Anemia in the ICU
Anemia of Chronic Disease Versus Anemia of Acute Illness

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KEYWORDS

• Anemia of chronic disease • Anemia of inflammation • Anemia in the ICU • Hepcidin
• Iron deficiency in the ICU • Transfusion and erythropoietin in the ICU

KEY POINTS

- Anemia is a common problem in the ICU and is of multifactorial etiology.
- Cytokine mediated increase in Hepcidin is an important mediator of anemia in critically ill patients, leading to poor iron utilization.
- There may be a concurrent iron deficiency in patients with anemia of inflammation which can be difficult to diagnose and treat.
- Transfusing patients with anemia in the ICU to an ideal target hemoglobin is deleterious and restrictive transfusion policies lead to better outcomes.
- Erythropoietin use is associated with worse outcomes and it should be used judiciously.

EPIDEMIOLOGY

Anemia is a common problem in the intensive care unit (ICU), occurring frequently in critically ill patients. Observational studies indicate an incidence of approximately 95% in patients who have been in the ICU for 3 or more days.[1] The presence of anemia has been associated with worse outcomes including increased lengths of stay and increased mortality.[2] The etiology of anemia is multifactorial and includes the following:

1. Frequent blood sampling; in one study, the average total volume of blood drawn was 41.1 mL per patient during a 24-hour period.[2] The quantity of blood phlebotomized accounted for 49% variation in amount of blood transfused in an observational study by Corwin and colleagues.[3]
2. Clinically apparent or occult blood loss through the gastrointestinal tract.

The author has nothing to disclose.
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3. Blood loss from preceding trauma.
4. Blood loss as a result of surgical interventions.
5. Impaired production of red cells secondary to a blunted erythropoietin response to anemia in critically ill patients. Erythropoietin (Epo) levels have been found to be inappropriately low in these patients, with a loss of the normal inverse correlation that exists between serum Epo levels and hematocrit levels.[4,5] The blunted Epo response appears to be a result of suppression by inflammatory cytokines.[6] These patients, however, retain their responsiveness to exogenously administered Epo.[7] There is also a direct suppressive effect on erythroid production secondary to direct bone marrow suppression by inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) and inhibitory effects of interferon-α, β, and γ.
6. It is being increasingly recognized that the anemia in a majority of critically ill patients is a result of poor iron utilization akin to that seen in the so-called anemia of chronic disease. This is now more accurately called anemia of inflammation (AI). Decreased serum iron, serum transferrin, transferrin saturation, and increased ferritin levels have been found in these patients, indicative of an inflammatory profile. In one study of 51 postoperative critically ill patients, decreased serum iron and increased ferritin were found in more than 75% of patients. Forty-one of these patients suffered 56 septic episodes. These were accompanied by a marked decrease in serum transferrin and increase in serum ferritin accompanied by a reduction in hemoglobin ($P<.001$). Recovery from sepsis was accompanied by a significant improvement in hemoglobin, serum iron, and transferrin.[8]

PATHOPHYSIOLOGY OF ANEMIA OF INFLAMMATION

To understand the pathophsiology of anemia of inflammation, it is important to first understand normal iron metabolism in the body. Iron has the capacity to donate and accept electrons easily, thus interconverting between the ferric (Fe^{3+}) and ferrous (Fe^{2+}) forms. This makes it a useful component of oxygen binding molecules (hemoglobin and myoglobin), cytochromes, and other enzymes involved in electron transfer reactions. On the flip side, iron must be bound to transporter/storage proteins at all times because free reactive iron causes tissue damage, most likely by catalyzing the production of free oxygen radicals from hydrogen peroxide. For this reason the concentration of iron in biological fluids is tightly regulated. Iron homeostasis in mammals is regulated at the level of intestinal absorption, as the body has no physiologic pathway to increase iron excretion.

A well balanced diet contains about 10 to 20 mg of iron daily, and roughly 10% of dietary iron is absorbed each day (**Fig. 1**). The efficiency of iron absorption can increase up to 20% in response to increased utilization in children secondary to growth, or increased requirements in pregnancy, and with greater iron loss as occurs with menstruation and with minor hemorrhages. A small amount of iron is lost from the body daily, mainly from the shedding of cells containing iron in the gastrointestinal tract and exfoliation of skin cells. About 1 mg of iron is lost per day, though menstruating women lose about 2 mg/day. This is balanced by absorption of 1 to 2 mg iron/day.

Normal adult males have 35 to 45 mg of iron per kilogram of body weight, and total body iron content of 4 to 6 g. Females tend to have lower amounts of body iron secondary to blood loss during menstruation. Roughly 80% of the total iron content is functional, the remainder being in the storage form. Approximately 80% of the functional iron is found bound to hemoglobin; the remainder is contained in myoglobin and iron-containing enzymes such as cytochromes. 20% of iron is stored as either ferritin or hemosiderin.