

Management of anemia among patients in intensive care units

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ABSTRACT

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Univ Med 2008; 27: 78-86.

Anemia is frequently encountered in critically-ill patients in the intensive care unit (ICU). Anemia may occur both at the time of admission, during treatment and after discharge from the ICU. The causes are multifactorial and include acute blood loss, blood loss from diagnostic testing and blunted red blood cell production. Blood transfusions are frequently given to patients in the ICU to treat low hemoglobin levels due to either acute blood loss or subacute anemia associated with critical illness. Although blood transfusion is a life-saving therapy, evidence suggests that it may be associated with an increased risk of morbidity and mortality. A feature of anemia of critical illness is lack of appropriate elevation of circulating erythropoietin concentrations in response to physiological stimuli. One important concern is that anemia may not be well tolerated by a critically ill patient. A number of blood conservation strategies exist that may mitigate anemia in hospital patients and limit the need for transfusion. These strategies include the use of hemostatic agents, hemoglobin substitutes and blood salvage techniques, the reduction of blood loss associated with diagnostic testing, the use of erythropoietin and the use of restrictive blood transfusion triggers. In this article we review the prevalence of anemia during critical illness specifically among patients in the ICU, and discuss the various factors that contribute to its development, the prevention and treatment of anemia by appropriate red cell transfusion and the place of erythropoietin in treatment.

Keywords : Anemia, blood transfusion, critically ill, hemoglobin, hematocrit

INTRODUCTION

Anemia frequently accompanies critically-ill patients under treatment in the intensive care unit (ICU).^(1,2) More than 85% patients or approximately five in six patients treated in the

ICU for more than 1 week requires daily blood transfusion because of anemia.⁽²⁾ Two observational studies reported that 35 to 45% of patients admitted to the ICU receive transfusions of almost 5 red-cell units while in the ICU.^(3,4) However, the view that red-cell

transfusion is beneficial for critically ill patients has been questioned because of data suggesting that red-cell transfusion may decrease the likelihood of survival in critically ill adults.^(5,6) The anemia in critically-ill patients is not exclusively due to loss of blood, as there are a number of reciprocally interacting factors playing a causative role.⁽¹⁻³⁾ Impaired production of red cells contributes to the development and persistence of anemia.

Anemia is defined by a hemoglobin (Hb) concentration below normal, when factors such as age, gender, pregnancy and environment (elevation above sea level) have been taken into account.⁽¹⁾ According to the World Health Organization (WHO), anemia is defined by a Hb level of <13 g/dL (hematocrit/Hct <39%) in adult men and <12 g/dL (Hct <36%) in adult non-pregnant women.⁽⁷⁾ Anemia is usually assessed by measurement of Hb or Hct levels, which indicate the relationship between red cell count and blood plasma. In critically-ill patients there are a large number of factors influencing both components, so that the prevalence of anemia in these patients requires a more precise interpretation in connection with therapy and pathophysiology.^(1,3)

Factors affecting the prevalence of anemia among critically-ill patients include the underlying disease, its severity, and aggravating factors. Based on the time of occurrence of the anemia, these patients may be subdivided into three groups, i.e. anemia at the time of admission, during ICU treatment and after treatment.

ANEMIA IN CRITICAL ILLNES

Characteristics

Production of RBCs by the bone marrow is impaired in critically ill patients and this phenomenon contributes to both the development and, more importantly, the persistence of

anaemia. Critically ill patients are anemic early in their ICU course and hemoglobin levels fall during the ICU stay.⁽³⁾

The prevalence of anemia on admission into the ICU turns out to be relatively high, as about 20-30% of patients experiences moderate to severe anemia with Hb levels of <9 g/dL.^(1,3) There are three sufficiently large studies on the prevalence of anemia in patients at the time of admission into the ICU, as follows: (i) Vincent et al. in their cohort study obtained a mean Hb level of approximately 11.3 g/dL, while around 29% of patients had a Hb level of <10 g/dL on admission to the ICU;⁽³⁾ (ii) Corwin et al. found a mean Hb level of approximately 11 g/dL in patients admitted to the ICU, and almost two-thirds of patients had a Hb level of <12 g/dL;⁽⁴⁾ (iii) Walsh et al., reported in a cohort study on patients admitted to the ICU that the patients showed a mean Hb level of around 10.5 g/dL, while about 25% of those patients had a Hb level of <9 g/dL.⁽⁸⁾

According to Nguyen et al. among ICU patients who didn't get transfusions, there was a mean reduction in Hb levels of 0.52 g/dL/day.⁽⁹⁾ A study showed that on average there was a reduction in Hb levels of 0.66 g/dL/day in the first three days and 0.12 g/dL in subsequent days. A notable reduction in Hb levels in the first days of ICU treatment was also seen in the CRIT study, where the mean Hb level of patients decreased from 12 g/dL at the time of admission to 11 g/dL at day 3-4, while afterwards the decrease would slow down.⁽¹⁰⁾

Walsh et al. estimated that moderate to severe anemia (Hb level <9 g/dL) within the ICU treatment period occurred in about 40-50% of the population. When anemia did not arise at the time of admission to the ICU, then in some patients it would soon occur within the first 2-3 days. In addition, they found that anemia occurring during ICU treatment remained constant until the patients were discharged from

the ICU, except when the patients received blood transfusion during ICU treatment.⁽¹⁾

The prevalence of anemia in patients convalescing from critical illness is still little known. A study in England on 283 patients receiving conditional transfusion during ICU treatment (transfusion if Hb = 7 g/dL) and after discharge from the ICU, showed that around 77.4% of patients suffered from anemia, with Hb levels below 10 g/dL in 32.5%, while 11.3% had levels of less than 9 g/dL. Above data indicate that the probability of anemia remains constant for a period of time after the patients have been discharged from the ICU.⁽¹⁾

Causes

Critically ill patients with anemia may be placed into two categories, i.e. patients suffering from anemia prior to admission to the ICU, and patients developing anemia during treatment in the ICU. Critically-ill patients often experience hypovolemia requiring fluid resuscitation in the

initial days of treatment. Currently the fluids given for resuscitation are crystalloids or colloids, while transfusion is restricted, except in patients with severe hemorrhage and Hb <7 g/dL.⁽¹⁻³⁾ Consequently there will be a change in blood plasma volume relative to red cell volume (RCV), effecting a reduction in Hb level, especially during fluid resuscitation. (Figure 1)

Loss of blood

Loss of blood is one of the main causes of anemia in critically ill patients. According to von Ahsen et al., based on their study on Hct level, blood volume and criteria for transfusion, it is estimated that on average patients treated in the ICU experience a blood loss of >100 mL/day,⁽¹⁰⁾ where the primary sources of blood loss in particular are multiple collections of blood for diagnostic samples, and hemorrhage elsewhere in the body.^(1,2,10) However, critically ill patients often have elevated levels of factor VIII and von Willebrand factor, both induced bleeding.⁽¹¹⁾

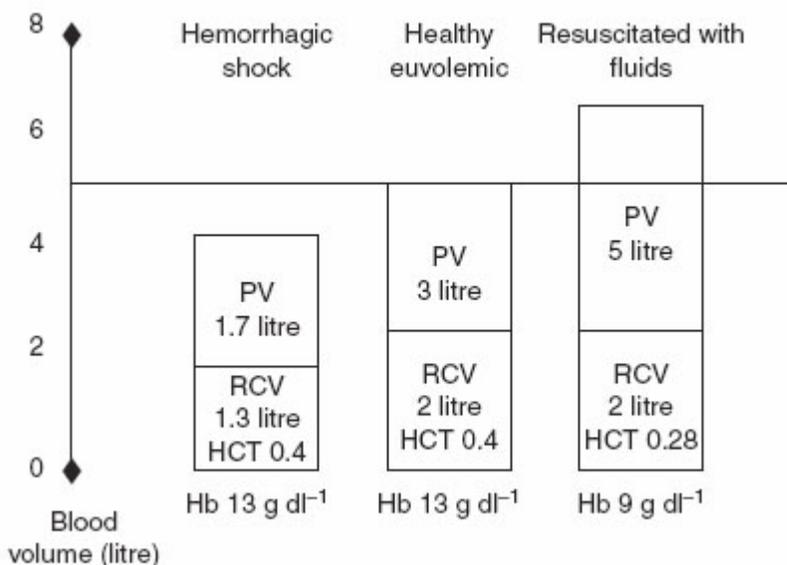


Figure 1. Relationship between red blood cell volume, plasma volume, hematocrit and hemoglobin concentration during hemorrhage, normovolemia and fluid resuscitation.⁽¹⁾

*PV = Plasma volume; RCV = red cell volume; HCT = hematocrit; Hb = hemoglobin concentration

Collection of blood for diagnostic samples plays a role in the development of anemia in patients treated in the ICU. A study showed about 30% of total blood transfusions is due to collection of blood for diagnostic purposes, with an average blood loss of around 40-70 mL/day.⁽¹²⁾ Loss of blood by this route occurs mainly within the first 24 hours of ICU treatment and will decline in the following days, in proportion to the need for routine blood examinations.^(3,12)

A potential source of hemorrhage in critically-ill patients is bleeding in the digestive tract, particularly in patients on ventilators, and in those with coagulation disorders and renal failure.^(1,2) According to Walsh et al., approximately 12% of patients under treatment in the ICU experience at least one significant episode of gastrointestinal tract hemorrhage (blood loss = 300 mL) and around 18% of patients require blood transfusion.⁽¹⁾

Reduction of red blood cells life span

Accurate data on the reduction in red cell life span in critically-ill patients, particularly those with sepsis, are still lacking, but there are a number of experimental data indicating that mediators of inflammation, such as tumor necrosis factor (TNF- α) and interleukin-1 (IL-1), and also free radicals, can cause premature red cell damage and programmed cell death (apoptosis).^(1,2,12,13)

Decreased production of red blood cells

There are a number of factors leading to a decreased in red cell production, *inter alia*: disordered iron metabolism, bone marrow depression, low erythropoietin levels and abnormal red cell maturation. The body normally responds to anemia by increasing red cell production, but in critically-ill patients this mechanism is inoperative. The pathophysiology of anemia in critically-ill patients is similar to

that in chronically-ill patients, especially the mechanism of inhibition of red cell formation (Figure 2).^(1,2,12,13)

Disorders of iron metabolism

The inflammatory process reduces the amount of serum iron available for erythropoiesis. In inflammation, most of the iron is located in the macrophages in the form of ferritin, resulting in a decrease in the total serum iron available to the erythropoietic process. This condition is known as functional iron deficiency.^(1,8,13)

According to Andrew et al, in patients with anemia due to chronic disease, inflammatory cytokines stimulate synthesis of hepcidin, a peptide produced by liver cells in response to interleukin-6 exposure. Hepcidin plays an important role in the regulation of iron metabolism by increasing the retention of iron in macrophages, hepatocytes and enterocytes through inhibition of iron ion efflux via ferroportin (see Figure 2). In addition, hepcidin may also inhibit absorption of iron in the digestive tract.^(8,10,12) Although an identical mechanism has still to be demonstrated in critically-ill patients, administration of supplementary iron by the intravenous and oral routes does not lead to increased red cell production.^(8,10,12)

Low erythropoietin levels in the circulation

The normal body response to anemia is to increase erythropoietin release from the kidneys. However, in critically-ill patients erythropoietin response to anemia is inadequate, due to inhibition by inflammatory cytokines.^(1,2,13)

Low erythropoietin levels in the circulation will cause decreased red cell production. It is this factor that causes the occurrence of anemia or the aggravation of existing anemia in critically-ill patients.

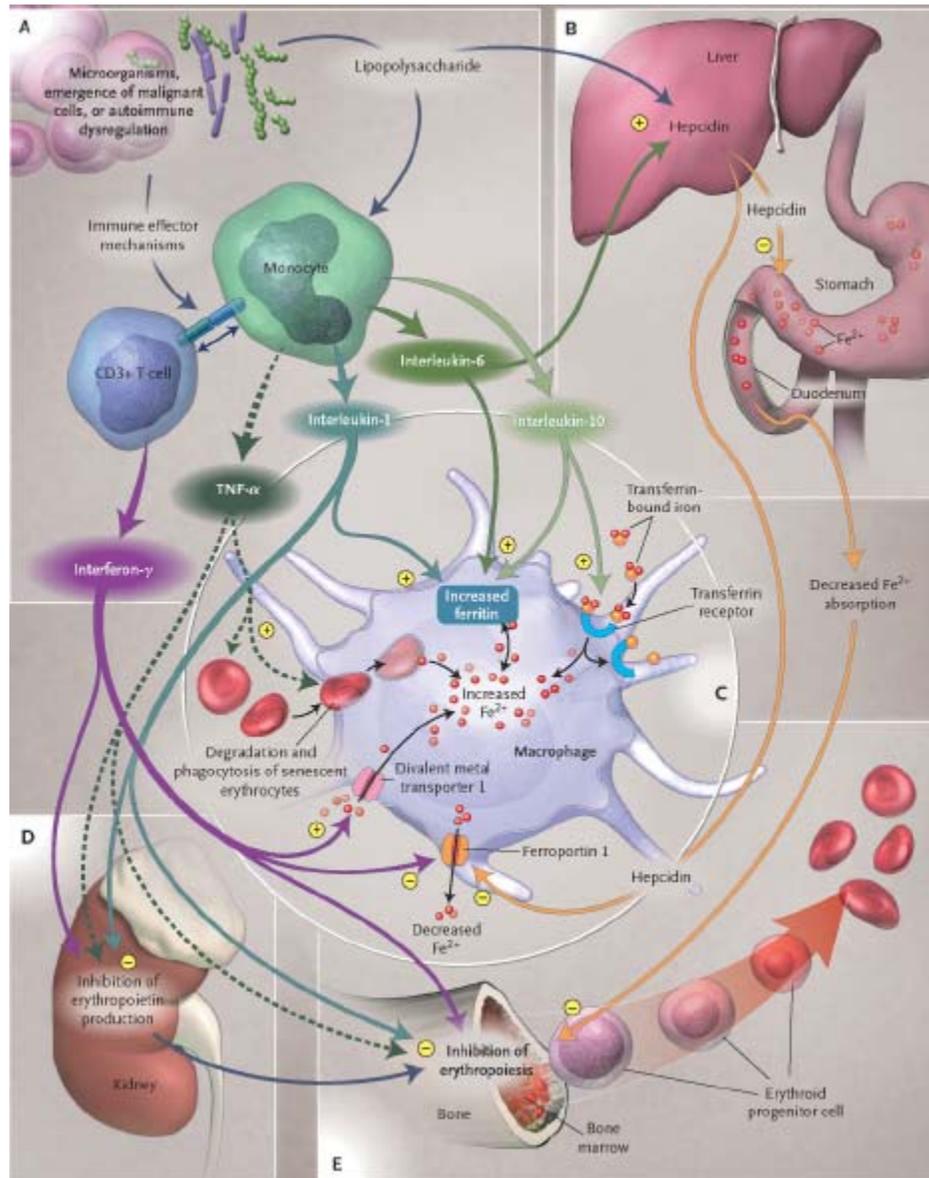


Figure 2. Pathophysiology of anemia of chronic disease. **Panel A.** Invasion of microorganisms, malignancies or autoimmune disorders activate T cells (CD3+) and monocytes. These cells produce cytokines such as tumor necrosis factor (TNF- α), interleukin-1, interleukin-6 and interleukin-10. **Panel B.** Interleukin-6 and lipopolysaccharide stimulate expression by hepatic cells of hepcidin, an acute-phase protein which inhibits absorption of iron in the duodenum. **Panel C.** Interferon- γ and liposaccharide increase expression of divalent metal transporter 1 on macrophages. The anti-inflammatory cytokine interleukin-10 increases ferrous ion uptake of transferrin-bound iron into monocytes. These mechanisms result in a decreased iron concentration in the circulation and lead to accumulation of iron in macrophages in the form of ferritin. **Panel D.** TNF- α and interferon- γ inhibit the production of erythropoietin in the kidneys. **Panel E.** TNF- α , interferon- γ and interleukin-1 directly inhibit differentiation and proliferation of erythroid progenitor cells. All of the above mechanisms in concert cause the development of anemia.⁽¹³⁾

Abnormal red cell maturation

Mediators of inflammation, such as tumor necrosis factor- α (TNF- α), interleukin-1 and interleukin-6, will increase in critically-ill patients, especially those with sepsis. These mediators have been proven to inhibit maturation of red blood cells. Moreover, in experimental studies the existence of interferon- γ capable of stimulating apoptosis of erythroid progenitor cells has successfully been demonstrated.^(1,2,13)

These factors, in combination with erythropoietin deficiency and functional iron deficiency, lead to an inadequate erythroid response to anemia.

MANAGEMENT

Reduction of blood loss in critical ill patients

Below is a list of measures for blood loss reduction in patients treated in the ICU:^(1,2,4) (i) avoidance of daily routine blood examination, blood chemistry and blood gas analysis, when unnecessary and without clinical indications; (ii) conversion of laboratory procedures by using microtubes to minimize the necessary blood volumes collected; (iii) use of diagnostic equipment requiring minimal blood samples, such as use of sticks in blood sugar determinations, etc.; (iv) use of monitoring equipment for alternative screening, such as pulse oxymetry for estimating oxygen saturation and arterial oxygen partial pressure, use of capnographs for determination of CO₂ partial pressure, etc.; and (v) prevention of stress ulcers in patients at high risk for gastro-intestinal hemorrhage, such as patients on mechanical ventilation, and those with renal failure and disorders of coagulation.

Blood transfusion

Red cell transfusion is one of the most rapid methods of anemia management for overcoming anemia and the most frequently applied in clinical practice. Although at present screening

tests for diseases transmitted through blood transfusions are increasingly being perfected, yet there are many harmful side effects of transfusions, particularly if inappropriately administered. Consequently, for blood transfusions to be right on target, it is necessary to pay attention to the criteria for starting blood transfusions and the targeted Hb levels in individual patients.⁽¹⁾ Red blood cells are often transfused to increase oxygen delivery and mitigate tissue ischemia; however, the ability of red blood cell transfusions to increase oxygen consumption has not been clearly demonstrated.

Critical Hb concentrations

Critical Hb concentrations are usually interpreted as Hb concentrations below the level where oxygen consumption will be dependent on supply, assuming that normovolemia is being maintained. This level has no absolute values, but differs in various organs and depends on the tissue metabolic activity and the capacity for oxygen extraction by the tissues.⁽¹⁾ A number of studies on human volunteers and on patients undergoing operations have acquired data showing that the critical Hb concentration in healthy and normovolemic individuals is around 4-5 g/dL, while hypoxia will be apparent at lower Hb levels.

Tolerable Hb concentrations in critically-ill patients

The Hb limits that is still tolerated by critically-ill patients depend on the balance between the risks of blood transfusions and the risks of low Hb levels themselves. There have been two relatively large-scale studies large showing the limits of Hb concentration still tolerated by patients with critical illness.

The Transfusion Requirements in Critical Care (TRICC) study divided the patients into two groups. The first group had as transfusion criterion a Hb level of <7 g/dL and a target Hb

level of 7-9 g/dL (restricted group), while the second group had a more liberal transfusion criterion, i.e. Hb level of <10 g/dL and target Hb level of 10-12 g/dL (liberal group). Between both groups there was no significant difference in mortality rate after 30 and 60 days of treatment. Even in the restricted group, patients <50 years old with the acute physiological and chronic health evaluation (APACHE II) scores <20 showed significantly lower mortality rates.⁽¹⁴⁾

Other study had used tissue hypoxia as a criterion for blood transfusion. The most frequently used parameters were tissue oxygen consumption, lactate concentration, mixed vein saturation and mixed vein partial pressure. The study showed that if the Hb level was >8 g/dL, administration of blood transfusion will not improve the above-mentioned indicators, as long as the patients were of normovolemic status.⁽¹⁵⁾ The above studies also confirm the results of the TRICC study that Hb levels of 7-9 g/dL were safe for the majority of patients with critical illness.

Criteria for transfusion in special patients

Although according to the TRICC study a Hb level between 7-9 g/dL is considered safe in the majority of critically-ill patients, there are some groups of patients that require a higher Hb level. Although still controversial, a list of such groups of patients is as follows:^(1,2,10,13) (i) patients with ischemic heart disease, most authorities suggest a Hb level of 7-8 g/dL as condition for starting blood transfusion with a target Hb of around 7-9 g/dL, except in cases of acute myocardial ischemia, when the criteria for starting blood transfusion will be higher, viz. blood transfusion is administered at a Hb level of 8 g/dL, with a target Hb level of >9 g/dL;^(1,13,15) (ii) for patients with sepsis, early goal-directed therapy (EGDT) carried out in the early stages has been proven to significantly reduce

the mortality rate. One of its algorithms uses a central vein oxygen saturation of <70% as indication for taking interventional measures, e.g. by maintaining the HCT = 30% and Hb = 10 g/dL.^(1,14,15)

Although it is still unclear which of the two components is responsible for the reduction of mortality rate in these patients, in general patients on EGDT will receive more blood transfusions. To date there is a consensus of opinion that in patients with sepsis the target Hb level should be 10 g/dL (HCT = 30%), if the central venous oxygen saturation < 70%.^(10,15,16)

Erythropoietin

The low endogenous erythropoietin response to anemia in critically-ill patients makes administration of exogenous erythropoietin one of the therapeutic alternatives. In critically-ill patients with multiple organ damage, recombinant human erythropoietin (rHuEPO) is capable of stimulating erythropoiesis.^(1,2,13,14) Erythropoietin acts as a cytokine with antiapoptotic activity.⁽¹⁷⁾ In this role, erythropoietin has been shown in preclinical and small clinical studies to protect cells from hypoxemia and ischemia. Multiple tissues express erythropoietin and the erythropoietin receptor in response to stress and also to mediate local stress responses. These nonhematopoietic activities of erythropoietin in the protection of cells suggest a role for erythropoietin in critically ill patients.⁽¹⁷⁾ There have been two clinical studies showing the success of erythropoietin use in critically-ill patients. Corwin et al. in their most recent study using recumbent human erythropoietin (rHuEPO) in doses of 40,000 units weekly for 4 weeks combined with oral iron supplementation, obtained a lower percentage of patients requiring red cell transfusion during the first 28 days in the group on rHuEPO, in comparison with the placebo group (50.5% vs 60.4%, $p < 0.001$).⁽¹⁸⁾ Corwin et al in their study showed that the use of

40,000 U epoetin alfa weekly, for a maximum of 3 weeks does not reduce the incidence of red-cell transfusion among critically ill patients, but may reduce mortality in patients with trauma.⁽¹⁹⁾

The above-mentioned studies have proven that administration of erythropoietin is effective in increasing Hb levels in critically-ill patients; however, its wide-spread use is still constrained by the high cost. Consequently some authorities suggest the use of erythropoietin according to the following strategy:⁽²⁾ (i) administration of rHuEPO in doses of 30000 - 40000 U weekly; (ii) weekly administration of rHuEPO is started on admission for all critically-ill patients suffering from anemia, who have a good prognosis and estimated ICU treatment of >7 days; (iii) avoid using rHuEPO in patients with minimal survival chances, non-anemic patients and those with ICU treatment estimate of <7 days, such as in asthma, COPD, drug overdose, diabetic ketoacidosis, etc.; and (iv) re-assessment at day 4-7 for deciding whether or not to continue rHuEPO administration. It is necessary to determine whether there are clinical outcome benefits in critically ill patients admitted to either the ICU and/or long-term acute care facilities associated with the reduction in the exposure to RBC transfusion with erythropoietin administration.⁽²⁰⁾

CONCLUSIONS

Management of anemia in critically-ill patients may take the form of prevention of excessive blood loss due to diagnostic blood sampling, prevention of stress ulcers in patients at high risk, red cell transfusion and administration of erythropoietin. The benefits and costs of blood transfusions should be taken into account, considering that on the basis of a number of clinical studies it has been proven that critically-ill patients are well capable of tolerating a Hb level of around 7-9 g/dL.

Although the supporting data are not fully accurate, certain groups of patients, for example those with acute ischemic heart disease or sepsis, possibly require a higher Hb concentration.

Administration of erythropoietin may indeed increase Hb levels and reduce the need for blood transfusion, but currently its use is still constrained and requires a special strategy because of the relatively high price of the drug.

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