# Hematologic Manifestations of Systemic Disease (Including Iron Deficiency, Anemia of Inflammation and DIC)

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**KEYWORDS**

- Function of hemoglobin • Anemia of inflammation • Iron deficiency anemia
- Disseminated intravascular coagulation

**KEY POINTS**

- A complete blood cell count (CBC) is a frequent test sent to aid in the diagnostic evaluation of ill patients.
- Not uncommonly hematologic abnormalities may be the first sign of an underlying systemic disorder.
- The astute clinician needs to understand how systemic disease can affect the CBC to direct further diagnostic investigations.

## INTRODUCTION

A complete blood cell count (CBC) is a frequent test sent to aid in the diagnostic evaluation of ill patients. Not uncommonly hematologic abnormalities may be the first sign of an underlying systemic disorder. The astute clinician needs to understand how systemic disease can affect the CBC to direct further diagnostic investigations. This article focuses on the 2 most common acquired anemias including iron deficiency and anemia of inflammation (AI) as well as disseminated intravascular coagulation (DIC).

## STRUCTURE AND FUNCTION OF HEMOGLOBIN

A red blood cell (RBC) is nonnucleated and survives for 120 days. The key functional component of an RBC is hemoglobin, a nearly spherical protein composed of

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tetramers of 2 alphalike globin chains and 2 betalike globin chains. The primary physiologic function of hemoglobin is to transport oxygen to the tissues from the lungs. Each of the subunits in the hemoglobin tetramer contains a heme prosthetic group. Heme is an iron-containing protoporphyrin IX with an iron atom at the center, typically in the ferrous form (+2). In the ferrous form the heme group can bind gaseous ligands specifically $O_2$, CO, and NO. Hemoglobin also binds and transports $CO_2$ (on a different binding site than $O_2$) to the lungs from the tissues.

Physiologically anemia compromises oxygen delivery to tissues. Symptoms depend on how severely anemic a patient is, how slowly they became anemic, and underlying comorbidities. Many patients may be asymptomatic or have vague generalized symptoms like fatigue. On physical exam, pallor is manifest as pale skin, mucosa, and palmar creases. More severe anemia will have evidence of a hyperdynamic circulation with tachycardia, a systolic flow murmur (more common once the hemoglobin is less than 8 g/dL), and potentially signs of heart failure.

## IRON DEFICIENCY ANEMIA

### *Epidemiology*

Iron deficiency is the most common nutrient deficiency worldwide and accounts for 50% of the world's anemia burden.[1] It is the only nutrient deficiency that is found in both industrialized and nonindustrialized countries.[1] There is a bimodal peak of occurrence in pediatrics with increased rates seen in infancy and menstruating adolescent women. It is estimated in the United States that up to 7% of toddlers, 9% of adolescents, and 16% of women of childbearing age is iron deficient.[2]

### *Pathophysiology*

Iron is a ubiquitous metal that is found in most cells within the human body. It is a critical ingredient for effective red cell production but also plays a role in other biochemical pathways including myoglobin formation, energy metabolism, neurotransmitter production, collagen formation, and immune system function.[3] Approximately 1 to 2 mg of iron enters and leaves the body daily. Gastrointestinal (GI) absorption of iron occurs primarily in the proximal duodenum and is a tightly controlled process that is responsive to iron status, erythropoietin demand, hypoxia, and inflammation. The main regulator of iron absorption is hepcidin, which serves as a negative regulator of iron absorption and macrophage iron release.[4]

Within the body, iron is distributed in 3 pools including transport, functional, and storage iron.[3] Absorbed iron is bound to transferrin for transport in the plasma and accounts for only 0.1% of total body iron. Functional iron accounts for 75% of the total body iron and is predominantly used for hemoglobin production (70%) with the remaining in muscle and other tissues. Excess iron is stored in tissues (primarily liver, bone marrow, and spleen) as ferritin. The amount of daily iron absorption is low relative to ongoing demands necessitating iron recycling of senescent red cells by macrophages. Although iron absorption is tightly regulated, there is no mechanism to regulate iron loss.

At birth, infants have high total body iron stores (75 mg/kg of iron).[5,6] These iron stores support rapid neonatal growth but are only adequate until about 6 months of age. At this point, iron-enriched cereals should be included in the first foods introduced into an infant's diet. In preterm infants, the total body iron stores are decreased compared with full-term infants although the proportion to body weight is similar.[7] Preterm infants should receive iron supplementation because they undergo more rapid postnatal growth than full-term infants and exhaust their iron stores by 2 to 3 months