Blood Transfusion and Risk of Infection
New Convincing Evidence

Jeffrey L. Carson, MD

In this issue of JAMA, Rohde and colleagues report results of a meta-analysis evaluating the association between a liberal transfusion strategy vs a restrictive strategy and risk of hospital-acquired infections.1 In the meta-analysis, which included 18 randomized trials that compared these strategies among 7593 patients, the absolute rates of hospital-associated infection were 16.9% in the liberal transfusion group and 11.8% in the restrictive transfusion group. The number needed to treat with a restrictive transfusion strategy to prevent serious infection was about 38 patients. Results were consistent when analyses were repeated in trials with concealed randomization and infrequent protocol violations. A prior meta-analysis of liberal vs restrictive transfusion strategies and infection outcomes reported a nonstatistically significant reduction in infections.2 The current meta-analyses by Rohde et al includes several newly published trials. Most trials define a restrictive transfusion strategy as the administration of red blood cells (RBCs) once hemoglobin falls below either 7 or 8 g/dL, and most trials define a liberal strategy as the administration of RBCs once hemoglobin level falls below 10 g/dL.

Experimental evidence demonstrates measurable adverse change in immune function in response to RBC transfusion.3,4 Observational studies have also shown high risks of infections associated with RBC transfusions.5 However, observational studies evaluating RBC transfusion are prone to bias and can overestimate the risk associated with transfusion because patients who receive transfusion are typically sicker than patients not transfused.6 For example, one meta-analysis of liberal vs restrictive transfusion strategies and infection outcomes reported a nonstatistically significant reduction in infections when analyses were repeated in trials with concealed randomization and infrequent protocol violations. A prior meta-analysis of liberal vs restrictive transfusion strategies and infection outcomes reported a nonstatistically significant reduction in infections.

The current meta-analyses by Rohde et al includes several newly published trials. Most trials define a restrictive transfusion strategy as the administration of red blood cells (RBCs) once hemoglobin falls below either 7 or 8 g/dL, and most trials define a liberal strategy as the administration of RBCs once hemoglobin level falls below 10 g/dL.

At the time a unit of blood is processed, white blood cells are removed by a procedure called leukofiltration or leukoreduction. Many countries use only leukoreduced blood, although leukoreduced blood is not required by the Food and Drug Administration for transfusions in the United States. A reduced risk of infection was one of the proposed benefits of leukoreduction because the white blood cells that are removed are thought to secrete cytokines and other mediators, which are immunosuppressive.4 However, results by Rohde et al challenge the conclusion that leukoreduction reduces the risk of infection, because the results in the subset of 8 trials using only leukoreduced blood also showed a benefit similar to the overall results favoring a restrictive transfusion approach.

The only outcome evaluated in the report by Rohde et al was infection risk. However, other important outcomes such as mortality, myocardial infarction, and functional improvement in hip fracture patients9 were not considered in the overall risk-benefit analysis of transfusion. A previously published meta-analysis found a statistically nonsignificant reduction in mortality associated with a restrictive transfusion approach2 and a recent trial in patients with upper gastrointestinal bleeding found a significantly lower risk of death at 45 days follow-up in the restrictive transfusion group compared with a liberal transfusion group.8 Also, liberal transfusion does not improve walking ability or other measures of daily functioning in hip fracture patients.9

The safety of a restrictive transfusion strategy in patients with cardiovascular disease is less clear. A clinical trial of patients with preexisting cardiovascular disease or risk factors for cardiovascular disease provided evidence for the safety of restrictive transfusion in this population of patients at risk for cardiovascular events.9 However, high-quality clinical trials are not available for patients with acute myocardial infarction. Observational studies have found an elevated risk of death in patients treated with a liberal transfusion approach.10-11 To date, only 2 small trials have been performed in patients with myocardial infarction.11-13 Among the 151 patients included in these 2 trials, there were 2 deaths (2.7%) in the liberal transfusion strategy group and 9 deaths (11.7%) in the restrictive transfusion strategy group. While small trials are unreliable and need to be replicated in large numbers of patients, the current evidence is not sufficient to establish the appropriate transfusion threshold for patients with myocardial infarction, and additional large trials are needed.13 Furthermore, it is reasonable to hypothesize that an acutely ischemic myocardium might benefit from higher hemoglobin levels. In contrast, patients with gastrointestinal tract bleeding may rebleed more frequently as a result of the higher portal pressures from liberal transfusion.8 Thus the ideal transfusion threshold at which the benefits of transfusion outweigh the risks may differ depending on the predominant pathophysiology of the underlying disorder.

It is likely that transfusion is life-saving, but not across the entire range of hemoglobin thresholds currently used to trigger a transfusion. Most trials have compared a hemoglobin transfusion threshold of 7 or 8 g/dL with a threshold of 10 g/dL, because these are the ranges of hemoglobin transfusion triggers that are widely used in clinical practice. Findings from these trials suggest that the 10-g/dL hemoglobin threshold is too high for most patients and is associated with increased rates of infection and other adverse effects. However, it is unknown whether a hemoglobin level of 7 or 8 g/dL is the optimal threshold because trials have not been completed that...
evaluated lower hemoglobin transfusion thresholds. Studies in patients of the Jehovah’s Witness faith suggest that mortality sharply increases when hemoglobin concentration declines to less than 5 g/dL, perhaps suggesting that 5 to 6 g/dL may be the optimal transfusion trigger. However, this threshold remains to be evaluated in clinical trials, such as those that compare lower thresholds with a transfusion threshold of 7 to 8 g/dL.

Over the past decade, there has been a substantial change in the management of anemia through either transfusion or agents such as erythropoietin. For many years the practice of increasing hemoglobin levels in the face of anemia was unquestioned. However, accumulating data suggest that in many circumstances this is not warranted and may be harmful. The study by Rohde et al3 confirms another potential adverse outcome associated with transfusion: serious infectious disease. Clinical trials are needed to establish the optimal transfusion thresholds, to provide additional information about the risks and benefits of RBC transfusion, and to determine how best to use RBC transfusion.

ARTICLE INFORMATION

Author Affiliation: Division of General Internal Medicine, Department of Medicine, Rutgers Biomedical and Health Sciences, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey.

Corresponding Author: Jeffrey L. Carson, MD, Division of General Internal Medicine, Department of Medicine, Rutgers Biomedical and Health Sciences, Rutgers Robert Wood Johnson Medical School, 125 Paterson St, New Brunswick, NJ 08901 (jeffrey.carson@rutgers.edu).

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Carson reports serving as a consultant to Cerus for a trial unrelated to this article and reports grant funding to his institution from the National Institutes of Health.

REFERENCES