Transfusion practice in the critically ill

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Background: **Anemia in the critically ill patient population is common. This anemia of critical illness is a distinct clinical entity characterized by blunted erythropoietin production and abnormalities in iron metabolism identical to what is commonly referred to as the anemia of chronic disease.**

Findings: **As a result of this anemia, critically ill patients receive an extraordinarily large number of blood transfusions. Between 40% and 50% of all patients admitted to intensive care units receive at least one red blood cell unit, and the average is close to five red blood cell units during their intensive care unit stay. There is little evidence that "routine" transfusion of stored allogeneic red blood cells is beneficial for critically ill patients. Most critically ill patients can tolerate hemoglobin levels as low as 7 mg/dL, so a more conservative approach to red blood cell transfusion is warranted.**

Conclusion: **Practice strategies should be directed toward a reduction of blood loss (phlebotomy) and a decrease in the transfusion threshold in critically ill patients. (Crit Care Med 2003; 31[Suppl.]:S668–S671)**

KEY WORDS: anemia; blood transfusion; erythropoietin

Red blood cell (RBC) transfusions date back to the mid-17th century, but it was not until the early part of the 20th century that RBC transfusion became a mainstay of clinical practice (1). The benefit of RBC transfusion in surgery, as well as in other clinical settings, was assumed, and RBC transfusion was viewed as relatively risk free. A dramatic change in thinking occurred in the early 1980s, primarily because of concerns of transfusion-related infection, particularly the human immunodeficiency virus (HIV). Although advances in transfusion medicine have greatly decreased the risk of viral transmission from blood transfusion, other issues related to the safety and efficacy of RBC transfusion now drive the debate over transfusion practice. Optimal RBC transfusion practice remains controversial. A tremendous variation in the indications for and timing of RBC transfusions still exists. The presence of a significant variation in RBC transfusion rates implies that the best practice has yet to be identified and that indications for transfusion are not consistent among providers. This review will focus on current issues related to transfusion practice.

Anemia of Critical Illness

Anemia is common in critically ill patients and appears early in their intensive care unit (ICU) course. By day 3 after ICU admission, almost 95% of patients are anemic (2–4). The anemia in these critically ill patients persists throughout the duration of their ICU and hospital stay, with or without RBC transfusion (CRIT). There are two main mechanisms that commonly contribute to anemia in the critically ill.

The first major factor contributing to anemia and the need for blood transfusions is phlebotomy. Smoller and Kruskall (5) reported that almost one half of their ICU patients receiving blood transfusions were phlebotomized more than the equivalent of one unit of blood. The ICU patients in this study were phlebotomized an average of 65 mL per day. Phlebotomy blood losses in this range are consistent with other reports of critically ill patients over the last two decades and are often associated with the development of anemia (6–8).

Phlebotomy still remains a significant source of blood loss in the ICU. A recent study of critical care practice in western Europe reported that phlebotomy blood losses averaged 41 mL/day (9). In general, patients in the ICU are phlebotomized twice as often and have three times as much blood drawn daily compared with patients on the wards (10). Patients who are phlebotomized less in the ICU receive fewer RBC transfusions (8). However, it is important to recognize that phlebotomy is not the only source of blood loss in the ICU, and occult blood loss unrelated to phlebotomy can contribute significantly to the anemia (11).

The second major mechanism for anemia in the critically ill patient is an inappropriately low production of red blood cells. It is now clear that excess phlebotomy by "medical vampires" is responsible for only a fraction of the blood transfusion requirements (12). Red cell production in critically ill patients is not normal, and decreased levels of RBC production is involved in the development and maintenance of anemia. There is a growing literature suggesting that the anemia observed in the critically ill is an underproduction anemia consistent with what is commonly referred to as the anemia of chronic inflammatory disease (13).

More than 90% of ICU patients have low serum iron, total iron binding capacity, and iron/total iron binding capacity ratio but have a normal or, more usually, an elevated serum ferritin level (3, 14). Similarly, low iron levels and elevated ferritin levels are observed in patients with multiple organ dysfunction (15). At a time when patients are anemic and the iron studies are abnormal, serum eryth-

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ropoietin levels are only mildly elevated, with little evidence of reticulocyte response to endogenous EPO (3). Rogiers et al. (16) compared EPO levels in critically ill patients with those in patients with iron deficiency anemia. Although EPO levels were somewhat elevated compared with adults without anemia, they were significantly lower compared with patients with iron deficiency anemia with similar levels of anemia. A comparably blunted EPO response to physiologic stimuli also has been reported in critically ill children (17).

This blunted EPO response observed in the critically ill appears to result from the inhibition of the EPO gene by inflammatory mediators (18, 19). It has also been shown that these inflammatory cytokines directly inhibit red cell production by the bone marrow and may produce the distinct abnormalities of iron metabolism (20, 21). Levels of interleukin interleukin-1 are elevated in patients with rheumatoid arthritis and are proportional to the degree of anemia. Interleukin-1 activates T-lymphocytes, which increase the production of interferon gamma that in turn directly inhibits red cell production *in vitro*. Likewise, levels of tumor necrosis factor are elevated in patients with inflammatory diseases, infectious diseases, and cancer. Tumor necrosis factor also inhibits erythropoiesis both *in vitro* and when administered to human beings (22). Thus, the anemia of chronic disease is an anemia from immune activation in reaction to new foreign antigens (bacteria, parasites, viruses, neoplasms), with the production of cytokines inhibiting the action of EPO on bone marrow cells and the production of EPO by the kidney, thereby producing an underproduction anemia. The anemia of critical illness can, therefore, be viewed as a distinct clinical entity, characterized by a blunted EPO production and abnormalities in iron metabolism identical to the anemia of chronic disease.

Transfusion Practice

The anemia observed in the critically ill results in an extraordinary number of RBC transfusions. Studies a decade ago found that 50% of all patients admitted to the ICU are transfused during their ICU admission (23). In the patients with a prolonged ICU length of stay (longer than 1 wk), 85% receive a transfusion (8). On average, these patients are transfused 9.5 units of RBCs during their ICU stay. These transfusions are not restricted to the early ICU course, and patients continue to have transfusions at a rate of two to three units per week. This same phenomenon was subsequently observed in ICUs across the country. In a descriptive study of critical care units in the United States, Groeger et al. (24) noted that on a single day, almost 14% of patients in critical care units are transfused (ranging from 4% in critical care units to 27% in surgical ICUs). Recent data suggest RBC transfusion rates remain high in the critically ill (4, 9)

In 2000–2001, an observational study of 4,892 patients (4) found that almost 50% of patients admitted to ICUs across the United States still receive transfusions. Initial RBC transfusion tends to occur early in the ICU stay, but there were ongoing RBC transfusions in these patients throughout their ICU stay. The mean pretransfusion hemoglobin observed, i.e., the "transfusion trigger," was 8.6 ± 1.7 g/dL, a value that is comparable with that described in earlier reports (8, 23). Interestingly, RBC transfusions were not restricted to the ICU. Thirteen percent of patients discharged from the ICU received almost three units following ICU discharge.

A similar observational study of transfusion practice in ICUs across western Europe has also been performed (9). Data were collected on 3,534 patients admitted to ICUs during a 2-wk period in late 1999. A total of 37% of patients were transfused with a mean of 4.8 RBC units while in the ICU, and 12.7% of patients were transfused in the post-ICU period, for a total of 42% of patients transfused during the 28-day study period. The mean pretransfusion hemoglobin level was 8.4 g/dL.

The similarity in the results of these two recent large observational trials is striking. These studies suggest that transfusion practice in response to the anemia of critical illness has changed little over the last decade. This is particularly surprising, given the scrutiny to which transfusion practice has been subjected during the last decade. In a prospective, randomized study of critically ill patients, Hebert and colleagues (25) demonstrated that maintaining hemoglobin levels above the 7 g/dL range is at least equivalent, and in some patients (Acute Physiology and Chronic Health Evaluation [APACHE] II, ≤ 20, or age, <55 yrs) superior, to maintaining hemoglobin levels above 10 g/dL with RBC transfusion. This finding also seemed to apply to most patients with cardiovascular disease, although patients with active ischemic cardiac disease may require a higher hemoglobin level (26). The studies by Hebert et al. and others (25–27) raised questions regarding the validity of the historic assumption that RBC transfusion was beneficial for critically ill patients with anemia. Recent recommendations advocate that automatic transfusion thresholds be abandoned in favor of a practice of RBC transfusion only for defined physiologic need (28, 29). However, the suggestion for a more conservative approach to RBC transfusion does not as yet appear to have resulted in any major alteration in practice patterns.

Variation in transfusion practice has been documented in several other clinical settings. In the coronary artery bypass graft surgery (CABG) population, a population that has been reported to consume up to 10% to 20% of national RBC transfusions (30), institutional RBC transfusion rates for elective primary CABG operations at 23 academic centers varied widely, from a low of 16% to a high of 90% of patients (31). In another study (32) in 18 institutions performing CABG surgery, the mean number of RBC transfusions ranged from 0.4 to 6.3 units per patient. The observed variation was not explained by patient or surgical variables, but rather by differences in transfusion practice. It was estimated that 15% of the RBC transfusions in this study were inappropriate (33).

The Collaborative Hospital Transfusion Study (CHTS) (34) also observed institution transfusion rates that ranged from 33% to 90% among males receiving internal mammary artery and venous conduits. Furthermore, CHTS documented a significant variation in the timing of these transfusions. In the hospital with the highest utilization rate, a high proportion of cases were transfused on the operative day. In contrast, at the hospital with the lowest utilization rate, $<20\%$ of transfusions were given on the operative day. CHTS also observed that the variation in transfusion practice did not differ significantly among surgeons within one hospital, with one exception. This suggests that the majority of surgeons are practicing similar transfusion policies within hospitals. The variability in RBCs transfusion practice among the five hospitals was ascribed to the unique process of care in each hospital.

Populations other than CABG patients have also been studied. Among non-ICU

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medical patients, 35% of RBC transfusions were judged either nonjustified or equivocal (35). The number of inappropriate transfusions in another study ranged from 4% to as high as 57% (36). In a study of ICU patients, almost one half of all transfusions, and almost two thirds of those for nonacute blood loss, were performed for either no identifiable indication or low hematocrit alone (8).

What determines whether a patient receives a blood transfusion? Salem-Schatz et al. (37) reported widespread deficiencies in physicians' knowledge of transfusion risks and indications. Physicians' confidence in their knowledge was negatively associated with actual knowledge. Senior physicians tended to have lower knowledge scores but were more confident, and they tended to influence the transfusion practice of the junior physicians. Therefore, it is not surprising that the variability in transfusion practice between individual physicians and institutions is striking. Decisions about transfusing RBCs are often made without a complete understanding of the risks and benefits of transfusion (37). Although a much clearer understanding of the risks of RBC transfusion has developed since the 1980s, the risks of anemia and the benefit of RBC transfusion are much less well characterized.

It has been observed in the ICU that pretransfusion hematocrit was the same, regardless of transfusion indication (8). This is consistent with the view that transfusion decisions tend to be driven by "transfusion triggers" rather than by specific physiologic indications. Data from the CRIT study lend support to this view (4). In the CRIT study, there was little evidence that either age or co-morbidities significantly influenced transfusion practice. Overall, these results support the hypothesis that RBC transfusion in many critically ill patients is driven by arbitrary transfusion "triggers" rather than clinical or physiologic findings (8).

Benefits of RBC Transfusion

The expected benefit from RBC transfusion is to immediately improve oxygen delivery and, thus, prevent cellular injury. However, it has been difficult to demonstrate benefit in clinical practice. In a study of patients with gastrointestinal bleeding, patients who received only colloid solutions had lower mortality and morbidity than patients who were transfused with RBCs (38). Other studies also document a lack of improvement in tissue oxygenation after RBC transfusion, despite increases in oxygen delivery (27, 39).

Transfused RBCs, especially during the time period immediately following transfusion, are not "normal." Routine storage of RBCs temporarily decreases two, three 2,3-diphosphoglycerate levels, interfering with the ability of RBCs to unload oxygen, and decreases RBC deformability. The duration of storage may be an important determinant of the efficacy of RBCs. In a study of septic patients, those patients who received RBC units stored for >15 days developed more evidence of splanchnic ischemia compared with those receiving units stored for <15 days (40). A follow-up study using a rat sepsis model demonstrated that transfusion of "fresh" RBCs acutely increased systemic oxygen uptake, whereas transfusion of RBCs stored for 28 days failed to improve tissue oxygenation (41). A recent study showed that the average age of RBCs transfused in the United States is 21 days (4).

The best evidence available regarding the efficacy of blood transfusion among critically ill patients is the randomized, controlled trial by Hebert et al. (24). They compared a liberal transfusion strategy (hemoglobin, 10–12 g/dL, with a transfusion trigger of 10 g/dL) to a restrictive transfusion strategy (hemoglobin, 7–9 g/dL, with a transfusion trigger of 7 g/dL). Patients in the liberal transfusion arm received significantly more RBC transfusions. Overall in-hospital mortality was significantly lower in the restrictive strategy group, although the 30-day mortality rate was not significantly different. However, in those patients who were less ill (APACHE, <20) or younger (<55 yrs of age), the 30-day mortality rates were significantly lower for the patients in the restrictive transfusion group. Therefore, a restrictive strategy is at least equivalent, and in some patients possibly superior, to a more liberal transfusion strategy. It should be noted that the liberal group used a transfusion trigger of 10 g/dL, which is considerably higher than current transfusion practice in many ICUs (4, 9).

Hebert et al. (26) in a subsequent analysis reported results from the subgroup of those critically ill patients who had cardiovascular disease. No significant difference in mortality between the two transfusion strategies in this subgroup was noted. However, in the patients with severe ischemic heart disease, a trend toward decreased survival was observed in the group managed with the restrictive strategy. This was the only subgroup in the study that favored the liberal transfusion strategy. A separate analysis of patients who required mechanical ventilation did not demonstrate any advantage in weaning from mechanical ventilation associated with a more liberal transfusion strategy (42).

For critically ill patients who are not actively bleeding and without cardiovascular disease, a hemoglobin level of 7.0 g/dL is well tolerated by most critically ill patients.

CONCLUSIONS

Anemia is common in the critically ill patient and results in a large number of RBC transfusions. Overall, there is little evidence that "routine" transfusion of stored allogeneic RBCs is beneficial to critically ill patients. Based on the available evidence regarding the risks and benefits of transfusion and the risks of anemia, we recommend the following approach to transfusion of critically ill patients (25). For critically ill patients who are not actively bleeding and without cardiovascular disease, a hemoglobin level of 7.0 g/dL is well tolerated by most critically ill patients. The exception to this may be the patient with active ischemic cardiac disease in whom a higher transfusion trigger would be appropriate (26). Strategies to minimize the loss of blood (43–47) and to increase the production of blood may also be important to the management of all critically ill patients (2, 48).

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