Transfusion practice in the ICU: When to transfuse?

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Introduction
Anemia is a common problem among critically ill patients, so much so that the majority of intensive care unit (ICU) patients will need a blood transfusion at some point during their ICU stay. However, the decision to transfuse is not always clearly defined and in recent years this issue has seen considerable debate and controversy. The traditional transfusion ‘trigger’ of 10 g/dl is no longer considered optimal with transfusions now being given at much lower hemoglobin levels. In this article we will consider current transfusion practice and arguments related to the question “When to transfuse?”

Hemoglobin levels in the critically ill
The ABC (anemia and blood transfusions in the critically ill) study, involving 3,534 patients in 146 western European ICUs, provided important epidemiological data on the occurrence of anemia and on transfusion practices among the critically ill. The mean admission hemoglobin level was 11.3 g/dl, and 29% of patients had a hemoglobin concentration of less than 10 g/dl. The hemoglobin concentration was inversely related to age: mean concentration was 11.7 g/dl for patients less than 50 years, but 11.0 g/dl for patients aged 80-90 years and just 9.9 g/dl for patients aged 90 years and older (P < 0.001). On admission, about 13% of patients had a recent history of anemia, more often related to a neoplasm than to chronic bleeding, a hematological disorder, renal dysfunction, or severe hepatitis.

There was an inverse correlation between the hemoglobin concentration and organ dysfunction (as estimated by the SOFA score) on admission. Anemic patients also had longer ICU stays (P < 0.001).

Causes of Anemia
Anemia can be due to various factors related to blood loss, reduced erythropoiesis, or increased red cell destruction.

Blood loss: while blood loss is usually obvious in the trauma or surgical patients, losses due to invasive procedures, such as catheter or drain insertion, tracheotomy, etc, and occult blood loss from the digestive tract, should not be forgotten. Repeated blood sampling can also impact on hemoglobin concentrations, despite improvements in analyzing techniques that are able to operate on smaller volumes of blood. In 1999, von Ahsen et al. noted that the average daily blood sampling volume was 41 ml. The ABC study reported the same figure of 41 ml, corresponding to an average of 4.75 samples per day each of 9.6 ml. There was a relation between the amount of blood sampled and the organ dysfunction estimated by the sequential organ failure assessment (SOFA) score.

Reduced erythropoiesis: Reduced erythrocyte synthesis can be secondary to nutritional or hematological factors. Pro-inflammatory cytokines, such as tumor necrosis factor (TNF), interferon-gamma, and transforming growth factor beta (TGF-β), often active in the ICU patient, can reduce the production of erythropoietin. Even though interleukin (IL)-6 can enhance erythropoietin synthesis, the inflammatory response results in inadequate erythropoietin levels in critically ill patients.

Increased red cell destruction: Hemolysis can contribute to red cell destruction. Without necessarily requiring
massive hemolysis, a red blood cell’s lifespan can be reduced in the critically ill, predominantly due to an alteration in red cell structure.\textsuperscript{10,11}

In reality, reduced hemoglobin concentrations in ICU patients are likely the result of several factors. Nguyen and colleagues\textsuperscript{12} recently studied the time course of hemoglobin levels in 91 non-bleeding ICU patients. Hemoglobin concentrations fell by $0.52 \pm 0.69$ g/dl/day. For the 33 patients who stayed in the ICU longer than three days, the fall was more marked in the first three days than later during their ICU stay ($0.66 \pm 0.84$ vs. $0.12 \pm 0.29$ g/dl/day). After the third day, the fall in hemoglobin was related to disease severity, as assessed by the APACHE II and SOFA scores. The fall in hemoglobin concentrations was more marked in septic than in non-septic patients; in particular, after the third day, hemoglobin concentrations continued to fall in septic patients ($-0.29 \pm 0.19$ g/dl/day), but stabilized in non-septic patients. This last observation supports the role of pro-inflammatory cytokines in the pathogenesis of anemia in the critically ill.

**Transfusion Practice**

Transfusion practice varies considerably from one institution to the next. In a study of 5,298 ICU patients in Canada, Hebert et al\textsuperscript{13} noted that 25% of patients received a transfusion during their ICU stay. In the US, Groeger and colleagues\textsuperscript{14} reported that 16% of patients in a medical ICU and 27% in a surgical ICU were transfused. Corwin et al\textsuperscript{15} found that 85% of patients staying more than one week on the ICU received a transfusion. More recently, the ABC study\textsuperscript{1} reported that 37% of patients in western European ICUs received a transfusion.\textsuperscript{1} This number increased with duration of stay (25% in patients staying 48 hours or less, 56% in those staying more than two days, and 73% in those staying more than a week). The very recent Sepsis Occurrence in Acutely Ill Patients (SOAP) study, performed during May and June 2002 and including 3,147 patients in 198 European ICUs, also noted that 33% of patients received a transfusion during their ICU stay (unpublished data).

While blood transfusions are more common in surgical patients they are also frequently required in non-surgical ICU patients. In the ABC study, transfusions were required in 57% of patients undergoing emergency surgery, 47% of trauma patients, 42% of patients undergoing a scheduled surgical intervention, and 32% of medical ICU patients.\textsuperscript{1} It is also important to note that transfusions are often necessary in patients with no signs of active bleeding. In the ABC study,\textsuperscript{1} 54% of patients were transfused because of an inadequate hemoglobin concentration, most often accompanied by diminished physiological reserves. The number of transfusions given also depends on the type of hospital, with the ABC study reporting transfusion rates of 44% of patients in university hospitals, 40% in regional hospitals, and 35% in community hospitals, even though the average transfusion trigger was the same (8.4 g/dl) across all hospital types. The differences may have been related to disease severity as the mean admission SOFA score was 5.4 in academic hospitals, 5.1 in regional hospitals, and 4.5 in community hospitals ($P < 0.001$).

Transfusion frequency was directly related to age, increasing from 30% for patients less than 30 years, to 40% for those between 50 and 60 years, and 54% for those older than 80 years ($P < 0.001$). However, older patients also had more severe disease as indicated by higher SOFA and APACHE II scores. They also had longer ICU stays (almost 6 days versus almost 3 days).\textsuperscript{1}

**Transfusion and Outcome**

The possible relationship between blood transfusion and poor outcome has led many to review their transfusion practices. There are two main reasons to give a blood transfusion in a critically ill patient:

1. To increase tissue oxygenation: The hemoglobin level is, with the cardiac output and the PaO$_2$, an essential determinant of oxygen transport. Nevertheless, increasing hemoglobin levels via transfusion will not necessarily increase tissue oxygenation. Indeed, increasing the number of red blood cells can increase blood viscosity, which in turn can decrease cardiac output, and hence, limit oxygen delivery. In addition, a reduction in the hematocrit can have beneficial effects on the microcirculation, with oxygen extraction capacities being greater when the hematocrit is reduced whether under physiological conditions\textsuperscript{16} or during sepsis.\textsuperscript{17} It should also be stressed that blood transfusions rarely increase oxygen uptake, except under extreme conditions, where oxygen uptake is directly dependent on oxygen delivery, essentially in circulatory shock associated with hyperlactatemia\textsuperscript{18-20} or in severe anemia with hemoglobin levels generally less...
than 6 g/dl. Hebert and Chin-Yee\textsuperscript{21} identified 14 studies in which the impact of blood transfusion on oxygen kinetics was assessed, and noted that only five reported an increase in VO$_2$ following transfusion.

Good tolerance to anemia is due to increases in cardiac index (CI) and oxygen extraction ratio (O$_2$ER), which maintain oxygen consumption (VO$_2$). Although a high CI in an anemic patient may appear to be adequate, if analyzed in isolation, the cardiac response may still be inadequate for the degree of anemia. The CI/O$_2$ER ratio can help to assess the adequacy of the CI during anemia in critically ill patients, with a low CI/O$_2$ER ratio suggesting an inadequate CI response to anemia.\textsuperscript{22}

2. To avoid myocardial ischemia: During anemia, the increased cardiac output (due to decreased viscosity and adrenergic stimulation) augments myocardial oxygen demands, and patients with acute myocardial instability tolerate anemia poorly. Indeed, a large retrospective study of 78,974 critically ill patients aged more than 65 years who were hospitalized for acute myocardial infarction,\textsuperscript{23} showed not only that patients with a low hematocrit had a higher mortality, but also that blood transfusion was associated with reduced mortality in patients with a hematocrit less than 33%. Nevertheless, this study is controversial because the anemic patients had a more unstable cardiovascular status on admission and benefited less from invasive therapeutic strategies.

The whole transfusion issue has become a hot area of debate in the last five years or so, triggered by the study by Hebert et al\textsuperscript{13} noting that a more restrictive transfusion protocol (transfusions given when the hemoglobin concentration dropped below 7.0 g/dl and hemoglobin concentrations maintained at 7.0-9.0 g/dl), was at least as effective and possibly more so than a more conservative approach (transfusions given when the hemoglobin concentration fell below 10.0 g/dl and hemoglobin concentrations maintained at 10.0-12.0 g/dl). In the ABC study,\textsuperscript{1} overall mortality was 13.5%, but 18.5% for transfused patients compared to 10.1% for those who were not transfused ($P < 0.001$). Of course, mortality was also higher among anemic patients, but a multi-variable analysis showed that transfusion rather than anemia was an independent prognostic factor. A transfusion during the ICU stay increased the risk of death by a factor of 1.37 (95% CI: 1.02-1.84). To examine more specifically the link between transfusion and mortality, a propensity score was used to adjust for confounding factors. The variables chosen were age, gender, type of admission, admission diagnosis, SOFA score, admission SOFA and APACHE II scores, the hemoglobin concentration on the first day, history of recent bleeding or anemia, presence of circulatory shock, and duration of hospital stay. Five hundred and sixteen transfused patients were matched with the same number of non-transfused patients. The mortality of the transfused propensity matched patients was 22.7% vs. 17.1% for the non-transfused patients ($P = 0.02$).

The ABC study was an observational study and no conclusions regarding cause and effect can be made, but nevertheless, the results suggested a deleterious effect of blood transfusion on outcome. Interestingly, however, results from the SOAP study, carried out just two and a half years after the ABC study, do not demonstrate a deleterious effect of transfusions. This may be related to favorable effects of deleukocytation,\textsuperscript{24} now practiced widely across Europe. At the time of the ABC study, deleukocytation was just being introduced, such that 46% of ICUs used deleukocyted blood most of the time, 35% some of the time, and 19% never.\textsuperscript{1}

So, where does this leave the ICU physician faced with an anemic patient? When should we transfuse and when not? The Hebert trial suggests that apart from patients with acute coronary syndromes, patients can tolerate much lower hemoglobin concentrations than previously thought and the well accepted transfusion trigger of 10 g/dl can be acceptably lowered in many patients. Using the hemoglobin value as a transfusion trigger requires definition of the ‘optimal’ hemoglobin. However, the optimal hemoglobin is a subjective measure and will vary according to multiple individual factors. For example, the optimal hemoglobin may be different for surgical and non-surgical patients, for children and the elderly, for a patient with chronic anemia, coronary artery disease, or compromised cardiac contractility, etc. Other factors including the severity of the disease process as well as the underlying cause of the anemia will also be important determinants of the optimal hemoglobin for any individual patient. The optimal hemoglobin is, in fact, a balance between the benefits of maximum hemoglobin levels and the potential adverse effects of blood transfusion.
sion and high hematocrit. The critical hemoglobin is perhaps more easily defined than the optimal hemoglobin, as the hemoglobin level below which oxygen delivery is compromised and regional ischemia may occur leading ultimately to organ dysfunction and failure. However, again the critical value is an individual factor and will vary with age, pre-existing disease, severity of disease, etc.

**Conclusion**

Concerns about the side effects of blood transfusion, along with suggestions that hemoglobin levels lower than the classically quoted 10 g/dl are well tolerated, and that more restrictive transfusion protocols may be beneficial, encourage us to re-evaluate our transfusion triggers. Importantly, there can be no one trigger for all patients. A hemoglobin level of 10 g/dl may be an appropriate trigger for some patients but be unnecessarily high in young fit patients, and too low in older patients with significant cardiac disease. Each patient must be assessed individually and the decision to transfuse based on many parameters including clinical condition, age, pre-existing and current disease processes, and oxygenation parameters with indexes of tissue hypoxia where available, as well as the traditional hemoglobin and hematocrit values.

Recent years have seen conflicting reports of the association of blood transfusions with outcome. One of the reasons for these apparent differences may be the more widespread use of deleukocytes blood. It would be interesting to conduct a randomized controlled trial similar to that performed by Paul Hebert et collaborators some years ago to see whether the results still hold true. Until then, patients need to be treated on an individual basis with careful consideration of their transfusion risk/benefit ratio.

**References**


