

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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The Shifting Paradigm for Transfusion of Red Blood Cells



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H&O Could you give a brief history of red blood cell transfusion for anemia, and the hemoglobin level that historically triggered transfusion?

JC In the mid-1980s, the National Heart, Lung, and Blood Institute created a panel to look at guidelines for red blood cell transfusion. What became clear from the review was that we had no evidence to guide what we were doing. We had been using a 10-g/dL hemoglobin concentration threshold for years, but the recommendation was based on expert opinion only. In response to this finding, we undertook clinical trials.

In 1999, the *New England Journal of Medicine* published the results of the TRICC (Transfusion Requirements in Critical Care) trial with Dr Paul Hébert as the first author. This trial looked at patients in the intensive care unit (ICU) who were randomly assigned to receive a red blood cell transfusion when their hemoglobin concentration dropped below either 10 g/dL—the liberal approach—or 7 g/dL—the restrictive approach. The results showed that there was no benefit to giving blood using the liberal approach rather than the restrictive approach. In fact, there was a trend toward better mortality rates in the group that received less blood. This finding represents the start of the movement toward a more restrictive transfusion approach. Since then, a series of clinical trials have supported the more restrictive approach in most settings. It is just as safe, and it might even be better than using more blood.

H&O Do the definitions of liberal and restrictive vary among studies?

JC Most of the recent trials have defined liberal transfusion as giving red blood cells when the hemoglobin concentration drops below 9 or 10 g/dL, and restrictive transfusion as giving red blood cells when the hemoglobin concentration drops below 7 or 8 g/dL.

H&O What are the risks of red blood transfusion?

JC There are many well-known risks related to red cell transfusion, all of which occur infrequently.

The most common side effect seems to be transfusion-associated cardiac overload (TACO), in which patients develop heart failure after receiving a blood transfusion. We estimate that between 1% and 5% of patients develop this side effect. Clinicians often know which patients are most likely to develop TACO based on their cardiac history, and can administer diuretics either before or after the transfusion as a preventive measure.

Another serious adverse event is transfusion-related acute lung injury (TRALI). People who develop TRALI may require ICU care. It is unclear how common this is, but a widely used statistic is that it occurs with 1 out of 5000 red blood cell transfusions. We do not know who is most likely to develop TRALI, and diagnosis is difficult because we often do not know whether the problem is related to the transfusion or to the underlying illness.

Does the patient have sepsis or acute respiratory distress syndrome, or is the blood the bad actor? We worry about TRALI a lot, but fortunately it is quite uncommon.

We also worry about the possibility of increased risk for bacterial infection. We have some data from clinical trials, notably a meta-analysis by Rohde and colleagues that appeared in the *Journal of the American Medical Association* in 2014, that suggest a higher risk of bacterial infections in patients who get more blood compared with those who get less.

Because of outstanding screening and blood testing, the risk of infection with human immunodeficiency virus (HIV), hepatitis, and other contagious diseases is so low as to be clinically irrelevant. Approximately 1 in 2 million units of blood may be contaminated with HIV, which should not influence the decision to give blood to an individual patient.

In another trial, which was published in the *New England Journal of Medicine* by Villanueva and colleagues, patients with gastrointestinal bleeding had a higher mortality rate if they received liberal transfusion than if they received restrictive transfusion. These results have not been replicated, but I suspect that the transfusion caused rebleeding of already-damaged blood vessels by increasing portal venous pressure. In other words, the problem may be related to blood pressure rather than to red blood cells.

H&O Is there a risk of thrombosis with red blood cell transfusion?

JC This is something that is talked about, but there is no evidence to support that. The clinical trials and the meta-analysis do not show that.

H&O How about an increased risk of cancer from changes in immune function?

JC This has never been demonstrated in a convincing way. We recently published a paper in the *Lancet* online in which we looked at long-term mortality and cause of death in our own trial, the FOCUS (Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair) trial. We did not see more deaths from cancer or infection among patients in the liberal group than the restrictive group.

H&O What factors play a role in when physicians decide to order a red blood cell transfusion?

JC Physicians generally use hemoglobin thresholds, and most of the trials that have been conducted have emulated that model. Some people believe that we should incorporate clinical symptoms and other findings into the

decision, such as tachycardia, low blood pressure, or chest pain that might be cardiac in nature. It seems reasonable to follow our clinical judgment in these instances. We incorporated symptoms into our own trials, however, the results of these studies do not show that symptoms should be a driving force in transfusion decisions. We simply do not have the evidence.

H&O What do the most recent guidelines on red blood cell transfusion from the AABB (formerly the American Association of Blood Banks) advise?

JC First, a bit of background. The guidelines acknowledge that clinicians largely use hemoglobin thresholds and perhaps some other clinical parameters that might trigger transfusion. And these guidelines apply only to patients who are hemodynamically stable—patients who are hemorrhaging need to be managed differently according to their blood pressure and other clinical factors. Finally, the guidelines are based on a systematic review of the literature, which looked at clinical trials.

The guidelines address 4 questions. First, when should transfusion be considered for hospitalized, hemodynamically stable patients? The wording was very carefully chosen because “consider” does not mean the same as “give blood.” Making individual decisions once the patient is below a particular threshold is good practice. The guidelines recommend considering transfusion at a hemoglobin concentration of 7 g/dL or below for adult and pediatric patients in the ICU and 8 g/dL or below for postoperative surgical patients. This is based on high-quality evidence from the TRICC, TRIPICU (Transfusion Requirements in the Pediatric Intensive Care Unit), and FOCUS trials. Does this mean that the requirements are actually different for ICU patients than for surgical patients? There is no particular reason to think they would be different. What this does reflect is the fact that the ICU trials used a 7-g/dL threshold, whereas the surgical trials used an 8-g/dL threshold.

The second question was when to consider transfusion in hospitalized, hemodynamically stable patients with preexisting cardiovascular disease. Based on the results of the FOCUS trial, we recommended that physicians should consider transfusion when hemoglobin concentration is less than 8 g/dL or symptoms are present. We rated the evidence for this recommendation as moderate quality because it had not been replicated.

The third question was when to consider red blood cell transfusion in hospitalized, hemodynamically stable patients with acute coronary syndrome. We were unable to give guidance on this because we had no adequately powered, randomized controlled trials.

The fourth question was whether transfusion should be guided by symptoms rather than hemoglobin

concentration in hospitalized, hemodynamically stable patients. We suggested that both might be used, but the quality of the evidence was poor.

H&O What has changed since 2011, when the literature search for the AABB guidelines was performed?

JC The large trial by Villanueva and colleagues is an important one that has been published since then. If we were to revise the guidelines, we would add a recommendation to initiate red blood cell transfusion at 7 g/dL in patients with gastrointestinal bleeding.

The other large trial was the one published by Holst and colleagues in the *New England Journal of Medicine* in October 2014. That paper further supports the 7-g/dL threshold for patients in septic shock, because the results did not show a benefit with liberal transfusion. A key principle here is that you should not give more blood unless you can show a benefit from giving it.

H&O Are there any ongoing trials?

JC A group of European researchers recently published observational data on nearly 15,000 patients who underwent coronary artery bypass grafting or valve surgery. They found that patients who received more than 2 units of red blood cells were significantly more likely to have a postoperative stroke or transient ischemic attack. So the research that is being done is mostly confirming what we have been seeing.

H&O Are clinicians cutting back on their use of red blood cell transfusions?

JC Yes, they are—perhaps in part because of the AABB guidelines but also because of the large clinical trials that have been published in the *New England Journal of Medicine*. The idea that less blood is fine is much more widely accepted than it used to be—I think the pendulum has clearly swung over the last 5 years or so.

Suggested Readings

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