

**TABLE 126-3** IRON STORE MEASUREMENTS

Iron Stores	Marrow Iron Stain, 0–4+	Serum Ferritin, $\mu\text{g/L}$
0	0	<15
1–300 mg	Trace to 1+	15–30
300–800 mg	2+	30–60
800–1000 mg	3+	60–150
1–2 g	4+	>150
Iron overload	—	>500–1000

ferritin values averaging 100  $\mu\text{g/L}$ , while adult females have levels averaging 30  $\mu\text{g/L}$ . As iron stores are depleted, the serum ferritin falls to <15  $\mu\text{g/L}$ . Such levels are diagnostic of absent body iron stores.

**Evaluation of Bone Marrow Iron Stores** Although RE iron stores can be estimated from the iron stain of a bone marrow aspirate or biopsy, the measurement of serum ferritin has largely supplanted these procedures for determination of storage iron (Table 126-3). The serum ferritin level is a better indicator of iron overload than the marrow iron stain. However, in addition to storage iron, the marrow iron stain provides information about the effective delivery of iron to developing erythroblasts. Normally, when the marrow smear is stained for iron, 20–40% of developing erythroblasts—called *sideroblasts*—will have visible ferritin granules in their cytoplasm. This represents iron in excess of that needed for hemoglobin synthesis. In states in which release of iron from storage sites is blocked, RE iron will be detectable, and there will be few or no sideroblasts. In the myelodysplastic syndromes, mitochondrial dysfunction can occur, and accumulation of iron in mitochondria appears in a necklace fashion around the nucleus of the erythroblast. Such cells are referred to as *ringed sideroblasts*.

**Red Cell Protoporphyrin Levels** Protoporphyrin is an intermediate in the pathway to heme synthesis. Under conditions in which heme synthesis is impaired, protoporphyrin accumulates within the red cell. This reflects an inadequate iron supply to erythroid precursors to support hemoglobin synthesis. Normal values are <30  $\mu\text{g/dL}$  of red cells. In iron deficiency, values in excess of 100  $\mu\text{g/dL}$  are seen. The most common causes of increased red cell protoporphyrin levels are absolute or relative iron deficiency and lead poisoning.

**Serum Levels of Transferrin Receptor Protein** Because erythroid cells have the highest numbers of transferrin receptors of any cell in the body, and because transferrin receptor protein (TRP) is released by cells into the circulation, serum levels of TRP reflect the total erythroid marrow mass. Another condition in which TRP levels are elevated is absolute iron deficiency. Normal values are 4–9  $\mu\text{g/L}$  determined by immunoassay. This laboratory test is becoming increasingly available and, along with the serum ferritin, has been proposed to distinguish between iron deficiency and the anemia of inflammation (see below).

### DIFFERENTIAL DIAGNOSIS

Other than iron deficiency, only three conditions need to be considered in the differential diagnosis of a hypochromic microcytic anemia (Table 126-4). The first is an inherited defect in globin chain synthesis:

the thalassemias. These are differentiated from iron deficiency most readily by serum iron values; normal or increased serum iron levels and transferrin saturation are characteristic of the thalassemias. In addition, the red blood cell distribution width (RDW) index is generally normal in thalassemia and elevated in iron deficiency.

The second condition is the anemia of inflammation (AI; also referred to as the anemia of chronic disease) with inadequate iron supply to the erythroid marrow. The distinction between true iron-deficiency anemia and AI is among the most common diagnostic problems encountered by clinicians (see below). Usually, AI is normocytic and normochromic. The iron values usually make the differential diagnosis clear, as the ferritin level is normal or increased and the percent transferrin saturation and TIBC are typically below normal.

Finally, the myelodysplastic syndromes represent the third and least common condition. Occasionally, patients with myelodysplasia have impaired hemoglobin synthesis with mitochondrial dysfunction, resulting in impaired iron incorporation into heme. The iron values again reveal normal stores and more than an adequate supply to the marrow, despite the microcytosis and hypochromia.

## TREATMENT IRON-DEFICIENCY ANEMIA

The severity and cause of iron-deficiency anemia will determine the appropriate approach to treatment. As an example, symptomatic elderly patients with severe iron-deficiency anemia and cardiovascular instability may require red cell transfusions. Younger individuals who have compensated for their anemia can be treated more conservatively with iron replacement. The foremost issue for the latter patient is the precise identification of the cause of the iron deficiency.

For the majority of cases of iron deficiency (pregnant women, growing children and adolescents, patients with infrequent episodes of bleeding, and those with inadequate dietary intake of iron), oral iron therapy will suffice. For patients with unusual blood loss or malabsorption, specific diagnostic tests and appropriate therapy take priority. Once the diagnosis of iron-deficiency anemia and its cause is made, there are three major therapeutic approaches.

### RED CELL TRANSFUSION

Transfusion therapy is reserved for individuals who have symptoms of anemia, cardiovascular instability, and continued and excessive blood loss from whatever source and who require immediate intervention. The management of these patients is less related to the iron deficiency than it is to the consequences of the severe anemia. Not only do transfusions correct the anemia acutely, but the transfused red cells provide a source of iron for reutilization, assuming they are not lost through continued bleeding. Transfusion therapy will stabilize the patient while other options are reviewed.

### ORAL IRON THERAPY

In the asymptomatic patient with established iron-deficiency anemia, treatment with oral iron is usually adequate. Multiple preparations are available, ranging from simple iron salts to complex iron compounds designed for sustained release throughout the small intestine (Table 126-5). Although the various preparations

**TABLE 126-4** DIAGNOSIS OF MICROCYTIC ANEMIA

Tests	Iron Deficiency	Inflammation	Thalassemia	Sideroblastic Anemia
Smear	Micro/hypo	Normal micro/hypo	Micro/hypo with targeting	Variable
Serum iron ( $\mu\text{g/dL}$ )	<30	<50	Normal to high	Normal to high
TIBC ( $\mu\text{g/dL}$ )	>360	<300	Normal	Normal
Percent saturation	<10	10–20	30–80	30–80
Ferritin ( $\mu\text{g/L}$ )	<15	30–200	50–300	50–300
Hemoglobin pattern on electrophoresis	Normal	Normal	Abnormal with $\beta$ thalassemia; can be normal with $\alpha$ thalassemia	Normal

**Abbreviation:** TIBC, total iron-binding capacity.