EDITORIAL

Transfusion Threshold of 7 g per Deciliter — The New Normal

Paul C. Hébert, M.D., and Jeffrey L. Carson, M.D.

Holst and colleagues[1] now provide definitive evidence in the *Journal* that a restrictive approach to blood transfusion not only reduced blood use by half but also did not cause harm to 998 critically ill patients with septic shock. It has been 15 years since the publication of the results of the Transfusion Requirements in Critical Care (TRICC) trial in the *Journal*.[2] In that Canadian Critical Care Trial Group study, 838 critically ill patients were randomly assigned to receive blood transfusions on the basis of a threshold of 7 g per deciliter or 10 g per deciliter while also agreeing to undergo transfusion 1 unit at a time. Much like the results of the Transfusion Requirements in Septic Shock (TRISS) trial by Holst et al., approximately 50% less blood was administered in the restrictive-strategy group than in the liberal-strategy group. In contrast to this latest trial, overall trends and all the secondary analyses suggested that a liberal transfusion strategy may have resulted in increased mortality, increased rates of pulmonary edema, and increased rates of organ failure.

In our 2012 Cochrane review of transfusion thresholds, we identified 19 randomized clinical trials involving 6264 patients.[3] A restrictive transfusion strategy was associated with more than one third fewer transfusions, without any apparent harm among a variety of patient populations including patients with perioperative care, those with cardiac surgery, and those with gastrointestinal hemorrhage. We did not identify any additional studies involving critically ill adults. However, a trial of transfusion in pediatric critical care patients included in the review also showed a dramatic decrease in blood transfusions with the adoption of a restrictive transfusion threshold, without increased rates of organ failure.[4]

Since the last Cochrane update, the results of four new trials involving critical care patients have been published,[5-7] including the results of a trial by Peake et al. now published in the *Journal*.[8] None have shown improved survival with a liberal transfusion strategy. Two trials evaluated early goal-directed therapy versus usual care in patients with septic shock. The Protocolized Care for Early Septic Shock (ProCESS) trial[7] included 1341 patients with severe sepsis and septic shock, and the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial compared 1600 patients with septic shock who received either usual care or early goal-directed therapy.[8] The early goal-directed therapy groups in these two trials included several interventions guided by an algorithm that was based on continuous central venous oxygen saturations first promoted by Rivers et al.[9] The clinical protocols of the two trials included a transfusion threshold of a hematocrit of 30% when central venous oxygen saturations remained below 70%. There were no differences in overall mortality at 90 days despite the fact that twice the number of patients in the goal-directed groups as in the usual-care groups were administered blood.

Even in patients with major gastrointestinal hemorrhage, Villanueva and colleagues found an absolute decrease in mortality of 4 percentage points when patients were transfused with the use of a restrictive transfusion strategy.[10] On the basis of the results of this study, a liberal transfusion strategy would result in a number needed to be harmed of 25.

We believe it has become abundantly clear that a transfusion threshold of 7 g per deciliter should become the new normal, recommended in all critically ill patients, including those with severe sepsis and septic shock. To speed up adoption, we should ensure that clinical practice

guidelines are rapidly updated with new information. Indeed, most transfusion guidelines have already been updated,[11-14] but this is not so for sepsis guidelines.

The Surviving Sepsis Campaign has been effective in promoting best practices. Among its many recommendations, the guideline advised on transfusion strategies. In the 2012 edition, the authors recommended adopting a transfusion threshold of 7 g per deciliter on the basis of the results of the TRICC trial and reports in cardiac surgery (evidence base for the recommendation,[15] grade 1B [moderate recommendation and evidence]).[13] However, the recommendation begins with the statement, "Once hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease, we recommend . . . ." This clause effectively allows clinicians to exclude most critically ill patients in the midst of any form of resuscitation from adopting a more restrictive approach to transfusion, in large part using the results of the trial by Rivers et al. as justification. With all the exceptions and citing the vague notion of hypoperfusion, the current guidance would suggest that the default option is to administer blood at a high transfusion threshold — perhaps because a liberal transfusion threshold is still considered safer, either by default or long-standing tradition.

It is time to adopt a transfusion threshold of 7 g per deciliter as the standard of care. To help promote this perspective, we suggest a substantial shift in the Surviving Sepsis Campaign guidelines. This may be easily accomplished with the use of the same recommendation without any of the caveats. Given the many new studies, we would also endorse upgrading the evidence base for the recommendation to 1A (strong recommendation and evidence).

Evidence stills remains weak in patients with an acute coronary syndrome. It may yet be proved that this distinct group of patients benefits from higher hemoglobin concentrations (9 or 10 g per deciliter).[14] Oxygen delivery to the myocardium is flow-dependent since the heart extracts a high percentage of oxygen, and myocardial ischemia may be precipitated by low hemoglobin concentrations.

The TRISS trial and two negative trials of early goal-directed therapy were unable to detect any benefit from the use of a liberal transfusion threshold. Although certainty would be nice, less is proving to be the safer option.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Canadian Critical Care Trials Group, Department of Medicine and Centre de Recherche, Centre Hospitalier de l'Université de Montréal (CRCHUM), Montreal (P.C.H.); and the Division of General Internal Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ (J.L.C.).

This article was published on October 1, 2014, at NEJM.org.

1. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med. DOI: 10.1056/NEJMoa1406617.
2. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409-17. [Erratum, N Engl J Med 1999;340:1056.]
3. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2012;4:CD002042.
4. Lacroix J, Hébert PC, Hutchison JS, et al. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med 2007;356:1609-19.
5. Walsh TS, Boyd JA, Watson D, et al. Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: a randomized pilot trial. Crit Care Med 2013;41:2354-63.
6. Robertson CS, Hannay HJ, Yamal JM, et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: a randomized clinical trial. JAMA 2014;312:36-47.
7. The ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014;370:1683-93.
8. The ARISE Investigators and the ANZICS Clinical Trials Group. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. DOI: 10.1056/NEJMoa1404380.
9. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
10. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368:11-21. [Erratum, N Engl J Med 2013;368:2341.]
11. Napolitano LM, Kurek S, Luchette FA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. Crit Care Med 2009;37:3124-57. [Erratum, Crit Care Med 2010;38:1621.]
12. Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: a clinical practice guideline from the AABB. Ann Intern Med 2012;157:49-58.
13. Retter A, Wyncoll D, Pearse R, et al. Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients. Br J Haematol 2013;160:445-64.
14. Patient blood management guidelines. Canberra, ACT, Australia: National Blood Authority Australia, 2012 (http://www.blood.gov.au/pbm-guidelines).
15. Surviving Sepsis Campaign (http://www.survivingsepsis.org/Guidelines/Pages/default.aspx).

DOI: 10.1056/NEJMe1408976