Review

# Pathophysiology of intensive care unit-acquired anemia

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## Abstract

The formation of red blood cells (RBCs) in the bone marrow is regulated by erythropoietin in response to a cascade of events. Anemia in the intensive care unit can be caused by a host of factors. Patients in the intensive care unit may have decreased RBC production and a blunted response to erythropoietin. Administration of recombinant human erythropoietin may stimulate erythropoiesis, increase hematocrit levels and hemoglobin concentration, and reduce the need for RBC transfusions.

**Keywords** anemia, erythropoietin, intensive care unit, recombinant erythropoietin

Anemia is a common problem in intensive care unit (ICU) patients. Included among the numerous factors that may contribute to the development of anemia in critically ill patients are the following.

- Frequent blood sampling for measurements of arterial blood gases and other laboratory parameters.
- Clinically apparent and/or occult blood loss from the gastrointestinal tract due to erosive gastrointestinal mucosal disease or tissue trauma caused by suctioning of gastric contents.
- Blood loss at the time of surgical procedures preceding admission to the ICU.
- Blood loss due to trauma preceding admission to the ICU.
- Inappropriately low circulating concentrations of erythropoietin (EPO) [1–6], the main humoral regulator of red blood cell (RBC) production.
- Diminished responsiveness of bone marrow precursor cells to EPO, for example due to decreased availability of iron.

Erythropoietin is a glycoprotein that regulates RBC production by modulating the survival and proliferation of erythroid colony-forming units in the bone marrow. Diminished tissue oxygen tension is the primary stimulus for EPO release, and in humans, the kidney is the main organ responsible for EPO production. Tissue oxygen tension is thought to regulate EPO production via an oxygen-responsive transcription factor called hypoxia-inducible factor (HIF)-1 [7]. First identified by Semenza and Wang [8], HIF-1 is a heterodimeric transcription factor composed of a hypoxia-inducible HIF-1$\alpha$ chain and a constitutively expressed HIF-1$\beta$ chain. Although mRNA for HIF-1$\alpha$ is expressed at relatively high levels in normoxic cells, HIF-1$\alpha$ protein is present at extremely low levels under these conditions. In normoxic cells, newly synthesized HIF-1$\alpha$ is subjected to polyubiquitination and targeted for degradation in proteosomes. Thus, the half-life for this protein is very short, and its concentration under normoxic conditions is low. However, when cells become hypoxic, polyubiquitinization of nascent HIF-1$\alpha$ decreases, and cytosolic levels of this protein increase. HIF-1$\alpha$ combines with HIF-1$\beta$ to form the fully functional transcription factor, which is capable of binding to *cis*-acting regulatory elements in a number of hypoxia-responsive genes, including the gene for EPO. A phosphorylation event also may be important in the regulation of HIF-1 activity.

Numerous clinical studies support the notion that the EPO response to anemia is blunted in critical illness. Rogiers and coworkers [4] took serial measurements of serum EPO levels in 36 critically ill adults. Eighteen ambulatory patients with iron-deficiency anemia served as a control group. As expected, a significant inverse correlation between hematocrit values and EPO levels was observed in the control individuals ($r = -0.81$; $P < 0.001$). However, no such correlation was apparent for the critically ill patients ($r = -0.09$; $P =$ NS).

EPO = erythropoietin; HIF = hypoxia-inducible factor; ICU = intensive care unit; RBC = red blood cell; rHuEPO = recombinant human erythropoietin.

Krafte-Jacobs and coworkers [5] conducted a similar study, but they evaluated EPO levels in critically ill pediatric patients instead of adults. In 21 acutely anemic critically ill patients, the mean hemoglobin concentration was 7.8 ± 1.5 g/dl and the mean EPO level was 39 ± 62 mU/ml. In comparison, the mean hemoglobin concentration in 21 chronically anemic patients was 7.3 ± 1.3 g/dl and the mean EPO level was 861 ± 758 mU/ml. Similar findings were obtained in a third study conducted by Von Ahsen and coworkers [6]. Studying patients in a medical ICU, those investigators also found that EPO levels were inappropriately low for the degree of anemia in critically ill adults. In addition, they found that iron deficiency (plasma transferrin saturated $<20\%$) is also common in critically ill patients. Inappropriately low EPO levels persist for the duration of critical illness [3].

Although endogenous EPO levels tend to be low in ICU patients, these patients appear to retain their responsiveness to the hormone. Three randomized prospective trials [9–11] documented that administration of recombinant human erythropoietin (rHuEPO) can stimulate reticulocytosis and increase circulating hemoglobin concentration in critically ill adults. Those studies demonstrated that the cumulative number of units of packed RBCs transfused was significantly less in the rHuEPO group than in the placebo group [9–11]. The third study found that patients receiving rHuEPO were less likely to undergo transfusion [11].

Functional iron deficiency is a major cause for anemia in critically ill patients and in patients with anemia of chronic disease [4]. In both groups, laboratory studies typically reveal low serum iron concentration, low transferrin level, low transferrin saturation, and elevated serum ferritin concentration; these findings are consistent with an acute-phase response and inflammation [1,9,12]. Despite evidence of increased iron storage, circulating iron concentrations are low, and thus less free iron is available to support erythropoiesis [13]. Similar observations have been reported from studies of patients with multiple organ failure [14], victims of multiple trauma [2], and patients recovering from major surgery [15].

Low concentrations of vitamin $B_{12}$ and folic acid, which are essential for normal RBC development, also might contribute to ineffective erythropoiesis in critically ill patients. Von Ahsen and coworkers [6] observed normal vitamin $B_{12}$ levels but abnormally low folic acid concentrations in some anemic ICU patients. RBC size was not increased, and therefore the significance of folic acid deficiency as a factor contributing to ICU-acquired anemia remains uncertain. Recently, Rodriguez and colleagues reported iron deficiency in 9% of ICU patients [1]; 2% of the patients were deficient in vitamin $B_{12}$, and another 2% suffered from folic acid deficiency.

## Competing interests

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## References

1. Rodriguez RM, Corwin HL, Gettinger A, Corwin MJ, Gubler D, Pearl RG: **Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness.** *J Crit Care* 2001, **16:**36-41.
2. Hobisch-Hagen P, Wiedermann F, Mayr A, Fries D, Jelkmann W, Fuchs D, Hasibeder W, Mutz N, Klingler A, Schobersberger W: **Blunted erythropoietic response to anemia in multiply traumatized patients.** *Crit Care Med* 2003, **29:**743-747.
3. Elliot JM, Virankabutra T, Jones S, Tanudsintum S, Lipkin G, Todd S, Bion J: **Erythropoietin mimics the acute phase response in critical illness.** *Crit Care* 2003, **7:**R35-R40.
4. Rogiers P, Zhang H, Leeman M, Nagler J, Neels H, Melot C, Vincent JL: **Erythropoietin response is blunted in critically ill patients.** *Intensive Care Medicine* 1997, **23:**159-162.
5. Krafte-Jacobs B, Levetown ML, Bray GL, Ruttimann UE, Pollack MM: **Erythropoietin response to critical illness.** *Crit Care Med* 1994, **22:**821-826.
6. von Ahsen N, Muller C, Serke S, Frei U, Eckardt KU: **Important role of nondiagnostic blood loss and blunted erythropoietic response in the anemia of medical intensive care patients.** *Crit Care Med* 1999, **27:**2630-2639.
7. Bertges DJ, Fink MP, Delude RL: **Hypoxic signal transduction in critical illness.** *Crit Care Med* 2000, **Suppl:**N78-N86.
8. Semenza GL, Wang GL: **A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation.** *Mol Cell Biol* 1992, **12:**5447-5454.
9. van Iperen CE, Gaillard CA, Kraaijenhagen RJ, Braam BG, Marx JJ, van de Wiel A: **Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients.** *Crit Care Med* 2000, **28:**2773-2778.
10. Corwin HL, Gettinger A, Rodriguez RM, Pearl RG, Gubler KD, Enny C, Colton T, Corwin MJ: **Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial.** *Crit Care Med* 1999, **27:** 2346-2350.
11. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Shapiro MJ, Corwin MJ, Colton T; EPO Critical Care Trials Group: **Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial.** *JAMA* 2002, **288:**2827-2835.
12. Baumann H, Gauldie J: **The acute phase response.** *Immunol Today* 1994, **15:**74-80.
13. Weiss G, Wachter H, Fuchs D: **Linkage of cell-mediated immunity to iron metabolism.** *Immunol Today* 1995, **16:**495-500.
14. Gabriel A, Kozek S, Chiari A, Fitzgerald R, Grabner C, Geissler K, Zimpfer M, Stockenhuber F, Bircher NG: **High-dose recombinant human erythropoietin stimulates reticulocyte production in patients with multiple organ dysfunction syndrome.** *J Trauma* 1998, **44:**361-367.
15. van Iperen CE, Kraaijenhagen RJ, Biesma DH, Beguin Y, Marx JJ, van de Wiel A: **Iron metabolism and erythropoiesis after surgery.** *Br J Surg* 1998, **85:**41-45.