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Anemia in the critically-ill patient: An examination of the rationale for recombinant erythropoietin

BY JEFFREY M. SINGH, MD, FRCPC, AND RANDY S. WAX, MD, FRCPC

Anemia frequently complicates the course of patients admitted to the intensive care unit (ICU) and is a common cause for red blood cell (RBC) transfusion. The premise that low hemoglobin levels impair tissue oxygen delivery and result in increased morbidity and mortality often leads clinicians to administer RBC transfusions to correct anemia. However, there is a growing body of literature challenging the efficacy of RBC transfusions to reduce tissue dysoxia and resultant morbidity since they carry the risk of significant morbidity and have a detrimental effect on immune status. In 1989, recombinant human erythropoietin (rHuEPO), the endogenous human peptide hormone responsible for stimulation of erythropoiesis, was introduced. With proven benefit and efficacy in the treatment of anemia related to several other medical conditions, rHuEPO has also become standard in the treatment of anemia associated with end-stage renal disease, cancer, and the human immunodeficiency virus (HIV). The availability of rHuEPO has led to the intriguing possibility of using it to treat or prevent anemia in the ICU setting. This issue of *Critical Care Rounds* reviews the rationale supporting the use of rHuEPO in anemic, critically-ill patients, and recent developments in the published literature regarding its use in this population.

The burden of anemia in the intensive care unit

Anemia is an extremely frequent finding in patients admitted to the ICU. Regardless of their admitting diagnosis and pathology, almost all patients with a prolonged ICU stay will have reduced hemoglobin concentrations. One prospective study found that >50% of patients admitted to a medical ICU for >3 days were anemic.¹ A recent observational study found that 63% of patients had an admitting hemoglobin level <120 g/L and 29% of patients had a value <100 g/L.² Furthermore, the majority of patients will have further reductions in their hemoglobin concentrations and subsequent red blood cell transfusions throughout the course of their ICU stay. By ICU day 3, approximately 95% of patients have hemoglobin concentrations below normal.³ The prevalence of anemia in the ICU is also reflected in the high number of RBC transfusions administered to critically-ill patients. Transfusion rates of 25%-44% have been reported, depending on the type of ICU and patient population studied.^{1,2,4,5} One study found that 85% of patients admitted to the ICU for >1 week received at least 1 RBC transfusion, with the majority of transfusions administered in the second week of ICU stay or later.³

Etiology of critical illness anemia

Anemia in the ICU is multifactorial, with an underlying perturbation of the normal equilibrium between RBC loss and destruction, the lifespan of circulating RBCs, and the rate of erythropoiesis.



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Blood loss

Patients may have blood loss secondary to the illness or surgery precipitating their admission to the ICU. Although blood loss is an important cause of anemia in post-operative or trauma patients, the majority of patients in a medical-surgical ICU do not have overt hemorrhage significant enough to account for the observed degree of anemia. In one study, almost 50% of patients with admitting hemoglobin levels <100 g/L had neither a history of anemia nor acute bleeding,² while another found that there was little difference between patients who had acute bleeding and those who did not in the overall calculated blood lost during ICU admission.¹ In fact, only a minority of RBC transfusion is associated with acute clinical bleeding, which further undermines the role of overt hemorrhage in the pathogenesis of anemia in the ICU.³

Once admitted to the ICU, ongoing blood losses are common and can relate to diagnostic phlebotomy, procedural losses, surgery, and gastrointestinal bleeding. Phlebotomy in the ICU has the potential to account for a significant blood loss, although the degree to which it contributes to overall blood loss remains controversial. Earlier studies have estimated that diagnostic blood loss accounts for as much as 60-70 cc/day.⁶ Recent studies have suggested that losses from diagnostic phlebotomy are much smaller due to judicious use of blood tests and technical improvements allowing for small blood sample volumes.⁷ Procedural losses are also common; one study found that patients requiring dialysis or hemofiltration had a 5.8-fold higher estimated blood loss compared with patients not requiring renal replacement.¹

Reduced red cell lifespan

Little is known of the intravascular lifespan of RBCs in the critically-ill patient, but decreased lifespan has been proposed as a contributing factor for anemia in the ICU. Signs of intravascular hemolysis are not often found in ICU patients, although RBC destruction may be mediated by systemic inflammation and enhanced complement activity. The entity known as anemia of chronic disease or anemia of inflammation may bear a common pathophysiology to that seen in the ICU. In anemia of chronic disease, RBC lifespan is reduced to 60-90 days.^{8,9} Enhanced RBC clearance by activated macrophages is thought to be a major cause of the abbreviated RBC lifespan.¹⁰

Impaired RBC production

Under normal circumstances, blood loss or a decrease in RBC lifespan is offset by an adaptive increase in serum erythropoietin (EPO) levels with a subsequent increase in erythropoiesis. In the ICU patient with critical illness anemia, there is a failure to mount a compensatory erythropoietic response, manifested clinically by low reticulocyte counts, a lack of immature RBC precursors, and

decreased hemoglobin concentrations.^{1,11} This failure of the erythropoietic response is currently thought to have at least 4 contributing factors:

- direct inhibition of erythropoiesis by circulating inflammatory mediators
- a reduction in available iron for erythropoiesis
- inappropriately low serum EPO levels
- blunted EPO response in RBC precursor cells.

Many patients admitted to the ICU have high-level systemic inflammation. Circulating inflammatory mediators (eg, IL-6, IL-1 and TNF- α) have been shown to depress RBC production by directly interfering with RBC progenitor proliferation and maturation,^{12,13} or through interference with the hypoxia-inducible transcription factors that regulate EPO production.¹⁴

Reduced iron availability during states of acute inflammation is mediated by iron-binding proteins such as ferritin, transferrin, ovalbumin, and lactoferrin.¹⁵ In addition, the reticuloendothelial system increases iron uptake during the acute phase response to systemic inflammation, thus removing iron from the circulating pool.¹⁰ It has been hypothesized that the evolutionary origin of this hypoferremic state was part of a “nutritional immunity,” in which iron is withheld to inhibit bacterial growth.¹⁰ Multiple studies have reported iron indices in critically-ill patients identical to those seen in chronic inflammation, namely low serum iron, total iron binding capacity, iron saturation, but high serum ferritin levels,¹¹ leading some investigators to suggest that critical illness anemia may represent an acute form of chronic disease anemia.¹⁶ Additionally, many critically-ill patients may have other nutrient deficiencies that interfere with erythropoiesis, for example, up to 25% of patients in one study had low folic acid levels.¹

Depressed erythropoietin response

Many ICU patients have perturbations in their erythropoietic response to anemia, and several studies have evaluated the EPO response to critical illness anemia.^{1,11,17,18} Von Ahsen and colleagues reported a prospective observation study that evaluated the incidence and etiology of anemia in patients admitted to a medical ICU for ≥ 4 days.¹ They found lower endogenous EPO levels than were expected for the degree of anemia or than seen in iron deficiency anemia with comparable hemoglobin levels.

Rogiers et al carried out a study exploring the relationship between EPO levels and hematocrit in 36 critically-ill patients, comparing them to a group of ambulatory patients with anemia (with serum ferritin < 100 $\mu\text{g/L}$, with no acute illness, and with no evidence of renal failure).¹⁸ Although EPO levels were higher in the critically-ill patients than in healthy non-anemic controls, they were considerably lower than in patients with iron-deficiency anemia and comparable hematocrits. A strong correlation

between EPO levels and hematocrit was observed in the control group, but this was not the case in the pooled group of ICU patients. In the subgroups of critically-ill patients, only patients with no sepsis and no renal failure had a significant correlation between EPO and hematocrit. The authors concluded that the endogenous EPO response to anemia is blunted in patients with critical illness and, in patients with sepsis, the correlation between EPO levels and hematocrit is virtually lost, irrespective of the presence of acute renal failure.

Red blood cell transfusions

RBC transfusions are commonplace in intensive care medicine, driven in part by the prevalence of anemia in critically-ill patients. Although a full review of the rationale, benefits, risks, and resultant controversy of RBC transfusions is beyond the scope of this article, there are several issues related to RBC transfusions that are important in the rationale for rHuEPO in the treatment of critical illness anemia.

Severe anemia in critically-ill patients is not benign; it carries with it substantial risks of morbidity and mortality. Anemia has been associated with increased mortality in critically-ill patients with cardiac disease.⁵ In patients undergoing aortocoronary bypass grafting, those with hematocrits <28% have been shown to suffer more adverse events and have a higher mortality.¹⁹ This increased morbidity with anemia has generally been ascribed to tissue hypoxia related to decreased oxygen delivery. In an attempt to increase oxygen delivery, historically, RBC transfusions have been administered to increase the hemoglobin concentration. Potential adverse effects from RBC transfusions include transmission of infectious disease, major ABO-incompatibility reactions, febrile, non-hemolytic transfusion reactions, and other immune-mediated complications such as transfusion-related acute lung injury (TRALI), and alloimmunization. RBC transfusions, even when leukocyte-depleted RBCs are administered, may have immunomodulatory and microcirculatory sequelae that may be detrimental to critically-ill patients.^{20,21}

Furthermore, the benefit from RBC transfusions has been called into question. Despite improvements in tissue oxygen delivery, transfusions did not improve peripheral oxygen consumption in patients with sepsis.^{22,23} Transfused allogenic red blood cells have impaired oxygen unloading to tissues (demonstrated by a “left-shift” of the hemoglobin-oxygen dissociation curve), decreased 2,3-diphosphoglycerate (DPG) levels, and decreased RBC deformability.²⁴ These abnormalities appear, at least in part, to be related to the storage period of the blood, with older blood demonstrating worse functioning. One study found that transfusing patients with blood that had been stored for longer periods was associated with increased splanchnic ischemia.²⁵

There are increasing clinical data casting doubt on routine transfusion of RBCs. A large multicentre observational study of transfusion practices noted that the number of RBC transfusions a patient receives is an independent risk factor for longer ICU length of stay, longer hospital length of stay, and risk of death.² It has been shown that the liberal transfusion of allogenic blood in patients undergoing surgery for colorectal cancer results in increased length of stay and increased hospital cost.²¹ A series of trauma patients who received blood transfusions were also found to have an increased incidence of multisystem organ failure.²⁶ A large, multicentre randomized, controlled trial demonstrated that in patients admitted to the ICU without cardiac disease, a restrictive RBC transfusion policy (maintaining hemoglobin levels between 70 and 90 g/L), was beneficial compared to a more liberal policy that maintained hemoglobin levels >100 g/L. Young patients and those who were less ill appeared to derive the most benefit from restricting blood transfusions.²⁷

In light of these adverse effects, an alternative to RBC transfusion in the management of anemia in critical illness is highly desirable. One recently explored alternative is the use of rHuEPO to stimulate erythropoiesis, thereby increasing hemoglobin levels. Several recent publications have examined the possible role of exogenous erythropoietin in reducing RBC transfusion requirements in critically-ill patients, as described below (Table 1).

Table 1: Studies on the use of rHuEPO in the critically-ill patient

Study	Lessons learned
von Ahsen et al ¹	<ul style="list-style-type: none"> • Anemia and red cell transfusion are common in the ICU • Anemia in the ICU is associated with low levels of endogenous erythropoietin
Rogiers et al ¹⁸	<ul style="list-style-type: none"> • Endogenous erythropoietin response to anemia is blunted in ICU patients • This loss of endogenous erythropoietin is more pronounced in patients with sepsis
van Iperen et al ¹¹	<ul style="list-style-type: none"> • The bone marrow of anemic, critically-ill patients is responsive to supraphysiologic doses of rHuEPO
Corwin et al ^{28,29}	<ul style="list-style-type: none"> • Administration of rHuEPO reduces transfusion requirements in a population of mixed ICU patients

rHuEPO = recombinant human erythropoietin ICU= intensive care unit

Response to supra-physiologic doses of rHuEPO

The fact that endogenous EPO response is blunted in critical illness anemia led to the hypothesis that pharmacologic doses of rHuEPO would help stimulate erythropoiesis. There was, however, initial concern that the failure of erythropoiesis was not only due to a relative EPO deficiency, but also to relative EPO resistance. Inflammation and infection are well-recognized causes of EPO resistance in patients with chronic renal failure treated with rHuEPO.

Van Iperen and colleagues studied endogenous EPO production and erythropoietic response to exogenous EPO in a mixed population of ICU patients.¹¹ Thirty-six patients with anemia (defined as Hb <112 g/L or <121 g/L in patients with cardiac disease) were enrolled and randomized to either folate supplementation, folate and iron supplementation, or folate, iron, and erythropoietin (300 units/kg on alternate days for 9 days). Clinical data, EPO levels, and laboratory markers of erythropoiesis were collected and the estimated blood loss including diagnostic phlebotomy was measured. Despite the small size of each subgroup (12 patients), several significant observations were made. Similar to the study of Rogiers et al, endogenous EPO levels were inversely related to the hemoglobin level and the EPO response to low hemoglobin levels was blunted compared to patients with other causes of anemia. The presence of acute renal failure did not affect the levels of endogenous EPO. Patients who received rHuEPO had significantly higher reticulocyte counts, although there was no difference between groups after 3 weeks. Despite increased markers of erythropoiesis in the rHuEPO group, there was no observed difference in hemoglobin or platelet counts throughout the duration of the study. The study, however, was not sufficiently powered to detect a small difference in transfusion requirements, and the 21-day observation period may have been too short to allow for clinical evidence of enhanced erythropoiesis. Iron indices were consistent with those previously observed in patients with severe systemic inflammation, although markers of iron-deficient erythropoiesis (zinc protoporphyrin) were significantly increased in the EPO group. These studies provide the rationale for clinical evaluation of rHuEPO in critically-ill patients with anemia.

Clinical experience with rHuEPO in the critically-ill patient

Two randomized, placebo-controlled trials have evaluated the use of rHuEPO in critically-ill patients. Corwin and colleagues carried out a preliminary study evaluating the efficacy of rHuEPO in a heterogeneous group of ICU patients.²⁸ This multicentre, random-

ized, placebo-controlled trial randomized patients to rHuEPO (300 units/kg daily for 5 days, then alternate days) or matching placebo (including iron supplementation for patients in both groups). Outcome measures, which were analyzed in an intention-to-treat fashion, were units of blood transfused and “transfusion independence” (those patients still alive and not having received a blood transfusion between days 8 and 42). Patients treated with erythropoietin received 45% fewer units of transfused RBCs (166 vs 305 units, $p<0.02$), and there was a trend towards greater transfusion independence. Erythropoietin therapy was generally well-tolerated with a non-significant, but higher incidence of thrombocytopenia and thrombocytosis in the treatment group.

A recent follow-up study randomly assigned 1302 patients admitted to the ICU for >3 days to receive rHuEPO (40000 u/wk) or matching placebo.²⁹ All patients received supplemental iron. The authors found that administering rHuEPO decreased exposure to allogenic RBC transfusions by 10% (60.4% placebo vs 50.5% rHuEPO, $p<0.001$). Administration of rHuEPO also decreased the number of RBC transfusions in those patients receiving blood. There were no differences in other clinical outcomes (mortality, ICU, or hospital length of stay), although the study was underpowered to detect differences in these outcomes. rHuEPO was well-tolerated, without a difference in adverse clinical outcomes. One of the major criticisms of this study has been that the transfusion trigger, set at a hemoglobin level of 85 g/L, was well above the level demonstrated to be safe by Hebert et al.²⁷ Although the level of 85 g/L likely represents the standard of practice at the centres involved in the study, it is interesting to note that a decrease in transfusion rates would also have been realized by dropping the transfusion trigger to 70 g/L. Also, only 13% of eligible patients were approached for consent, raising concerns regarding the widespread generalizability of this study.

Remaining controversies

The optimum dose and duration of rHuEPO therapy in the ICU remains unknown. It should be noted that the reviewed studies administered considerably higher doses of rHuEPO than those recommended for the management of anemia in other diseases. For example, the National Kidney Foundation-Dialysis Outcomes Quality Initiative (NKF-DOQI) recommends an initial rHuEPO dose of 80 to 120 units/kg/wk to treat anemia of end-stage renal disease.³⁰ Recent studies evaluating preoperative administration of rHuEPO to patients undergoing orthopedic surgery demonstrated efficacy at doses of 600 units/kg/week, and there is a suggestion that

300 units/kg/week may be effective. Given the considerable cost of rHuEPO, it is paramount that the lowest efficacious dose of rHuEPO be determined. It would also be desirable to prospectively identify patients who are likely to have prolonged ICU stays and anemia, in order to target rHuEPO therapy to those most likely to benefit. Incorporation of a strategy identifying individual patients who will not respond to rHuEPO could prevent prolonged administration of this drug at high cost with little benefit.

With such limited clinical experience, little is known about the incidence of adverse effects of rHuEPO therapy in a population of critically-ill patients, particularly at such high doses. The clinical studies evaluating ICU patients have not detected a significant difference in adverse event rates between high dose rHuEPO patients and patients receiving placebo, although these studies were not powered to do so.²⁹ Recent reports of pure red-cell aplasia following the development of anti-erythropoietin antibodies in patients treated with exogenous erythropoietin have alarmed clinicians caring for patients with chronic renal disease.³¹ This rare but devastating complication has now been reported worldwide with both epoetin alpha and epoetin beta, but not yet with the newer erythropoietin analogue darbepoetin.³¹ Although still an extremely rare event in patients treated chronically with rHuEPO, it will have to be weighed carefully before EPO is considered for widespread use in the treatment of critical illness anemia.

The cost-effectiveness of rHuEPO administration to avoid allogenic RBC transfusion is yet unproven. Although the cost of rHuEPO is high, it is small in comparison to the cost incurred by an infectious complication of an allogenic RBC transfusion, particularly with chronic diseases such as hepatitis C. One editorial estimated that 10 patients would have to be treated at US \$1200 each to save the cost of 1 patient being transfused during a 28-day period.³² This observation at least gives momentum for the evaluation of the cost-effectiveness of a transfusion-conserving strategy involving rHuEPO administration.

Conclusion

The reviewed studies complement each other in presenting a rationale for the administration of rHuEPO in the critically-ill anemic patient. Anemia is common in the ICU setting; it is usually multifactorial and associated with low endogenous EPO levels. The administration of exogenous EPO is associated with increased markers of erythropoiesis, suggesting that the critically-ill patient can respond to EPO. Finally, the 2 studies by Corwin and colleagues demonstrate that administration of rHuEPO reduces transfusion requirements in critically-ill patients.

There is a good physiologic rationale for the administration of exogenous erythropoietin in critically-ill patients to reduce anemia and exposure to allogenic blood transfusions. Studies evaluating clinically relevant outcomes are currently limited to 2 trials that demonstrated a reduction in transfusion requirements for ICU patients who were administered high doses of rHuEPO. Further investigation is required to confirm the clinical benefit and safety suggested by these early studies, as well as to identify the optimum dosing regimen and selection of patients. Although not indicated for generalized use in all critically-ill patients, rHuEPO may represent an additional tool for blood conservation, especially in patients who are expected to have a long ICU admission and are at risk for anemia.

Jeffrey M. Singh, MD, FRCP, is a Fellow in the Interdepartmental Division of Critical Care Medicine, University of Toronto.

Randy S. Wax, MD, FRCP, is a physician in the Interdepartmental Division of Critical Care Medicine, University of Toronto and the Critical Care Unit, Mount Sinai Hospital, Toronto.

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