

## From Tolerating Anemia to Treating Anemia

**T**ransfusion trials undoubtedly have transformed our view of the role of allogeneic blood in patient care, leading to a welcome shift toward reduced use of allogeneic red blood cell (RBC) transfusion. Nonetheless, this change arguably has also given rise to unintended consequences. As the name implies, a transfusion trial stays focused on comparing different transfusion strategies while placing the alternatives for managing anemia on the so-called back burner (1).

The recent study by Roubinian and colleagues (2) is a timely revelation of some of these possible ramifications. Drawing on an extensive database of almost a half-million patient records, the authors reported that parallel to a consistent decrease in RBC transfusions, the prevalence of moderate anemia upon hospital discharge and at 6 months afterward increased from 2010 to 2014. This rise in anemia prevalence was not associated with an increase in the studied outcomes at 6 months: mortality, rehospitalization, and subsequent RBC transfusions. The authors considered these findings to be evidence of safety and effectiveness of strategies to reduce transfusions (2). In their words, the data support the “recommendations to limit RBC transfusion and tolerate anemia during and after hospitalization” (2).

In our opinion, this statement highlights the crux of the matter. Given the ample evidence on harms of allogeneic blood transfusions and anemia (3), when the decision is reduced to choosing between transfusion and “tolerance” (that is, acceptance) of anemia, we are left to choose the lesser of 2 evils. With this mindset, we are trapped in a possibly endless quest to find a magical hemoglobin number, below which the risk for anemia becomes greater than the risk for transfusion and, hence, transfusion is recommended. This question must be addressed in every specific surgical and nonsurgical patient population with further consideration of other factors, such as comorbid conditions (such as the presence of cardiovascular diseases) and patient characteristics (such as older age) (4). It is not difficult to imagine how easily these possible scenarios can get out of hand.

Recently, we questioned this approach and the inevitable calls that have ensued for even more transfusion trials (1). Let's take a step back and put the transfusion in its rightful place—a short-term treatment method with an equivocal risk-benefit profile—and look at the patients and their diagnoses. If anemia is present, the question must be asked whether its severity undermines adequate oxygen consumption; if so, transfusion should be considered part of the supportive strategies to prevent tissue hypoxia and ischemia. Once the patient's urgent needs are met, we must address anemia with proper treatments, such as iron therapy, that will sustainably increase hemoglobin levels (5, 6). This approach contrasts with the common practice of RBC

transfusion as the default therapy for anemia, while forgetting that allogeneic blood is but a temporary patchwork and ignoring the anemia's cause, which might be treated with other therapies.

Roubinian and colleagues (2) describe the multidisciplinary patient blood management (PBM) programs that have been implemented in their hospitals. Study results are emerging that support the effectiveness of network-wide PBM programs in reducing reliance on transfusion and improving patient outcomes (the end point that matters) (7). A look at the PBM approaches described by Roubinian and colleagues (2) may cast some light on areas that might be improved: It seems that their PBM program has been targeted primarily at certain surgical services, even though nonsurgical patients also are at risk and should be provided the benefits of PBM. In addition, although their program includes evaluation and management of anemia in the preoperative period (a critical time and opportunity that should not be missed) (8–10) and use of effective intraoperative blood-sparing methods, they make no mention of strategies for the often-ignored postoperative period (2, 10). If PBM does not extend to postoperative patients and they are left with anemia at discharge and beyond, this might explain the authors' observation that in parallel with reduced transfusion rates, anemia became more prevalent at discharge as well as during follow-up. The increase in prevalence, therefore, may be viewed as a failure to properly manage anemia during the full course of hospitalization and after discharge, not necessarily a consequence of reduced use of allogeneic blood.

The observation in this study that the outcomes—postdischarge transfusion, mortality, and readmission—apparently were unaffected requires some scrutiny as well (2). Transfusion rate is not a clinical outcome, and mortality and readmission—although important—might not provide an accurate or comprehensive snapshot of patient well-being. Missing here is a wide spectrum of morbidity outcomes and issues related to diminished quality of life that do not reach the level of severity that would necessitate admission but nonetheless detract from patients' health and well-being. Given the many consequences of anemia (3), proper management after hospital discharge will probably improve outcomes (5).

Transfusion trials were designed to address a simple question—whether performing transfusion at a certain hemoglobin threshold versus another would lead to better outcomes. This is a valid question that helps in formulating indications for transfusion, but the answer should not be taken out of the context. Transfusion trials do not address anemia treatment, and we cannot assume that once we find the “right” hemoglobin threshold at which to initiate transfusion (assuming that such a magical number exists), the problem of anemia

will be solved on its own. Anemia is a serious medical condition with substantial ramifications (and certainly not an “innocent bystander”), and allogeneic blood cannot provide more than a temporary relief—at a potentially hefty price. We look forward to future studies, not to retest the current study's hypothesis (that moderate anemia is acceptable after implementation of a restrictive transfusion practice and would not affect outcomes), but to examine the more sensible hypothesis that proper management of anemia, including during the postdischarge period, will lead to better outcomes. Let's increase efforts to prevent and treat anemia properly, rather than requiring patients to tolerate it.

*Aryeh Shander, MD*  
Englewood Hospital and Medical Center  
Englewood, New Jersey  
Icahn School of Medicine at Mount Sinai  
New York, New York  
and Rutgers University  
Newark, New Jersey

*Lawrence Tim Goodnough, MD*  
Stanford University  
Stanford, California

**Disclosures:** Disclosures can be viewed at [www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-3145](http://www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-3145).

**Corresponding Author:** Lawrence Tim Goodnough, MD, Department of Pathology, Stanford University, 300 Pasteur Drive, Room H-1402, Stanford, CA 94305; e-mail, [ltgoodno@stanford.edu](mailto:ltgoodno@stanford.edu).

Current author addresses are available at [Annals.org](http://Annals.org).

*Ann Intern Med.* doi:10.7326/M18-3145

## References

1. Shander A, Kim TY, Goodnough LT. Thresholds, triggers or requirements—time to look beyond the transfusion trials [Editorial]. *J Thorac Dis.* 2018;10:1152-1157. [PMID: 29708142]
2. Roubinian NH, Murphy EL, Mark DG, Triulzi DJ, Carson JL, Lee C, et al. Long-term outcomes among patients discharged from the hospital with moderate anemia: a retrospective cohort study. *Ann Intern Med.* 2018. [Epub ahead of print]. doi:10.7326/M17-3253
3. Shander A, Javidroozi M, Ozawa S, Hare GM. What is really dangerous: anaemia or transfusion? *Br J Anaesth.* 2011;107 Suppl 1:i41-59. [PMID: 22156270]
4. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, et al. Clinical trials evaluating red blood cell transfusion thresholds: an updated systematic review and with additional focus on patients with cardiovascular disease. *Am Heart J.* 2018;200:96-101. [PMID: 29898855]
5. Muñoz M, Acheson AG, Bisbe E, Butcher A, Gómez-Ramírez S, Khalafallah AA, et al. An international consensus statement on the management of postoperative anaemia after major surgical procedures. *Anaesthesia.* 2018;73:1418-1431. [PMID: 30062700]
6. Goodnough LT, Shander A. Current status of pharmacologic therapies in patient blood management. *Anesth Analg.* 2013;116:15-34. [PMID: 23223098]
7. Gross I, Trentino KM, Andreescu A, Pierson R, Maietta RA, Farmer S. Impact of a patient blood management program and an outpatient anemia management protocol on red cell transfusions in oncology inpatients and outpatients. *Oncologist.* 2016;21:327-32. [PMID: 26865590]
8. Muñoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. *Anaesthesia.* 2017;72:233-247. [PMID: 27996086]
9. Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. *Blood.* 2010;116:4754-61. [PMID: 20826717]
10. Goodnough LT, Shander A. Patient blood management. *Anesthesiology.* 2012;116:1367-76. [PMID: 22487863]

**Current Author Addresses:** Dr. Shander: Englewood Hospital and Medical Center, 350 Engle Street, Englewood, NJ 07631.

Dr. Goodnough: Department of Pathology, Stanford University, 300 Pasteur Drive, Room H-1402, Stanford, CA 94305.