

# Red Blood Cell Transfusions in Critically Ill Patients

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**T**RANSFUSIONS OF PACKED RED BLOOD CELLS (RBCs), a complex biological product prepared from donated blood, are unique in many respects when compared with other health interventions. Despite one of the worst epidemics in recent times being caused, in part, by transfusion of blood products in the 1980s, RBC transfusion remains an essential and frequently performed medical intervention. In the United States, 11.5 million units of blood were donated in 1997.<sup>1</sup> Of all units donated yearly, it is estimated that 50% to 70% are transfused in the surgical setting.<sup>2-6</sup>

In this issue of THE JOURNAL, the international epidemiologic study by Vincent and colleagues<sup>7</sup> highlights the frequent use of RBC transfusions in the intensive care unit (ICU). The Anemia and Blood Transfusion in Critical Care (ABC) investigators conducted a cross-sectional study during a 2-week period in November 1999 to evaluate transfusion practices involving 3534 patients from 146 western European ICUs. From a sample of 1136 of these patients, the investigators recorded the volume of blood drawn per day, and found that blood sampling occurs on average 4.6 times in the first few days of intensive care, and removes approximately 41 mL of blood per 24-hour period. Approximately 29% of patients had a hemoglobin concentration below 10 g/dL on admission to the ICU. The average pretransfusion hemoglobin concentration was 8.4 g/dL during this study, and 37% of patients received a blood transfusion during their ICU stay. The authors also observed a significant association between transfusions of RBCs and increased mortality. These data describe the prevalence of anemia and the use of RBCs as well as a relationship between transfusions and adverse outcomes in critically ill patients.

The study results show that the average hemoglobin concentration prior to the administration of an RBC transfusion was lower than anticipated, and certainly lower than average values recorded in Canadian ICUs in 1993.<sup>8,9</sup> Vincent et al hypothesize that pretransfusion hemoglobin concentrations were lower than those recorded in the past, perhaps because of the influence of the Canadian, multicenter, randomized Transfusion Requirements in Critical Care (TRICC) trial, which failed to show a mortality advantage with RBC transfusion.<sup>10</sup> While it is plausible that RBC transfusion triggers may now be lower than previ-

ously observed, this hypothesis is not based on direct comparisons of transfusion data before and after publication of the TRICC trial, adjusting for other factors.

The most controversial finding in the report by Vincent et al is the association between mortality and RBC transfusions. The investigators used a matching strategy based on propensity scores to define 2 well-balanced groups, to control for the confounding created by illness severity and the need for transfusions (ie, confounding by indication), and to determine the influence of RBC transfusions on mortality. Using this approach, the associated risk of death was increased 33% for patients who received a transfusion compared with similar patients who did not receive blood. However, the lower boundary of the 95% confidence interval (CI) bordered on unity, suggesting that these results might be modified by many factors and thus may not be robust under all circumstances. For example, the results may differ if the propensity scores were derived separately for categories of pretransfusion hemoglobin concentrations (<8.0, 8.0-10.0, and >10.0 g/dL) instead of hemoglobin concentration at ICU admission. It is improbable that the observed 33% increase in mortality is proportional at all hemoglobin levels (eg, 6.0 g/dL), or transfusions would never be recommended.

In another observational study of 78974 Medicare records of patients with acute myocardial infarction, Wu et al<sup>11</sup> suggested that RBC transfusions were beneficial, rather than harmful, when hematocrit values were less than 33%. These investigators observed that blood transfusion was associated with a reduction in 30-day mortality for patients who received at least 1 RBC transfusion if their admitting hematocrit value was less than 33%. For instance, compared with patients who did not receive RBC transfusion, patients with an admitting hematocrit value between 5% and 24% had a significantly lower risk of death (adjusted odds ratio, 0.22; 95% CI, 0.11-0.45) following blood transfusion. This study, and the accompanying editorial,<sup>12</sup> recommended adoption of high hematocrit values as transfusion triggers, despite infrequent RBC transfusions in patients with low hematocrit values and spurious associations between the severity of illness, the disease process, and the physician's decision to administer RBCs. Group imbalances and spurious associations are threats to the validity of observational studies that attempt to assess the impact of treatments such as RBC transfusions on clinical outcomes,

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and cannot always be overcome by analytic techniques. Of note, Wu et al concluded that RBC transfusions were beneficial for patients following a myocardial infarction, whereas Vincent et al suggest that transfusions are harmful for critically ill patients. Obviously, patient groups in these 2 studies are not similar, and differences in interpretation also may be due to the observational design of these studies and to differences in analytic techniques.

Perhaps the major clinical concern is not the apparent discordance between these observational studies, but lack of evidence about the effect of transfusions from large randomized trials examining RBC transfusion perioperatively and in the critical care setting. In the only large randomized trial addressing the issue of transfusion triggers in the perioperative and critical care setting, the TRICC study<sup>10</sup> documented an overall nonsignificant trend toward decreased 30-day mortality (18.7% vs 23.3%,  $P = .11$ ) and significant decreases in mortality among patients who were less acutely ill (8.7% vs 16.1%,  $P = .03$ ) in the group treated using a transfusion trigger reflected in a hemoglobin level of 7.0 g/dL compared with a more liberally transfused group that received 54% more RBC transfusions. Despite the frequent use of RBC transfusions, this trial did not address optimal transfusion practice in postoperative care, in critically ill children, or in patients with significant cardiac risk or following a myocardial infarction. Most transfusion practice guidelines published prior to the completion of the TRICC trial are now dated,<sup>13-15</sup> and need to have expert opinion informed by solid evidence in diverse clinical settings.

If RBC transfusions increase the risk of death, as suggested by the results of the study by Vincent et al<sup>7</sup> and by the TRICC study,<sup>10</sup> it is possible that several factors related to the processing and storage of blood products may have important clinical consequences. For example, decreasing the number of leukocytes using leukofiltration by an order of 4 logs in packed units of RBCs prior to storage may have significant clinical ramifications.<sup>16</sup> As a second example, there is limited information establishing the efficacy of RBCs after prolonged storage. One of the first clues to the disturbing possibility of harm associated with transfusion of older vs newer RBCs was an association between RBCs older than 15 days and gut ischemia measured using gastric tonometry.<sup>17</sup> Both examples illustrate the need for further research regarding the clinical consequences of blood transfusions.

Several studies and initiatives to evaluate alternatives to RBC transfusions and to improve current understanding of transfusion practices are under way. For example, use of erythropoietin as a blood conservation technique in the ICU<sup>18</sup> has rekindled interest in alternatives to RBC transfusions. A large clinical trial involving more than 1300 patients has completed enrollment (Corwin HL, MD, oral communication, September 2002) and should provide data to help determine whether erythropoietin decreases transfusion requirements in the critical care setting, improves morbidity and mortality, and is cost-effective, before its widespread use occurs. In addition, the Canadian Institutes of Health Research<sup>19</sup> has funded

several randomized trials in transfusion and blood conservation, including 2 transfusion trigger studies (one in premature infants and the other in critically ill children); and a randomized trial of 3000 high-risk cardiovascular surgical patients is under way to compare 3 commonly used antifibrinolytic agents for prevention of catastrophic bleeding, reoperations, and deaths due to hemorrhage.<sup>20</sup> Likewise, the National Institutes of Health<sup>21</sup> and the United Kingdom's Medical Research Council<sup>22</sup> are establishing clinical research networks in transfusion medicine to conduct important clinical trials in the field.

Collaborative multicenter efforts such as these, along with other international epidemiologic investigations such as the study by Vincent et al, should bring much-needed evidence to help answer many of the important remaining questions regarding RBC transfusions and the use of blood conservation strategies for critically ill patients.

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