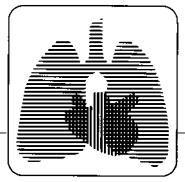

critical care reviews

Anemia, Allogenic Blood Transfusion, and Immunomodulation in the Critically Ill*

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Anemia and allogenic RBC transfusions are exceedingly common among critically ill patients. Multiple pathologic mechanisms contribute to the genesis of anemia in these patients. Emerging risks associated with allogenic RBC transfusions including the transmission of newer infectious agents and immune modulation predisposing the patient to infections requires reevaluation of current transfusion strategies. Recent data have suggested that a restrictive transfusion practice is associated with reduced morbidity and mortality during critical illness, with the possible exception of acute coronary syndromes. In this article, we review the immune-modulatory role of allogenic RBC transfusions in critically ill patients. ***(CHEST 2005; 127:295–307)***

Key words: blood transfusion; critically ill; ICU; immune modulation; infections; microchimerism; nosocomial infection

Abbreviations: APC = antigen-presenting cell; CABG = coronary artery bypass graft; CI = confidence interval; CJD = Creutzfeldt-Jakob disease; CMV = cytomegalovirus; EPO = erythropoietin; GVHD = graft-vs-host disease; HLA = human leukocyte antigen; IL = interleukin; MHC = major histocompatibility complex; SEN-V = SEN virus; TAGVHD = transfusion-associated graft-vs-host disease; Th = T helper; TNF = tumor necrosis factor; TRALI = transfusion-related lung injury; TRIM = transfusion-induced immunomodulation; TTV = TT virus

In recent years, blood transfusion requirements have been increasing due to the increasing burden of chronic disease in an aging population, improvement in life-support technology, increasing severity of illness in patients treated in the ICU, and other blood-intensive surgical procedures.[1,2] On the other hand, there is a trend toward decreasing blood donation and increasing cost due to the requirement for rigorous screening for transmittable infectious agents. In the United States alone, nearly 15 million U of blood are donated and 14 million U are transfused annually.[2] On average, 16% of patients in medical ICUs and 27% of those in surgical ICUs receive transfusions every day in the United States.[3] In one series,[4] 85% of patients with an ICU length of stay of > 1 week received at least 1 U of blood, with these patients receiving, on average, 9.5 U during their ICU stay. For decades, blood donation and transfusion were considered to be a life-saving strategy, and an arbitrary threshold of 10 g/dL was used as a transfusion trigger in critically ill patients.[5] However, it has become evident that blood transfusion has immunomodulating effects that may increase the risk of nosocomial infections and cancer recurrence, and the possible development of autoimmune diseases later in life.[6–10] Furthermore, the risk of "newer" transfusion-transmitted diseases has become recognized. Consequently, the safety of blood transfusions has been questioned and has led to a reevaluation of our blood transfusion practice.

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Anemia and Critical Illness

"Anemia of critical illness" is a common problem in the ICU. More than 90% of critically ill patients have subnormal hemoglobin levels by the third day of ICU admission.[11] In one series,[12] the mean hemoglobin level of patients admitted to the ICU was

11.3 g/dL, with 29% having a hemoglobin level of < 10 g/dL. Although anemia often results in extensive allogenic RBC transfusions among critically ill patients, there are insufficient data in the literature to support this widespread practice.

The etiology of anemia of critical illness is multifactorial and complex. Repeated phlebotomy procedures, GI blood loss, and other surgical procedures contribute significantly to the development of anemia.[13,14] Critically ill patients lose approximately 25 to 40 mL blood daily through phlebotomy, and patients with indwelling arterial catheters lose approximately 900 mL blood during their ICU stay.[9,15,16] Other important contributing factors that exacerbate anemia in critically ill patients include coagulopathies, pathogen-associated hemolysis, hypoadrenalism, and nutritional deficiencies.[17–19]

RBC production in critically ill patients is often abnormal, and is involved in the development and maintenance of anemia. The pathophysiology of this anemia is complex, and includes the decreased production of erythropoietin (EPO), impaired bone marrow response to EPO, and reduced RBC survival.[16] Critically ill patients have inappropriately low EPO concentrations, irrespective of the presence of acute renal failure.[20–24] The suppression of EPO production by EPO gene inhibition[25] and EPO resistance are mediated by a variety of inflammatory mediators.[26] Interleukin (IL)-1, and tumor necrosis factor (TNF)-α have been shown to inhibit EPO production.[27] Furthermore, IL-1, IL-6, and TNF-α suppress erythropoiesis by direct inhibitory effects on bone marrow RBC production, while these effects can be reversed by exogenous EPO administration.[28]

Decreased RBC synthesis and consequent anemia are also common during sepsis syndromes. Many ICU patients have low serum iron levels, total iron binding capacity, and elevated serum ferritin concentrations, suggesting the presence of "anemia of inflammation." Bacteria require iron for their growth, and several studies[29,30] have shown a link between iron and infection. It is therefore conceivable that the human host down-regulates iron metabolism and EPO synthesis as a component of nonspecific immunity during critical illness and sepsis. In addition, during sepsis low serum iron levels may also protect the host against iron-catalyzed oxidant cell damage.[31] As RBCs also require iron for growth and maturation, anemia during sepsis may represent an adaptive mechanism by the host to starve the pathogen of iron. Thus, anemia of critical illness may also be viewed as "anemia of immune activation" and may have evolved as a protective mechanism against foreign antigens.

The most important physiologic consequence of anemia is a reduction in the oxygen-carrying capacity of blood. These changes are accompanied by increased cardiac output, a shift of the oxyhemoglobin dissociation curve, and increased oxygen extraction. RBC transfusions in the past have been routinely employed to augment tissue oxygen delivery. Although RBC transfusions increase systemic oxygen delivery, the immediate effectiveness of stored RBC transfusions to augment tissue oxygen uptake has been questioned in several studies.[7,32,33] Furthermore, RBC transfusion has been associated with a higher incidence of postoperative infections and nosocomial ICU infections, and poorer outcome in critically ill patients.[34–37]

Trends in Transfusion Practice Among the Critically Ill

In a recent, large, multicentered observational study in the United States, Corwin et al[38] studied transfusion practices in 4,892 patients across 284 ICUs. Approximately 70% of patients who were admitted to the ICU had a baseline hemoglobin concentration of < 12 g/dL, and 44% of these patients received RBC transfusions. The mean (± SD) pretransfusion hemoglobin level was 8.6 ± 1.7 g/dL. The mortality rate was 10% for patients without transfusion, increasing to 25% for patients with ≥ 6 U transfused. Low hemoglobin levels were a common trigger for transfusion in approximately 90% of the patients, and the mean age of the RBCs transfused was 3 weeks; however, > 25% of transfused RBCs were > 1 month old.[38]

In an earlier, large, multicentered, Canadian prospective trial published in 1999, Hebert et al[39] demonstrated that maintaining a hemoglobin level in the range of 7 to 9 g/dL was superior to a hemoglobin level of 10 g/dL, thereby raising questions regarding the validity of the historical assumption that RBC transfusions are beneficial for critically ill patients. The investigators enrolled 838 patients from 25 centers over a period of 3 years. Only normovolemic, anemic (plasma hemoglobin concentration, < 9 g/dL) patients who were expected to stay in the ICU for > 24 h were included in the study. Important exclusion criteria were evidence of active bleeding (*ie*, > 3 U transfused over 24 h), chronic anemia (plasma hemoglobin concentration < 9 g/dL in the preceding month), and cardiac surgery. The enlisted patients were randomized to receive either a restrictive transfusion strategy (hemoglobin concentration transfusion trigger, 7 g/dL; maintenance hemoglobin concentration range, 7 to 9 g/dL) or a liberal transfusion strategy (hemoglobin concentration transfusion trigger, 10 g/dL; maintenance hemoglobin con-