Causes of Anemia in Critically Ill Patients

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Abstract

Anemia is a common occurrence in critically ill patients and is associated with considerable morbidity and worse outcomes. The prevalence of anemia among critically ill patients is influenced by factors that include patient case mix, illness severity, and preexisting comorbidity. Several factors may lead to anemia in critically ill patients and the etiology of anemia in individual patients is commonly multifactorial and may be related either to the underlying disease process or occur as a consequence of diagnostic or therapeutic interventions in the intensive care unit (ICU). Anemia of chronic disease is the most important form of anemia related to preexisting morbidity on admission to ICU. Blood loss considerably contributes to the development of anemia during the ICU stay. Other factors that may lead to anemia in critically ill patients include reduced red blood cell (RBC) production, abnormal RBC maturation, decreased RBC survival, or excessive RBC destruction. This chapter reviews the possible etiologic factors of anemia with a special emphasis on the underlying pathophysiology of these factors.

2.1 Introduction

Anemia is a common occurrence in critically ill patients and is associated with considerable morbidity and worse outcomes [1, 2]. The prevalence of anemia among critically ill patients is influenced by factors that include patient case mix, illness severity, and preexisting comorbidity [3]. A cohort study of 3,534 patients admitted

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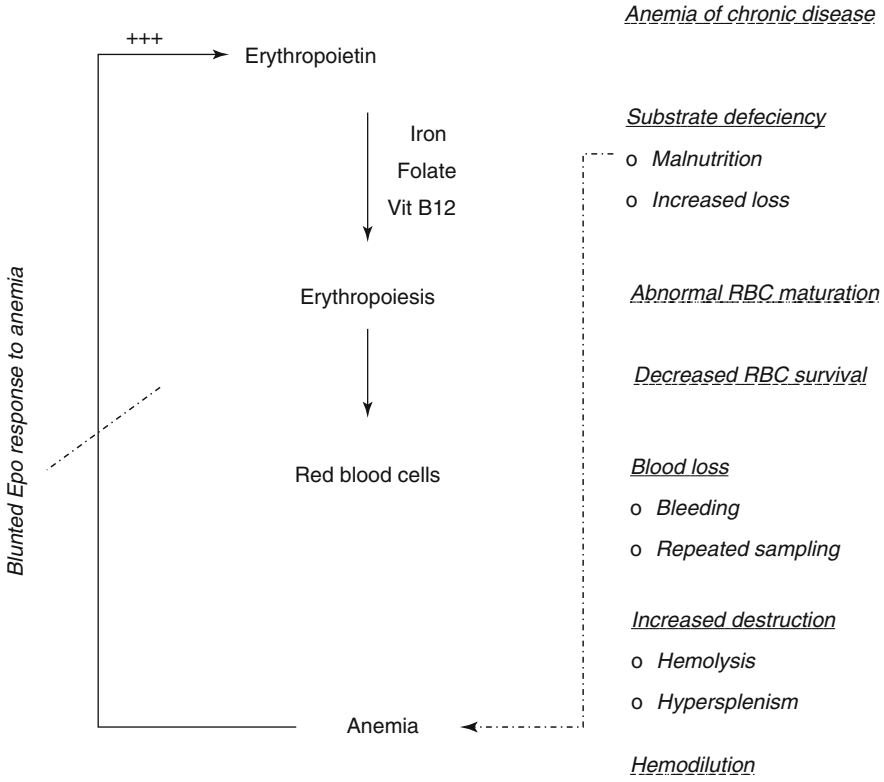

Fig. 2.1 Schematic diagram demonstrating the possible causes of anemia in critically ill patients

to Western European intensive care units (ICUs) reported that 63 % of patients had a hemoglobin concentration <12 g/dl at ICU admission and 29 % had hemoglobin concentrations <10 g/dl [1]. In this study, anemia was more frequent and severe in older patients. During the ICU stay, hemoglobin concentrations decreased on average by 0.66 g/dl/day for the first 3 days and by 0.12 g/dl/day thereafter. An early rapid decrease in hemoglobin values was also reported in a prospective observational single-center cohort study of patients present for more than 24 h in the ICU [4]. Another study found that 77.4 % of all ICU survivors were anemic (defined as hemoglobin concentration < 13 g/dl for men and < 11.5 g/dl for women) when discharged home from the hospital and 32.5 % had a hemoglobin concentration <10 g/dl. Fifty percent of patients who spent >7 days in the ICU had hemoglobin concentrations <10 g/dl at hospital discharge [5].

Several factors contribute to anemia in critically ill patients (Fig. 2.1). The etiology of anemia in individual patients is commonly multifactorial [3] and may be related either to the underlying disease process or occur as a consequence of diagnostic or therapeutic interventions in the ICU. The most important factors are discussed in the following section.

2.2 Anemia of Chronic Disease

Anemia of chronic disease (ACD) is a common form of anemia that occurs in patients suffering from longstanding and/or advanced chronic disease [6]. Patients can be considered to have ACD when they present the following: (1) a chronic infection or inflammation, autoimmune disease or malignancy or renal disease; (2) a hemoglobin concentration <13 g/dl for men and <12 g/dl for women; and (3) a low transferrin saturation (<20 %), but normal or increased serum ferritin concentration (>100 ng/ml) or low serum ferritin concentration (30–100 ng/ml) [7]. Measurement of reticulocyte counts, endogenous erythropoietin (EPO) secretion (ratio of observed EPO to expected EPO), and serum creatinine (glomerular filtration) may be helpful in defining the cause of ACD. Because critically ill patients often have multiple comorbidities, this type of anemia may contribute to the prevalent low hemoglobin levels described on admission to the ICU in large epidemiologic studies [1, 2]. Fifty percent of patients admitted to ICUs with hemoglobin concentrations <10 g/dl have a history of either acute bleeding or ACD [1].

2.3 Blood Loss

Blood loss is a significant cause of anemia in intensive care patients. Potential sources of blood loss are diagnostic blood sampling and hemorrhage.

2.3.1 Phlebotomy Losses

Early studies found that, on average, a critically ill patient lost 1–2 units of blood through blood sampling during their hospital stay or up to 30 % of the total blood transfused in the ICU [8]. More recent data indicate that 30–40 ml are removed in blood samples per 24 h, with more blood sampled in sicker patients and those receiving renal replacement therapy [1]. Laboratory testing plays a critical role in diagnosis and guiding appropriate patient management during critical illness; a recent study in trauma patients suggested that laboratory testing is becoming more frequent with an increase in the number of blood tests ordered and blood volumes drawn in 2009 compared to 2004 [9].

2.3.2 Hemorrhagic Losses

There are many potential sources of bleeding in critically ill patients. Gastrointestinal bleeding may play a less important role than in the past with more widespread use of prophylaxis and rapid resuscitation and management, but some groups of patients, for example, those receiving mechanical ventilation or with coagulopathy and renal failure [10], remain at higher risk of bleeding. A recent study in Australia and New Zealand reported that bleeding was the reason for transfusion in 46 % of transfusion events [11].

2.4 Reduced Red Cell Production

Red blood cell (RBC) production, or erythropoiesis, occurs in the bone marrow and is controlled by EPO, a 165 amino acid glycoprotein hormone produced by interstitial fibroblasts in the kidney [12]. EPO promotes the proliferation and differentiation of early erythroid progenitors in the bone marrow into mature erythrocytes. Effective erythropoiesis requires various factors, including iron, zinc, folate and vitamin B_{12}, thyroxine, androgens, cortisol, and catecholamines [13]. RBC formation occurs at a basal rate of 15–20 ml/day under physiological conditions but can increase up to tenfold after hemolysis or heavy blood loss [14].

2.4.1 Substrate Deficiency

Iron deficiency may play a major role in decreased RBC production in critically ill patients. Around 70 % of the iron in the body is located within RBC hemoglobin. The body absorbs 1–2 mg of dietary iron a day, which balances the iron lost through shed intestinal mucosal cells, menstruation, and other blood loss. Regulation of the absorption of dietary iron from the duodenum plays a critical role in iron homeostasis [15]. Most of the dietary iron is absorbed at the apical surface of duodenal enterocytes. Iron released into the circulation then binds to transferrin, which has two binding sites for one atom of iron each; about 30–40 % of these sites are occupied in normal physiological conditions. Transferrin carrying iron interacts with specific surface receptors (transferrin-receptor 1, TfR1) to form transferrin-receptor complexes that are endocytosed into the target cells. Erythroid precursors express high levels of TfR1 to ensure the uptake of iron.

Iron homeostasis can be disturbed by inflammation. Activation of the immune and inflammatory systems inhibits iron absorption and iron recirculation and increases ferritin synthesis and iron storage [16]. These effects lead to hypoferremia, iron-restricted erythropoiesis, and finally to mild to moderate anemia [17, 18].

Theoretically, vitamin B12 and folate deficiency may play a role in the development of anemia in ICU patients. However, the few data that are available suggest that these vitamins do not limit RBC production in most anemic critically ill patients [19].

2.4.2 Inappropriately Low Circulating Erythropoietin Concentrations

The normal response to anemia is an increase in EPO release from the kidneys. Values of circulating EPO concentrations have been established in otherwise healthy patients with various degrees of anemia [7]. Using these data as references for an appropriate response to anemia, many studies have shown that critically ill patients have inappropriately low EPO concentrations for their degree of anemia [20, 21]. The blunted EPO response during critical illness probably results from inhibition of the EPO gene by inflammatory cytokines [22, 23].

2.5 Abnormal RBC Maturation

Critical illness is often associated with increased concentrations of inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, particularly during sepsis. Many of these cytokines have been shown to directly inhibit RBC formation. Other circulating factors, such as interferon-γ, have been shown to induce apoptosis of erythroid precursors in experimental studies. In addition to the relative deficiency of circulating EPO and decreased iron availability, these factors help explain the poor erythroid response to anemia in critically ill patients. Bone marrow hyporeactivity is also suggested by the fact that reticulocyte counts are usually not increased in anemic critically ill patients unless pharmacological doses of EPO are being administered to stimulate erythropoiesis [19, 24].

2.6 Reduced Red Cell Survival

In healthy humans, erythrocytes have a lifespan of approximately 100–120 days. Normal RBC aging leads to changes in membrane characteristics with decreased deformability, loss of volume and surface area, increased cell density and viscosity, and alterations in the intracellular milieu [13]. These changes result in a decrease in cellular energy levels, increased hemoglobin-oxygen affinity, reduced ability to repair oxidant injury, and decreased ability of the cells to deform when passing through the microvasculature [25]. These changes also indicate that the RBCs are ready for removal by the spleen and reticuloendothelial system. Other determinants of RBC survival include the premature death of mature RBCs (eryptosis) and the removal of RBCs just released from the marrow (neocytolysis). Eryptosis, an apoptosis-like process, is thought to be, in part, triggered by excessive oxidant RBC injury and is inhibited by EPO, which therefore prolongs the lifespan of circulating RBCs [26]. Excessive eryptosis may lead to the development of anemia [27]. Neocytolysis is a process initiated by a sudden decrease in EPO levels by which young circulating RBCs are selectively removed from the circulation [28]. Eryptosis and neocytolysis act at different points in the lifespan of the RBC and thus provide a flexible means of controlling the regulation of total RBC mass.

The normal aging alterations in RBC rheology may occur earlier in critically ill patients, which may have clinical implications [29]. It is likely that critical illness and sepsis, in particular, reduce RBC lifespan, but there is as yet no direct evidence to support this. Experimental data have shown that inflammatory mediators, such as TNF-α and IL-1, can decrease erythrocyte survival time in other settings [30], and oxidative stress has been shown to induce premature apoptosis in RBCs [31].

2.7 Increased RBC Destruction

Hemolysis may be associated with several pathologic conditions, including hemoglobinopathies, hemolytic anemias, bacterial infections, malaria, and trauma. Hemolysis can also occur in conditions in which mechanical forces can lead to RBC

rupture, such as surgical procedures, hemodialysis, and blood transfusion. Extracorporeal circuits may lead to complete RBC destruction or cause less severe damage resulting in altered rheological properties. Hemolysis results in release of free plasma hemoglobin and heme, which are toxic to the vascular endothelium [32]. Although most RBC destruction in standard cardiopulmonary bypass procedures can be managed by the endogenous clearing mechanisms, in some cases, for example, in extensive surgery and with prolonged support, higher degrees of hemolysis may occur, and levels of plasma free hemoglobin can rise substantially. These patients are especially susceptible to the toxic influence of un-scavenged RBC constituents and the loss of RBC rheological properties [33].

Hypersplenism may also lead to excessive RBC destruction and is characterized by a significant reduction in one or more of the cellular elements of the blood in the presence of normocellular or hypercellular bone marrow and splenomegaly [34]. In patients with chronic liver disease, hypersplenism secondary to portal hypertension is an important cause of anemia. The main characteristics of hypersplenism are related to the presence of pancytopenia; hemolytic anemia occurs because of intrasplenic destruction of erythrocytes [35].

2.8 Hemodilution

Critically ill patients frequently develop intravascular hypovolemia requiring fluid resuscitation. Current management involves administering crystalloid or colloid solutions during resuscitation and withholding RBC transfusion unless there is severe hemorrhage. The resultant relatively modest hemodilution contributes to the rapid decrease in hemoglobin concentrations seen early after ICU admission in many critically ill patients [36] and can cause anemia without decreasing RBC mass.

2.9 Conclusion

Anemia is a common occurrence in critically ill patients and is associated with considerable morbidity and worse outcomes. The etiology of anemia in individual patients is commonly multifactorial. Understanding the possible etiologic factors of anemia is crucial to prevent its occurrence and identify the appropriate therapeutic approach to treat this condition in critically ill patients.

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