REVIEW ARTICLE

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Microcytic Anemia

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The microcytic anemias are those characterized by the production of red cells that are smaller than normal. The small size of these cells is due to decreased production of hemoglobin, the predominant constituent of red cells (Fig. 1). The causes of microcytic anemia are a lack of globin product (thalassemia), restricted iron delivery to the heme group of hemoglobin (anemia of inflammation), a lack of iron delivery to the heme group (iron-deficiency anemia), and defects in the synthesis of the heme group (sideroblastic anemias). This review highlights new aspects of the most common microcytic anemias: thalassemia, anemia of inflammation, and iron-deficiency anemia.

THALASSEMIA

Thalassemias are diseases of hemoglobin synthesis, with subtypes named after the hemoglobin chain involved (Table 1). Given that each chromosome 16 carries two copies of the gene encoding the α chain, there are four types of α-thalassemia: trait 1, trait 2, hemoglobin H disease, and hemoglobin Bart's. Patients with the trait thalassemias present with no or very mild anemia and variable microcytosis — both more pronounced in patients with the trait-2 form. Deletion of or mutations in three α-chain genes lead to hemoglobin H disease, which is marked by more prominent anemia, often with a hemolytic component. Hemoglobin Bart's is characterized by a lack of α-chain production, resulting in hydrops fetalis due to the lack of fetal and adult hemoglobin production.

The main geographic locations where α-thalassemia is found are Africa, the Mediterranean area, and Southeast Asia, but the more severe forms — hemoglobin H disease and hemoglobin Bart's — are seen only in the Mediterranean area and Southeast Asia.[1] The reason for this geographic association with severity concerns the two molecular forms of α-thalassemia trait 2 — one in which one copy of the gene is mutated on each chromosome (*trans*) and the other in which one chromosome has both genes mutated (*cis*). The predominant genotype of thalassemia trait in Africa is *trans*, but the *cis* form is found in other areas, which can lead to hemoglobin H disease and hemoglobin Bart's.

β-Thalassemia is common in the Mediterranean area and Southeast Asia. Because there is one copy of the hemoglobin β chain on chromosome 11, patients can be either heterozygous (thalassemia minor) or homozygous (thalassemia major) for the defective hemoglobin chain. Some patients are homozygous for β-chain mutations but still have residual β-chain synthesis, resulting in an intermediate phenotype (thalassemia intermedia). Patients with thalassemia minor present with mild microcytic anemia. Thalassemia major is manifested soon after birth as severe transfusion-dependent anemia. As the name implies, thalassemia intermedia can range in presentation from transfusion-dependent anemia to anemia that is slightly more severe than that in patients with thalassemia minor.

Also common in Southeast Asia is hemoglobin E disease, in which lysine is substituted for glutamine at position 26 of the β chain. This mutation also activates

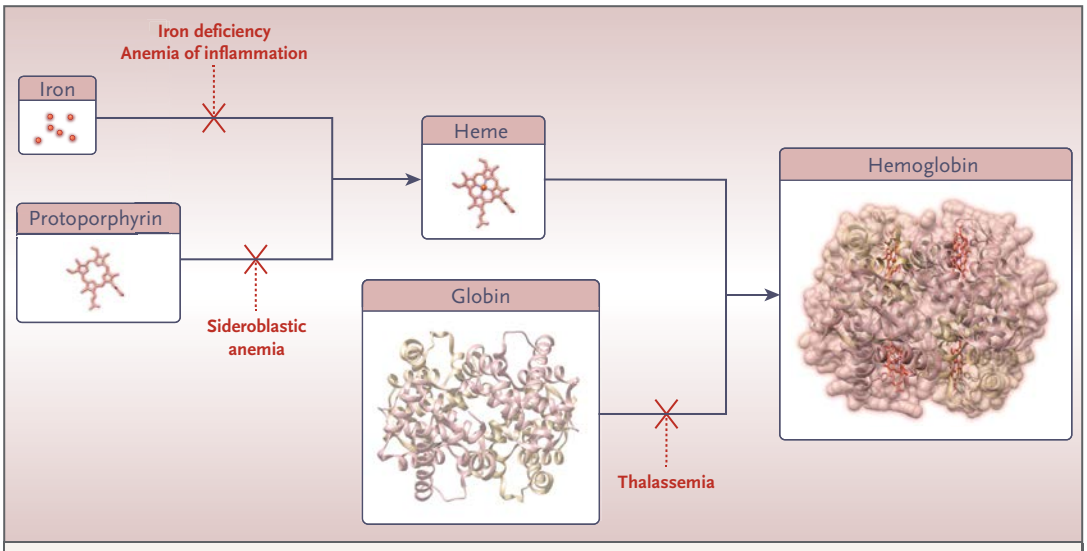


Figure 1. Disorders Characterized by Microcytosis.

Red cells become microcytic because of a lack of hemoglobin. This can result from a lack of iron (deficiency or inflammation), defects in heme synthesis (sideroblastic anemias), or defects in the production of hemoglobin protein (thalassemia).

an alternative messenger RNA (mRNA) splice site, leading to a marked reduction in protein synthesis. People who are heterozygous for hemoglobin E have microcytosis with target cells, and those who are homozygous have only mild anemia. However, children with one copy each of the β-thalassemia gene and the hemoglobin E gene will have a severe phenotype, resulting in a transfusion-dependent anemia.

ANEMIA OF INFLAMMATION

Inflammatory states are often accompanied by microcytic anemia. The cause of this anemia is twofold.[2] First, renal production of erythropoietin is suppressed by inflammatory cytokines, resulting in decreased red-cell production. Second, lack of iron availability for developing red cells can lead to microcytosis. The lack of iron is largely due to the protein hepcidin,[3] an acute-phase reactant that leads to both reduced iron absorption and reduced release of iron from body stores. The protein ferroportin mediates cellular efflux of iron. Hepcidin binds to and down-regulates ferroportin, thereby blocking iron absorbed by enterocytes from entering the circulation and also preventing the release of iron from its body stores to developing red cells (Fig. 2).

IRON DEFICIENCY

The most common anemia is iron-deficiency anemia. Besides playing a crucial role as an oxygen carrier in the heme group of hemoglobin, iron is found in many key proteins in the cells, such as cytochromes and myoglobin, so it is not unexpected that a lack of iron has effects other than anemia. Three studies have focused on nonanemic iron deficiency leading to fatigue. Two studies showed that oral iron supplementation reduces fatigue, with no significant change in hemoglobin levels, in women with a ferritin level of less than 50 ng per milliliter,[4,5] and a third study showed a lessening of fatigue with parenteral iron administration in women with a ferritin level of 15 ng per milliliter or less or an iron saturation of 20% or less.[6]

Owing to obligate iron loss through menses, women are at greater risk for iron deficiency than men. Iron loss in all women averages 1 to 3 mg per day, and dietary intake is often inadequate to maintain a positive iron balance.[7,8] A 1967 study showed that 25% of healthy, college-age women had no bone marrow iron stores and that another 33% had low stores.[9] Pregnancy adds to demands for iron, with requirements increasing to 6 mg per day by the end of pregnancy.[10]

Table 1. Features of the Thalassemias.*

Type	Mean Corpuscular Volume	Hemoglobin	Findings on Electrophoresis	Other Features
	fl	*g/dl*		
β-Thalassemia				
Major	50–75	<7	Increased hemoglobin A_2	Severe anemia
Intermedia	50–75	<9	Increased hemoglobin A_2	Target cells on smear
Minor	65–75	9–10	Increased hemoglobin A_2	Target cells on smear
α-Thalassemia				
Trait 1 ($\alpha\,\alpha/\alpha$–)	80–85	12–14	Normal	
Trait 2 (α–/α–) or ($\alpha\,\alpha$/–)	65–75	12–13	Normal	
Hemoglobin H disease (α–/–)	60–69	9–8	Hemoglobin H	Hemolysis, splenomegaly
Hemoglobin Bart's (– –/–)			Hemoglobin H, hemoglobin Bart's	Hydrops fetalis
Hemoglobin E disease				
Heterozygous	80–85	12	Hemoglobin E present	Rare target cells on smear
Homozygous	70–79	11–12	Hemoglobin E predominant	Target cells on smear

* The normal range for mean corpuscular volume is 80 to 100 fl. The normal range for hemoglobin level is 13.5 to 17.5 g per deciliter in men and 12 to 16 g per deciliter in women.

Athletes are another group at risk for iron deficiency.[11] Gastrointestinal tract blood is the source of iron loss, and exercise-induced hemolysis leads to urinary iron losses.[12] Decreased absorption of iron has also been implicated as a cause of iron deficiency, because levels of hepcidin are often elevated in athletes owing to training-induced inflammation.[11] Although it is clear that frank anemia can affect exercise performance, evidence is increasing that nonanemic iron deficiency may also be detrimental.[13]

An interactive graphic showing blood smears is available at NEJM.org

Obesity and its surgical treatment are also risk factors for iron deficiency. Obese patients are often iron-deficient, with increased hepcidin levels being implicated in decreased absorption.[14] After bariatric surgery, the incidence of iron deficiency can be as high as 50%.[15] Because the main site of iron absorption is the duodenum, surgeries that involve bypassing this part of the bowel are associated with an increased incidence of iron deficiency. However, iron deficiency is seen as a sequela of most types of bariatric surgery.[16]

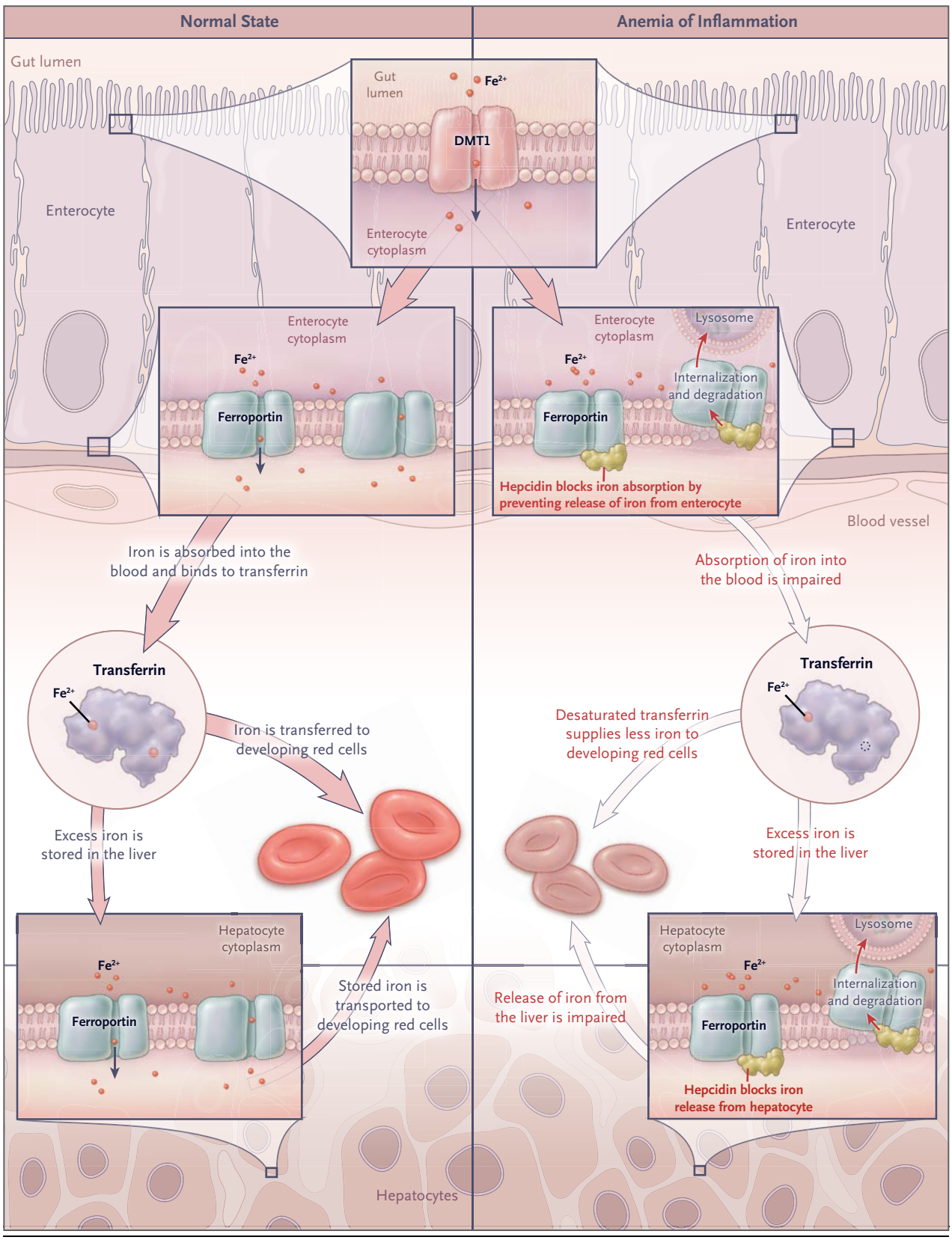
DIAGNOSIS

In a patient who presents with microcytosis, the extent to which the mean corpuscular volume is reduced can be a clue to etiologic factors, because a value of less than 70 fl is rare in patients with anemia of inflammation. There have been a variety of proposed prediction rules with the use of blood indexes to differentiate between thalassemia and iron deficiency, but these have limited predictive power; therefore, specific testing is required.

On the blood smear, microcytic cells can be recognized because they are smaller than a lymphocyte nucleus. Hypochromia — an increase in the size of the central pallor of red cells — can also be observed. In iron-deficiency anemia and anemia of inflammation, microcytic cells predominate, but in β-thalassemia and hemoglobin

Figure 2 (facing page). Mechanism of Anemia of Inflammation.

Normally, iron is absorbed in the gastrointestinal tract and is delivered to transferrin for transport to the developing red cells, with any excess stored in hepatocytes. In inflammatory states, decreased absorption of iron leads to reduced saturation of transferrin and impaired release of iron from storage, resulting in a lack of iron delivery to the developing red cells. These changes are mediated by hepcidin, which binds and inhibits ferroportin, the main iron-export protein. DMT1 denotes divalent metal transporter 1.



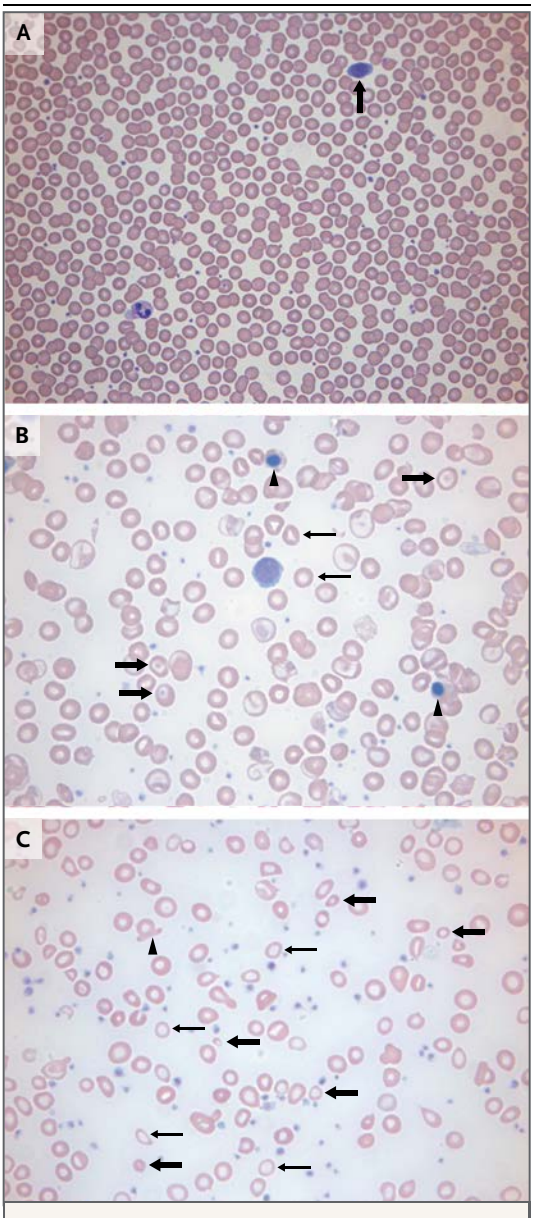


Figure 3. Blood-Smear Features of Microcytic Anemias.

Panel A shows normal red cells. Central pallor is less than one third of the cell diameter, and the size of the red cells is similar to that of a lymphocyte nucleus (arrow). Panel B shows β-thalassemia and hemoglobin E disease, characterized by target cells (thick arrows), red cells that are smaller than a lymphocyte nucleus (thin arrows), and occasional nucleated red cells (arrowheads). Panel C shows severe iron deficiency, with hypochromia (thin arrows), microcytosis (thick arrows), and a pencil cell (arrowhead). Photomicrographs courtesy of Michael Cascio, Oregon Health and Science University.

E disease, target cells are also apparent (Fig. 3 and interactive graphic, available with the full text of this article at NEJM.org).

Patients with β-thalassemia minor present with a hemoglobin level of 10 to 13 g per deciliter and a mean corpuscular volume of 65 to 75 fl. These patients have an increased production of hemoglobin that contains the δ chain (hemoglobin A_2), so electrophoresis typically shows an increased hemoglobin A_2 fraction. The previous concern that concurrent iron deficiency may blunt the rise in hemoglobin A_2 appears not to be relevant for most patients.[17]

α-Thalassemia trait is electrophoretically silent. The diagnosis can be made by exclusion in a patient who presents with microcytosis but only mild or no anemia and who is iron-replete. A precise diagnosis requires DNA analysis. The presence of hemoglobin H (a tetramer of β chains) on electrophoresis, along with severe microcytosis, is diagnostic of hemoglobin H disease. Hemolysis may also be evident and splenomegaly is observed on physical examination in patients with hemoglobin H disease.

Currently, the diagnosis of anemia of inflammation is one of exclusion. Three findings are supportive of the diagnosis: an erythropoietin value that is not appropriately increased in patients with anemia and preserved renal function, the presence of adequate iron stores, and no other cause for the anemia. Iron studies in these patients show low iron saturation and a low-to-normal total iron-binding capacity. In the future, more widespread availability of hepcidin assays will be of value, with an increased hepcidin level supportive of the diagnosis of anemia of inflammation.

For the diagnosis of iron deficiency, many tests have been proposed over the years, but the serum ferritin assay is currently the most efficient and cost-effective test, given the shortcomings of other tests.[14,18] The mean corpuscular volume is low with severe iron deficiency, but coexisting conditions such as liver disease may blunt the decrease in red-cell size. Reticulocyte hemoglobin content is low with both iron-deficiency anemia and thalassemia, and it is also reduced with anemia of inflammation, reflecting restricted iron delivery to developing red cells. Serum iron levels are low in patients with anemia of inflammation and can be falsely ele-

vated with oral iron intake. An increased total iron-binding capacity is specific for iron deficiency, but because total iron-binding capacity is lowered by inflammation, aging, and poor nutrition, its sensitivity is low. Iron saturation is low with both iron-deficiency anemia and anemia of inflammation. Serum levels of soluble transferrin receptor will be elevated in patients with iron deficiency, and this is not affected by inflammation. However, levels can be increased in patients with any condition associated with an increased red-cell mass, such as hemolytic anemias, and in patients with chronic lymphocytic leukemia. Bone marrow iron staining is the most accurate means of diagnosing iron-deficiency anemia, but this is an invasive and expensive procedure.

Although the transcription of ferritin mRNA is up-regulated by inflammation, the synthesis of ferritin is regulated by cellular iron content, with ferritin mRNA being translated to protein only when the cell is iron-replete.[8] Thus, a patient with adequate iron may have a very high ferritin level with inflammation, whereas it is rare for a patient with iron deficiency to have a ferritin level of more than 100 ng per milliliter. The lower limit of the normal range depends on the clinical situation. A ferritin level of 15 ng per milliliter is very specific for iron deficiency, but in older patients or those with inflammatory states, one cannot rule out iron deficiency until the ferritin level is more than 100 ng per milliliter. Guyatt et al. found that the likelihood ratio for iron deficiency is positive up to a ferritin level of 40 ng per milliliter in the absence of inflammation and up to 70 ng per milliliter in the presence of inflammation.[19] Although not perfect, the serum ferritin assay is the test most likely to provide information about a patient's iron status, but the patient's age and clinical condition need to be considered in the interpretation of results.

The other essential priority in iron deficiency is determining the cause. Given that there are no natural mechanisms (other than menstruation) for ridding the body of iron, blood loss must always be assumed. In patients in whom the source of loss is not obvious, examination of the gastrointestinal tract for lesions is mandatory, because a high percentage of patients will have an identifiable source of iron loss.[20]

THERAPY

THALASSEMIA

For children born with severe forms of thalassemia, chronic transfusions will lead to normal growth and development. However, without aggressive iron chelation, endocrine failure will ensue, and most will die in the second or third decade of life from iron overload. Aggressive iron chelation will prevent or delay these complications. Stem-cell transplantation, if available, is the best treatment option: in young patients, there will be fewer complications than with other treatments, and if transplantation is successful, there is no need for lifelong therapy with transfusion and chelation.

Treatment of patients with thalassemia intermedia or hemoglobin H disease is more challenging because of the variety of presentations. For patients who are transfusion-dependent, iron chelation is essential. These patients have increased iron absorption, so iron overload can occur even in those with minimal transfusion requirements. Patients with thalassemia trait require no specific therapy. However, if they are considering childbearing, the partner should be screened for thalassemia by checking the mean corpuscular volume; if it is less than 75 fl, more specific genetic testing is necessary.

ANEMIA OF INFLAMMATION

The most effective therapy for anemia of inflammation is to eliminate the underlying cause, but in many patients that cannot be done. Because of the low erythropoietin levels, erythropoiesis-stimulating agents have been used successfully in patients with anemia of inflammation to increase the red-cell count, but the use of these agents is limited owing to their cost and safety concerns. In animal models of anemia, blocking hepcidin reduces anemia, and this strategy holds much promise for the future.[21]

IRON DEFICIENCY

Oral Iron Therapy

Traditionally, ferrous sulfate (325 mg [65 mg of elemental iron] orally three times a day) has been prescribed for the treatment of iron deficiency. Several trials suggest that lower doses of iron, such as 15 to 20 mg of elemental iron daily, can

be as effective as higher doses and have fewer side effects.[22,23] The reason may be that enterocyte iron absorption appears to be saturable; one dose of iron can block absorption of further doses.[24] Consuming the iron with meat protein can also increase iron absorption.[25] Calcium and fiber can decrease iron absorption, but this can be overcome by taking vitamin C.[26] A potent inhibitor of iron absorption is tea, which can reduce absorption by 90%.[27] Coffee may also decrease iron absorption but not to the degree that tea does. With regard to dietary iron, the rate of absorption of iron from heme sources is 10 times as high as that of iron from nonheme sources.

There are many oral iron preparations, but no one compound appears to be superior to another.[28] A pragmatic approach to oral iron replacement is to start with a daily 325-mg pill of ferrous sulfate (usually the least expensive form), taken with a meal that contains meat. Avoiding tea and coffee and taking vitamin C (500 units with the iron pill once daily) will also help absorption. If ferrous sulfate has unacceptable side effects, ferrous gluconate at a daily dose of 325 mg (35 mg of elemental iron) can be tried. The reticulocyte count should rise in 1 week, and the hemoglobin level starts rising by the second week of therapy. Iron therapy should be continued until iron stores are replete.

In patients who do not have a response to oral iron, several factors may be contributing to the lack of response. First, the side effects of stomach pain and constipation can reduce adherence. Taking smaller doses of iron may decrease these symptoms. Second, in a patient who has ongoing bleeding (e.g., from inflammatory bowel disease), the iron loss may be too great for oral iron to overcome. Finally, absorption of iron may be decreased owing to celiac disease or bowel surgery.

Parenterally Administered Iron

For patients who do not have an adequate response to oral iron therapy, there are several intravenous options (Table 2). Parenteral iron can improve iron stores without concern about absorption or gastrointestinal side effects. The major disadvantage is infusion reactions. High-molecular-weight iron dextran is associated with a significantly higher reaction rate than other forms of parenteral iron and should not be used.[29] Iron sucrose (Venofer) and ferric gluconate (Ferrlecit) are recently introduced products with lower reaction rates, but they require frequent infusions to fully replete iron stores. There is increasing evidence that low-molecular-weight iron dextran (INFeD) is associated with an incidence of reactions that is similar to that with the newer products but allows for higher doses of iron replacement — up to 1000 mg — in a single session.[30,31] Ferumoxytol (Feraheme) is a superparamagnetic iron oxide coated with carbohydrate that is marketed as both an iron-replacement agent and a magnetic resonance imaging (MRI) contrast agent. One unique complication is severe hypotension, which was observed in 1.9% of patients in postmarketing studies.[32] In addition, if MRI studies will be needed within 3 months, the radiologist should be aware that the patient has received ferumoxytol. Another option is ferric carboxymaltose (Injectafer), which the Food and Drug Administration approved in 2013 for the treatment of iron-deficiency anemia.

Use of parenteral iron should be considered in any case of iron deficiency that is refractory to oral iron. Low-molecular-weight iron dextran may be the least inexpensive and most convenient option. For patients who have hypersensitivity reactions to iron dextran, the use of other agents is indicated. Patients who have ongoing blood loss — for example, from hereditary hemorrhagic telangiectasia — may need ongoing iron infusions.

Table 2. Intravenous Iron Preparations.

Agent	Typical Replacement Dose
Low-molecular-weight iron dextran	25 mg as test dose; if no adverse reaction within 1 hr, then 975 mg over 4–6 hr for total dose of 1000 mg
Ferric gluconate	125 mg over 1 hr; repeat in seven subsequent sessions for total dose of 1000 mg
Iron sucrose	200 mg over 15–60 min, 300 mg over 1.5 hr, or 500 mg over 4 hr; repeat in one to four subsequent sessions for total dose of 1000 mg
Ferumoxytol	510 mg over 17 sec; repeat in 3–8 days for total dose of 1020 mg
Ferric carboxymaltose	750 mg over 15–30 min; repeat in 7 days for total dose of 1500 mg

THE FUTURE

As a genetic disease, thalassemia remains an ideal target for gene therapy. Several clinical trials are under way, and several patients have undergone treatment with some preliminary signs of success.[33] There is also increasing interest in raising fetal hemoglobin levels to ameliorate anemia in patients with β-thalassemia major and especially those with thalassemia intermedia. Manipulation of the hepcidin pathway holds great promise for treating anemia of inflammation. Although tremendous progress has been made, much remains to be elucidated about iron metabolism, including the receptor for absorption of heme iron. Finally, the role of new markers — such as polymorphisms in a key iron-sensing protein, transmembrane protease serine 6 (TMPRSS6), which may increase the risk of iron deficiency — remains to be explored.[34]

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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