, mediated by TNF- α	Increased iron storage within the RES Unknown (may be through damage of red cells by radicals)	Hypoferremia, hyperferritinemia Erythrophagocytosis
	Interleukin-6	Induces ferritin transcription or translation Stimulates formation of hepcidin	Increased iron storage within the RES Iron absorption and export from macrophages decreased by hepcidin	Hypoferremia, hyperferritinemia Hypoferremia
	Interferon- γ or lipopolysaccharide	Stimulates DMT1 synthesis; down-regulates ferroportin 1 expression	Increased iron uptake and inhibition of iron recirculation (e.g., derived from erythrophagocytosis) in macrophages	Hypoferremia
	Interleukin-10	Induces transferrin-receptor expression; stimulates ferritin translation	Increased uptake and storage of transferrin-bound iron in macrophages	Hypoferremia, hyperferritinemia
	Erythrophagocytosis	Reduces erythrocyte half-life through increased uptake of erythrocytes damaged by TNF- α	Recirculated iron restricted within macrophages	Hypoferremia, anemia
Impaired erythropoiesis	Interferon- γ , interleukin-1, or TNF- α	Inhibits proliferation and differentiation of CFU-E and BFU-E	Induction of apoptosis; down-regulation of erythropoietin-receptor expression; reduced formation of stem-cell factor	Anemia with normal or decreased reticulocyte counts
		Causes hypoferremia through diversion of iron to the RES	Iron-restricted erythropoiesis	Anemia with increased levels of tin protoporphyrin
		Induces formation of nitric oxide	Erythroid aminolevulinate synthase inhibited	Anemia with increased levels of levulinic acid
	Alpha ₁ -antitrypsin	Limits iron uptake by erythroid cells	Reduced proliferation of BFU-E or CFU-E	Anemia
	Tumor cells or microbes	Infiltrate bone marrow	Displacement of progenitor cells	Anemia, pancytopenia, or both
		Produce soluble mediators Consume vitamins	Local inflammation and formation of cytokines and radicals Inhibition of progenitor-cell proliferation	Anemia, pancytopenia, or both Systemic deficiency of folate or cobalamin
	Hypoferremia	Caused by cytokine-mediated diversion of iron into the RES and reduced iron absorption	Impaired heme biosynthesis, erythropoietin responsiveness; reduced proliferation of CFU-E	Anemia
Blunted erythropoietin response	Erythropoietin deficiency	Inhibits erythropoietin production by interleukin-1 and TNF- α	Reduction of erythropoietin transcription; radical-mediated damage of erythropoietin-producing cells	Decreased levels of circulating erythropoietin
	Hypoferremia	Reduces erythropoietin responsiveness of progenitor cells owing to iron restriction	Blunted heme biosynthesis and progenitor-cell proliferation	Anemia, hypoferremia
	Interferon- γ , interleukin-1, and TNF- α	Impair responsiveness of progenitor cells to erythropoietin	Reduced erythropoietin-receptor expression on CFU-E; damage of erythroid progenitors mediated by cytokines or radicals; possible interference with erythropoietin signal transduction	Anemia

* TNF- α denotes tumor necrosis factor α , RES reticuloendothelial system, DMT1 divalent metal transporter 1, CFU-E erythroid colony-forming units, and BFU-E erythroid burst-forming units.

evaluation of anemia of chronic disease must also include a determination of the status of whole-body iron in order to rule out iron-deficiency anemia,^{2-4,49} usually hypochromic and microcytic. The difference between anemia of chronic disease and iron-defi-

ciency anemia thus relates to the latter as an absolute iron deficiency, whereas the pathophysiology of anemia of chronic disease is multifactorial, as described in Table 2.

In both anemia of chronic disease and iron-

deficiency anemia, the serum concentration of iron and transferrin saturation are reduced, reflecting absolute iron deficiency in iron-deficiency anemia and hypoferrinemia due to acquisition of iron by the reticuloendothelial system in anemia of chronic disease.²⁻⁴ In the case of anemia of chronic disease, the decrease in transferrin saturation is primarily a reflection of decreased levels of serum iron. In iron-deficiency anemia, transferrin saturation may be even lower because serum concentrations of the iron transporter transferrin are increased, whereas transferrin levels remain normal or are decreased in anemia of chronic disease.

The search for an underlying cause of iron deficiency should include a history taking to rule out a dietary cause.⁴² Frequently, iron deficiency indicates pathological blood loss such as an increased loss of menstrual blood in women or chronic gastrointestinal bleeding in the setting of ulcerative gastrointestinal disease, inflammatory bowel disease, angiodysplasia, colon adenomas, gastrointestinal cancer, or parasitic infections.

Ferritin is used as a marker of iron storage, and a level of 15 ng per milliliter is generally taken as indicating absent iron stores.⁵⁰ However, a ferritin level of 30 ng per milliliter provides better positive predictive values for iron-deficiency anemia (92 to 98 percent) when studied in several populations.⁵¹ For patients with anemia of chronic disease, however, ferritin levels are normal or increased (Table 3), reflecting increased storage and retention of iron

within the reticuloendothelial system, along with increased ferritin levels due to immune activation.²⁹

The soluble transferrin receptor is a truncated fragment of the membrane receptor that is increased in iron deficiency, when the availability of iron for erythropoiesis is low.⁵² In contrast, levels of soluble transferrin receptors in anemia of chronic disease are not significantly different from normal, because transferrin-receptor expression is negatively affected by inflammatory cytokines.⁵³ A determination of the levels of soluble transferrin receptors by means of commercially available assays can be helpful for differentiation between patients with anemia of chronic disease alone (with either normal or high ferritin levels and low levels of soluble transferrin receptors) and patients with anemia of chronic disease with accompanying iron deficiency (with low ferritin levels and high levels of soluble transferrin receptors).^{52,54}

As compared with patients who have anemia of chronic disease alone, patients with anemia of chronic disease and concomitant iron-deficiency anemia more frequently have microcytes, and their anemia tends to be more severe. The ratio of the concentration of soluble transferrin receptors to the log of the ferritin level may also be helpful.⁵² A ratio of less than 1 suggests anemia of chronic disease, whereas a ratio of more than 2 suggests absolute iron deficiency coexisting with anemia of chronic disease (Table 3). The determination of the percentage of hypochromic red cells or reticulocyte hemoglobin content can also be useful in detecting accompanying iron-restricted erythropoiesis in patients with anemia of chronic disease.⁵⁴

Table 3. Serum Levels That Differentiate Anemia of Chronic Disease from Iron-Deficiency Anemia.*

Variable	Anemia of Chronic Disease	Iron-Deficiency Anemia	Both Conditions†
Iron	Reduced	Reduced	Reduced
Transferrin	Reduced to normal	Increased	Reduced
Transferrin saturation	Reduced	Reduced	Reduced
Ferritin	Normal to increased	Reduced	Reduced to normal
Soluble transferrin receptor	Normal	Increased	Normal to increased
Ratio of soluble transferrin receptor to log ferritin	Low (<1)	High (>2)	High (>2)
Cytokine levels	Increased	Normal	Increased

* Relative changes are given in relation to the respective normal values.

† Patients with both conditions include those with anemia of chronic disease and true iron deficiency.

ERYTHROPOIETIN

Measurement of erythropoietin levels is useful only for anemic patients with hemoglobin levels of less than 10 g per deciliter, since erythropoietin levels at higher hemoglobin concentrations remain well in the normal range.⁴³ Furthermore, any interpretation of an erythropoietin level in anemia of chronic disease with a hemoglobin level less than 10 g per deciliter must take into account the degree of anemia.^{55,56} Erythropoietin levels have been analyzed for their predictive value with respect to the response to treatment of anemia of chronic disease with erythropoietic agents.^{13,57} After treatment with recombinant human erythropoietin (epoetin) for two weeks, either a serum erythropoietin level of more than 100 U per liter or a ferritin level of more than 400 ng per milliliter predicts a lack of response in 88

percent of patients with cancer who are not receiving concomitant chemotherapy.¹³ Such predictors have not been validated in patients with cancer who are undergoing chemotherapy.⁵⁷ Rather, changes in hemoglobin levels or reticulocyte counts over time indicate a response to treatment with epoetin.⁵⁷

TREATMENT

RATIONALE FOR TREATMENT

The rationale for the treatment of anemia of chronic disease is based on two principles. First, anemia can be generally deleterious in itself, requiring a compensatory increase in cardiac output in order to maintain systemic oxygen delivery; second, anemia is associated with a poorer prognosis in a variety of conditions. Thus, moderate anemia warrants correction, especially in patients older than 65 years of age, those with additional risk factors (such as coronary artery disease, pulmonary disease, or chronic kidney disease), or a combination of these factors.^{7,58} In patients with renal failure who are receiving dialysis and in patients with cancer who are undergoing chemotherapy, correction of anemia up to hemoglobin levels of 12 g per deciliter is associated with an improvement in the quality of life.^{59,60}

Anemia has been associated with a relatively poor prognosis among patients with various conditions, including cancer, chronic kidney disease, and congestive heart failure.⁹ This relationship has been explored most fully in patients undergoing long-term hemodialysis. In a retrospective review of nearly 100,000 patients undergoing hemodialysis, levels of hemoglobin of 8 g per deciliter or less were associated with a doubling of the odds of death, as compared with hemoglobin levels of 10 to 11 g per deciliter.⁶¹ Moreover, the odds ratios for death among patients who entered the study with hematocrit levels that were under 30 percent but that increased to 30 percent or more did not differ from those of patients who began and finished the study with hematocrit levels of 30 percent or more. Subsequent analyses have determined that hematocrit levels that were maintained between 33 and 36 percent were associated with the lowest risk of death among patients undergoing dialysis.^{20,21} This evidence contributed to the development of guidelines for the management of anemia in patients with cancer or chronic kidney disease, guidelines that recommend a target hemoglobin level of 11 to 12 g per deciliter.^{14,62,63}

However, a normal target hematocrit may not

be optimal. A prospective, multicenter trial involving patients who are undergoing dialysis — a study of an intervention that is designed to achieve normal hematocrit levels (above 42 percent), as compared with lower levels (above 30 percent), with the use of a combination of erythropoietin therapy and intravenous iron dextran — was halted because of increased mortality in the high-hematocrit cohort.⁶⁴ The patients who had high hematocrit levels in that study received higher doses of erythropoietin and intravenous iron than did patients who had low hematocrit levels. The link between iron stores and morbidity or mortality rates is controversial, since it involves issues that are related to infections in patients undergoing dialysis⁶⁵ and detrimental coronary outcomes in men.⁶⁶ An editorial⁶⁷ concluded that intravenous iron should be administered, if necessary, to improve the response to therapy with epoetin in order to reach a target hematocrit of 33 to 36 percent in patients with chronic kidney disease.⁶² Careful studies of the potentially harmful effects of iron supplementation in patients with various forms of anemia of chronic disease are still needed.

Despite management guidelines, anemia of chronic disease remains underrecognized and undertreated. In a study of 200,000 patients enrolled in a health maintenance organization between 1994 and 1997, 23 percent of patients with chronic kidney disease had hematocrit levels under 30 percent, and only 30 percent of those with hematocrit levels below the target were receiving treatment for anemia.⁹ It is important to note that anemia of chronic disease, if marked, can be a reflection of a more progressive underlying disease.^{3,4,6,49} Thus, the notion that correction of anemia alone may improve the prognosis of other underlying chronic diseases such as cancer or inflammatory disease remains unproven.

TREATMENT OPTIONS

When possible, treatment of the underlying disease is the therapeutic approach of choice for anemia of chronic disease.³⁻⁵ Improvement in hemoglobin levels has been demonstrated, for example, in patients with rheumatoid disease⁶⁸ who were receiving therapy with anti-TNF antibodies. In cases in which treating the underlying disease is not feasible, alternative strategies are necessary (Table 4).

Transfusion

Blood transfusions are widely used as a rapid and effective therapeutic intervention. Transfusions are

Table 4. Therapeutic Options for the Treatment of Patients with Anemia of Chronic Disease.

Treatment	Anemia of Chronic Disease	Anemia of Chronic Disease with True Iron Deficiency
Treatment of underlying disease	Yes	Yes
Transfusions*	Yes	Yes
Iron supplementation	No	Yes†
Erythropoietic agents	Yes‡	Yes, in patients who do not have a response to iron therapy

* This treatment is for the short-term correction of severe or life-threatening anemia. Potentially adverse immunomodulatory effects of blood transfusions are controversial.

† Although iron therapy is indicated for the correction of anemia of chronic disease in association with absolute iron deficiency, no data from prospective studies are available on the effects of iron therapy on the course of underlying chronic disease.

‡ Overcorrection of anemia (hemoglobin >12 g per deciliter) may be potentially harmful to patients; the clinical significance of erythropoietin-receptor expression on certain tumor cells needs to be investigated.

particularly helpful in the context of either severe anemia (in which the hemoglobin is less than 8.0 g per deciliter) or life-threatening anemia (in which the hemoglobin is less than 6.5 g per deciliter), particularly when the condition is aggravated by complications that involve bleeding. Blood-transfusion therapy has been associated with increased survival rates in anemic patients with myocardial infarction,⁶⁹ but transfusion itself has also been associated with multiorgan failure and increased mortality in patients who are in critical care.⁷⁰ Whether blood transfusions modulate the immune system, causing clinically relevant adverse effects, remains undetermined.⁷¹ It is important to note that existing guidelines for the management of anemia of chronic disease in patients with cancer or chronic kidney disease do not recommend long-term blood transfusion therapy in their management algorithms because of the risks associated with long-term transfusion, such as iron overload and sensitization to HLA antigens that may occur in patients before renal transplantation.⁵³⁻⁵⁵

Iron Therapy

Oral iron is poorly absorbed because of the down-regulation of absorption in the duodenum.^{37,38} Only a fraction of the absorbed iron will reach the sites of erythropoiesis, owing to iron diversion mediated by cytokines, which directs iron into the reticuloendothelial system. In addition, iron therapy for

patients with anemia of chronic disease is controversial.⁷² Iron is an essential nutrient for proliferating microorganisms, and the sequestration of iron from microorganisms or tumor cells into the reticuloendothelial system is believed to be a potentially effective defense strategy to inhibit the growth of pathogens.⁷² A study investigating measures to predict the risk of bacteremia among patients undergoing hemodialysis who are receiving iron parenterally showed that patients with a transferrin saturation above 20 percent and ferritin levels greater than 100 ng per milliliter had a significantly higher risk of developing bacteremia,⁷³ possibly at least in part because of the fact that iron has an inhibitory effect on cellular immune function that can be traced back to down-regulation of interferon- γ -mediated immune effector pathways.⁵³ In addition, iron therapy in a setting of long-term immune activation promotes the formation of highly toxic hydroxyl radicals that can cause tissue damage and endothelial dysfunction and increase the risk of acute cardiovascular events.^{65,66,72}

On the other hand, iron therapy may confer benefit. By inhibiting the formation of TNF- α , iron therapy may reduce disease activity in rheumatoid arthritis or end-stage renal disease.^{74,75} Furthermore, patients with inflammatory bowel disease and anemia respond well to parenteral iron therapy, with an increase in hemoglobin levels.¹⁵

In addition to possible absolute iron deficiency accompanying the anemia of chronic disease, functional iron deficiency develops under conditions of intense erythropoiesis^{54,76} during therapy with erythropoietic agents, with a decrease in transferrin saturation and ferritin to levels 50 to 75 percent below baseline.^{54,76} Parenteral iron has been demonstrated to enhance rates of response to therapy with erythropoietic agents in patients with cancer who are undergoing chemotherapy⁷⁷ and in patients undergoing dialysis.⁶²

On the basis of current data,⁷⁷ patients with anemia of chronic disease and absolute iron deficiency should receive supplemental iron therapy.^{14,62,63} Iron supplementation should also be considered for patients who are unresponsive to therapy with erythropoietic agents because of functional iron deficiency. In this setting, iron is more likely to be absorbed and utilized by the erythron rather than by pathogens, as indicated by an increase in hemoglobin levels without demonstrable infectious complications.^{73,77} However, iron therapy is currently not recommended for patients with anemia of chronic

disease who have a high or normal ferritin level (above 100 ng per milliliter), owing to possible adverse outcomes in this setting.^{53,65,66,72,78,79}

Erythropoietic Agents

Erythropoietic agents for patients with anemia of chronic disease are currently approved for use by patients with cancer who are undergoing chemotherapy, patients with chronic kidney disease, and patients with HIV infection who are undergoing myelosuppressive therapy. The percentage of patients with anemia of chronic disease who respond to therapy with erythropoietic agents is 25 percent in myelodysplastic syndromes,⁸⁰ 80 percent in multiple myeloma,⁸¹ and up to 95 percent in rheumatoid arthritis and chronic kidney disease.⁶² The therapeutic effect involves counteracting the antiproliferative effects of cytokines,^{46,49} along with the stimulation of iron uptake and heme biosynthesis in erythroid progenitor cells.³ Accordingly, a poor response to treatment with erythropoietic agents is associated with increased levels of proinflammatory cytokines, on the one hand, and poor iron availability, on the other hand.^{13,76,82}

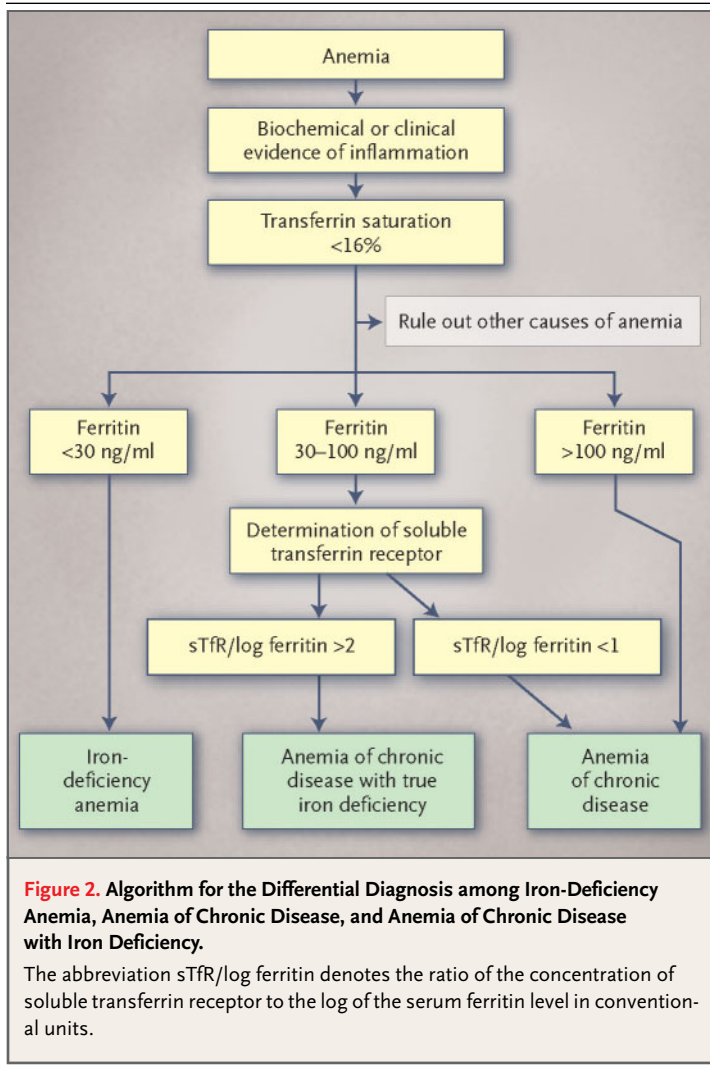
Three erythropoietic agents are currently available — epoetin alfa, epoetin beta, and darbepoetin alfa, which differ in terms of their pharmacologic compounding modifications, receptor-binding affinity, and serum half-life, thus allowing for alternative dosing and scheduling strategies.⁸³ Concern was recently aroused by the identification of 191 epoetin-associated cases of pure red-cell aplasia between 1998 and 2004, as compared with only 3 such cases between 1988 and 1998.⁸⁴ The estimated exposure-adjusted incidence was 18 cases per 100,000 patient-years for the formulation of epoetin alfa in Eprex (Janssen-Cilag) without human serum albumin, 6 cases per 100,000 patient-years for the Eprex formulation with serum albumin, 1 case per 100,000 patient-years for epoetin beta, and 0.2 case per 100,000 patient-years for the formulation of epoetin alfa in Epogen (Amgen). After procedures were adopted to ensure appropriate storage, handling, and administration of Eprex to patients with chronic kidney disease, the exposure-adjusted incidence decreased by 83 percent worldwide.

Although the positive short-term effects of therapy with erythropoietic agents on the correction of anemia and avoidance of blood transfusions are well documented,^{14,60,76} few data are available on possible effects on the course of underlying disease, particularly since epoetin can exert additional bio-

logic effects, including interference with the signal-transduction cascade of cytokines.⁴⁵ For example, the long-term administration of epoetin has been reported to decrease levels of TNF- α in patients with chronic kidney disease⁸¹; reportedly, those who responded well to epoetin therapy had a significantly higher level of expression of CD28 on T cells and lower levels of interleukin-10, interleukin-12, interferon- γ , and TNF- α than did those with a poor response.⁸⁵ Such antiinflammatory effects might be of benefit in certain diseases such as rheumatoid arthritis, a disease in which combined treatment with epoetin and iron not only increased hemoglobin levels but also resulted in a reduction of disease activity.⁷⁴

In addition, erythropoietin receptors are found on several malignant cell lines, including mammary, ovarian, uterine, prostate, hepatocellular, and renal carcinomas, as well as on myeloid cell lines.⁸⁶⁻⁸⁸ However, there are contradictory reports concerning the effects of treatment with epoetin on such cells. Although the drug led to tumor regression in a murine model of myeloma,⁸⁹ administration to erythropoietin-receptor-expressing human renal carcinoma cells in vitro stimulated their proliferation.⁹⁰ High amounts of erythropoietin receptors are found in 90 percent of biopsies from human breast carcinomas.⁹¹ The production of erythropoietin receptors by cancer cells appears to be regulated by hypoxia, and in clinical cancer specimens the highest levels of erythropoietin receptors were associated with neoangiogenesis, tumor hypoxia, and infiltrating tumors.^{88,91} Potentially adverse effects may be due to induction of neoangiogenesis by the hormone, since erythropoietin increases inflammation and ischemia-induced neovascularization by enhancing the mobilization of endothelial progenitor cells.⁹² Implantation of erythropoietin-receptor-expressing cell lines into nude mice with subsequent inhibition of erythropoietin-receptor signaling resulted in inhibition of angiogenesis and destruction of tumor masses.⁸⁷

A recent study investigating the effect of therapy with epoetin on the clinical course of patients with metastatic breast carcinoma was discontinued because of a trend toward higher mortality among patients receiving the drug.⁹³ Controversy concerning the use of epoetin in patients with cancer who have anemia of chronic disease has also arisen in two studies involving patients with head and neck tumors. In one study, the increase in hemoglobin levels with epoetin therapy was associated with a



favorable clinical outcome, improved tumor oxygenation, and increased susceptibility of tumors to preoperative chemoradiation therapy.⁹⁴ In contrast, a double-blind prospective study investigating whether target hemoglobin levels greater than 13 g per deciliter for women and greater than 14 g per deciliter for men improved regional tumor control among patients undergoing radiation therapy for squamous-cell carcinoma of the head or neck showed a recurrence rate among patients who were treated with epoetin that was higher than that among patients treated with placebo.⁹⁵

Current findings indicate that for patients receiving erythropoietic agents, target hemoglobin levels should be 11 to 12 g per deciliter.^{14,62,63} Overcorrection of anemia to normal hemoglobin levels⁹⁵ and insufficient treatment⁶⁴ have each been associated with unfavorable clinical courses.

Monitoring Therapy

Before the initiation of therapy with an erythropoietic agent, iron deficiency should be ruled out (Fig. 2). For monitoring the response to erythropoietic agents, hemoglobin levels should be determined after four weeks of therapy and at intervals of two to four weeks thereafter. If the hemoglobin level increases by less than 1 g per deciliter, the iron status should be reevaluated (Table 2) and iron supplementation considered.^{14,63} If iron-restricted erythropoiesis is not present, a 50 percent escalation in the dose of the erythropoietic agent is indicated. The dose of the erythropoietic agent should be adjusted once the hemoglobin concentration reaches 12 g per deciliter.^{14,62} If no response is achieved after eight weeks of optimal dosage in the absence of iron deficiency, a patient is considered nonresponsive to erythropoietic agents.

CONCLUSIONS

Advances in our understanding of the pathophysiology of anemia of chronic disease — including disturbances of iron homeostasis, impaired proliferation of erythroid progenitor cells, and a blunted erythropoietin response to anemia — have made possible the emergence of new therapeutic strategies. These include treatment of the underlying disease and the use of erythropoietic agents, iron, or blood transfusions. Needed are prospective, controlled studies to evaluate the effect of the management of anemia on underlying diseases, with defined end points and analysis of the possible clinical significance of erythropoietin-receptor expression on certain tumor cells. Future strategies may include the use of iron-chelation therapy to induce the endogenous formation of erythropoietin,⁹⁶ hepcidin antagonists that overcome the retention of iron within the reticuloendothelial system, and hormones or cytokines that might effectively stimulate erythropoiesis under inflammatory conditions. End points that correlate with improvements in morbidity and mortality in well-designed, prospective studies must be identified in order to determine the optimal therapeutic regimen for patients with anemia of chronic disease.

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