

## Blood, Bleeding, and Transfusion—A Theme Issue

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**More than 16 million units of blood** are transfused in the US each year.<sup>1</sup> Blood transfusion is a cornerstone of modern medicine and far from a new idea. The first successful human blood transfusion was nearly 250 years ago, now used in the treatment of life-threatening hemorrhage, surgical bleeding, and countless other indications. Blood is also a scarce resource and should not be wasted. Despite the frequency with which clinicians administer blood to patients, there are many unknowns, including adherence to transfusion guidelines, strategies to prevent blood wasting, and treatment algorithms for blood and blood adjuncts in emergencies. Prompted by the release of 2023 guidelines from the AABB (Association for the Advancement of Blood & Biotherapies), *JAMA* presents a theme issue focused on blood, bleeding, and transfusion. This issue includes 4 original reports with new evidence, accompanied by 2 Editorials, 3 Viewpoints, and updated information about blood donation.



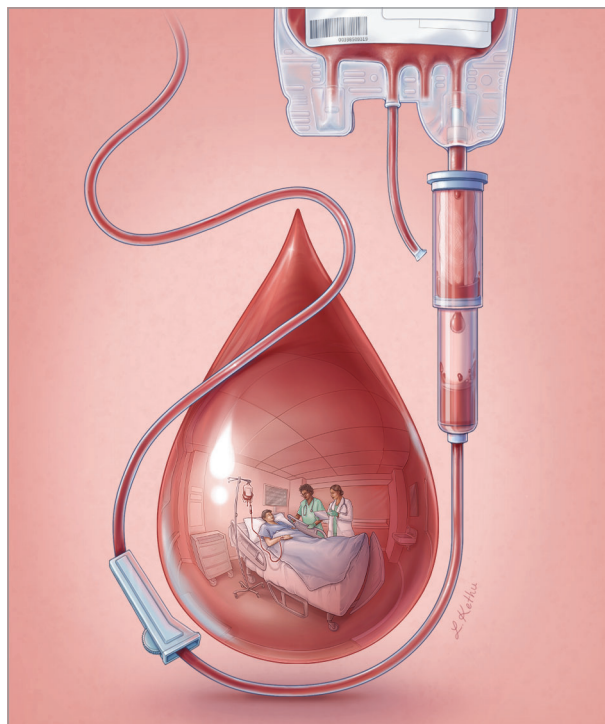
Viewpoint pages 1837, 1839, and 1841 and Editorial pages 1847 and 1849



Related articles pages 1852, 1862, 1872, 1882, and 1903 and JAMA Patient Page page 1921 and Related article page 1892

In the new AABB guidelines by Carson and colleagues,<sup>2</sup> the authors evaluated 45 randomized trials among 20 599 adults and children to examine the evidence for transfusion thresholds in hospitalized, hemodynamically stable patients. The primary recommendation among adult patients was to use a restrictive strategy in which red blood cell (RBC) transfusion is considered when the hemoglobin concentration is less than 7 g/dL (strong recommendation, moderate certainty evidence). This was also suggested for adults with hematologic and oncologic disorders (conditional recommendation, low certainty evidence, new from 2016 guidelines). Among children without a transfusion-dependent hemoglobinopathy, cyanotic cardiac condition, or severe hypoxemia, the panel also recommended transfusion when a hemoglobin level is less than 7 g/dL compared with one of less than 9.5 g/dL (strong recommendation, moderate certainty evidence). The authors place their recommendations in line with other societies and cite opportunities for more evidence. Most importantly, they highlight the importance of considering symptoms, signs, laboratory data, patients' values and preferences, and clinical context when deciding to transfuse, not just a hemoglobin value.

In the first original report, Raasveld and colleagues place these guidelines in context of current practice using an international, prospective cohort study of 3643 adult patients from 233 intensive care units (ICUs).<sup>3</sup> They found wide variability in stated transfusion thresholds, transfusion event triggers, and measured hemoglobin values at the time of transfusion. In fact,



they describe that, on average, 8 of 10 ICUs transfused RBCs when the patient's median hemoglobin value was greater than 7.0 g/dL. Although case mix, ICU, and hospital characteristics likely explain some variability, this work emphasizes the opportunity to harmonize transfusion practice with guidelines.

In another original report, Jansen and colleagues<sup>4</sup> tested an approach to limit uncontrolled hemorrhage in trauma: temporary aortic occlusion with the resuscitative endovascular balloon (REBOA). Amidst position statements and observational studies, the authors successfully performed the first randomized trial in humans of REBOA in traumatic injury. They used a multicenter, open-label, bayesian, group-sequential, registry-enabled design to randomize 90 patients over 5 years at 16 major trauma centers in the UK to REBOA plus standard care vs standard care alone in the emergency department. Accolades are due to the investigators for conducting this complex trial. The trial was stopped at the second interim analysis for harm in the REBOA group, and the authors take care to illustrate the many, varied treatment pathways that were present after randomization to REBOA.

Also in this issue, Siegal and colleagues<sup>5</sup> tackled the epidemic of wasted blood in a randomized trial of small-volume blood collection tubes vs standard-volume tubes for laboratory testing. Most sampled blood from hospitalized patients

is discarded, and despite the common-sense goal of minimizing iatrogenic blood loss, small-volume tubes are not standard of care in adults. The authors performed a pragmatic multicenter, stepped-wedge, cluster randomized trial in 25 ICUs in Canada among more than 21 000 patients, finding that small-volume tubes did not affect laboratory analyses and may reduce the risk of RBC transfusion per ICU stay (relative risk, 0.91). As a cost-neutral option, this work suggests it may be time to embrace “less is more” when it comes to how blood is sampled in the ICU.

In life-threatening bleeding, the transfusion of RBCs alone is not sufficient. Multifactorial clotting disorders arise in trauma, for example, that require adjuncts such as fibrinogen, platelets, or plasma. In their original report, Davenport and colleagues<sup>6</sup> investigated whether early, empirical administration of 3 pools of cryoprecipitate (6-g fibrinogen equivalent) could improve survival at 28 days when added to massive hemorrhage protocols. In 1604 randomized patients, the open-label administration of cryoprecipitate did not improve clinical outcomes compared with standard care for patients who were injured and bleeding. Of particular interest, though, was the report of significant effect modification by the mechanism of injury. For example, in the prespecified subgroup (36% of the total) with penetrating injury, cryoprecipitate was associated with a 74% increase in the odds of 28-day mortality compared with standard care (*P* for interaction = .004). No difference was observed in those with blunt injury.

These data are placed into context by Hunt and Neal in their Editorial.<sup>7</sup> They describe the biology of trauma-induced coagulopathy to emphasize that a “one-size-fits-all” approach to blood product administration is insufficient. They call for more precision transfusion research, with novel designs, enriched trial populations, and greater donor-recipient matching.

In another Editorial, Tisherman and Brenner reflect on the need for improvements in evidence generation in the bleeding trauma patient.<sup>8</sup> Amidst the fast-paced, stressful environment of the trauma bay, future trials need easy-to-use, accurate, and measurable inclusion criteria. The tested interventions require rigorous training and immediate administration in order to draw inference on the intervention itself, not the operator or system.

The issue also includes 3 important Viewpoints. First, Warner and colleagues<sup>1</sup> remind us that “the best blood for the patient is undoubtedly that which is already circulating within their vasculature.” When not available, they recommend that patients and systems collaborate in patient blood management (PBM) systems, a comprehensive program that maintains blood health. The Viewpoint from Young and Saa<sup>9</sup> brings a perspective on the role of the American Red Cross in blood collection and safety, and the authors update readers on new policy changes that embrace inclusivity in donation. They share the ongoing movement toward more equitable policies and a deep commitment to evidence and humanity. Finally, Holcomb and colleagues<sup>10</sup> describe a “tenuous latticework” that supplies patients and hospitals with blood products. They use examples from the US civilian and military settings to illustrate needs for broader donor blood collection, new reimbursement programs, and consistent research funding.

The theme issue concludes with a Patient Page on blood donation by Walter.<sup>11</sup> This piece summarizes the eligibility for donation, the step-by-step process, and locations to donate.

What have we learned at the end of this issue of *JAMA*? Blood is precious. We all must sacrifice to maintain a supply. That being so, health care professionals, scientists, and policymakers must strive to manage this resource with responsibility, curiosity, and enthusiasm.

#### ARTICLE INFORMATION

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