# Known and Unknown Unknowns in Making Erythrocyte Transfusion Decisions

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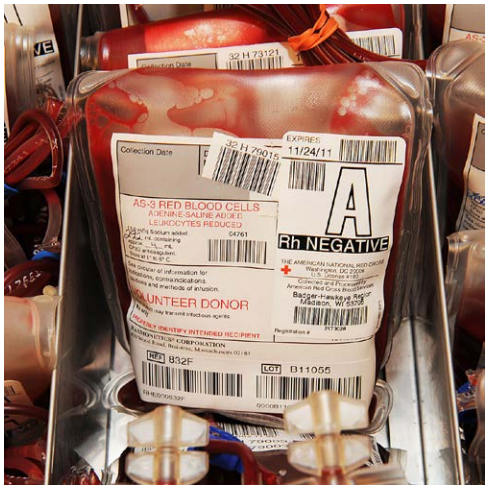
Erythrocyte transfusion, used as both a prophylactic and therapeutic intervention, is a cellular transplantation that comes with consequent sequelae including immediate[1–3] and long-term[4] engraftment of donor leukocytes in the recipient, and other immunologic adversities. It is, therefore, incumbent upon clinicians to identify when erythrocyte transfusion is indicated. This issue of Anesthesiology contains an important publication by Zeroual *et al.*[5] that investigates the consequence of increasing the restrictiveness of transfusion guidelines.




**"…the correct direction [is] finding and implementing physiologic criteria to dictate erythrocyte transfusion."**

Non–actively bleeding post-cardiac surgery patients in the intensive care unit (ICU) in whom hemoglobin concentration fell to less than 9 g/dl were randomly allocated by Zeroual *et al.* to either standard-of-care erythrocyte transfusion or to an experimental arm in which individuals would be transfused only if their hemoglobin was less than 9 g/dl *and* their superior vena cava oxyhemoglobin saturation (which does not include contribution from the inferior vena cava, thus distinguishing it from true mixed venous oxyhemoglobin saturation, usually clinically obtained from the pulmonary artery) was less than or equal to 65%. The addition of this criterion for transfusion naturally led to a decreased incidence of erythrocyte transfusion in the ICU (from 100% to 68%), with half of the individuals who were untransfused in the ICU remaining untransfused at hospital discharge; the fraction of patients requiring transfusion from randomization to hospital discharge was also significantly different between the two arms ($P = 0.0058$).

The importance of Zeroual *et al.*'s work is the implementation of adding a physiologic criterion, to the sole traditional criterion of hemoglobin concentration. It was noted in an earlier article[6] that to understand when oxygen delivery no longer meets oxygen need, an accurate measure of oxygenation at the cellular or tissue level is required, along with an understanding of the physiologic/pathophysiologic consequences of anemia for the critical organ(s) in each individual patient. Two decades later, erythrocyte transfusion decision-making still requires: (1) an ability to define when erythrocyte transfusion is physiologically required; and (2) clear understanding of the relative safety of transfusing erythrocytes *versus* not (untransfused anemia).

Zeroual *et al.* believe that superior vena cava oxyhemoglobin saturation is a measure that can be used to define erythrocyte need. All surrogates, including superior vena cava oxyhemoglobin saturation are second best to the real measure of interest, must be validated, and should be used only when the latter cannot be assessed. Unfortunately, in this circumstance we have been offered no data to support the notion that at a superior vena cava oxyhemoglobin saturation of less than or equal to 65% oxygen delivery is inadequate: no systemic or individual organ measures of inadequate oxygenation are presented. Decreased venous oxygen content is a consequence of increased tissue oxygen extraction—a normal physiologic response—but not a demonstration that the response mechanisms (increased cardiac output, increased oxygen extraction, or both) are not sufficient to compensate for the lesser hemoglobin concentration. Healthy humans respond to acute severe anemia with increased cardiac output and increased tissue extraction of oxygen as measured by decreased mixed venous (pulmonary artery) oxyhemoglobin saturation (the latter at a hemoglobin concentration of 5 g/dl is a mean of 69.6%), but without

*Image: J. P. Rathmell.*

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systemic evidence of inadequate oxygen delivery (normal, unchanged oxygen consumption and lactate concentration).[7] However, not all organs are equally sensitive to decrements in oxygen delivery, with the brain likely being the most sensitive. Healthy humans have central processing[8] and subtle cognitive function deficits at a hemoglobin concentration of 6 g/dl, (and more so at 5 g/dl),[9] despite an absence of systemic markers of inadequate oxygen delivery. These deficits are reversed by augmentation of oxygen delivery by erythrocyte transfusion[9,10] or breathing oxygen[11] when applied approximately 30 min after the onset of the severe anemia. It is unknown whether anemia-induced deficits would be fully reversible after a longer duration. Subtle cognitive function deficits are not generally detectible in an operating room or an ICU. Thus, we should seek other direct measures or validated surrogates that assess brain oxygenation and function. While assessment of superior vena cava oxyhemoglobin saturation or mixed venous oxyhemoglobin saturation might be available for a few selected patients, these data would not be available for typical patients requiring one to a few erythrocyte units. Nevertheless, Zeroual *et al.* point the field in the correct direction: finding and implementing physiologic criteria to dictate erythrocyte transfusion.

The trial was neither designed nor powered for safety, and there were no measures assessing higher central nervous system function. The results for ischemic events show a tantalizing four-fold, but statistically insignificant, numerical difference: 2% in the standard of care group *versus* 8% in the superior vena cava oxyhemoglobin saturation group; the 95% CI for the corresponding odds ratio ranges from 0.4 to 214, reflecting overwhelming uncertainty and the need for a trial with a substantially larger sample size. Renal function was appropriately assessed using the Kidney Disease Improving Global Outcomes criteria, but again, the results are inconclusive with the 95% CI for the odds ratio being 0.28 to 1.48. It would be helpful in such safety assessments to compare pretherapy data with posttherapy data, as well as assessing sensitive biomarkers (*e.g.,* urinary N-acetyl-β-D-glucosaminidase or neutrophil gelatinase–associated lipocalin). As with ischemic events, the incidence of renal deterioration to Kidney Disease Improving Global Outcomes stage 3 should be evaluated in a larger study.

Evidence guiding erythrocyte transfusion practice has at times come from misleading retrospective analysis of observational databases, which can suggest outcomes, but not provide definitive results. Randomized trials testing the hypotheses generated from such analyses can lead to a considerable expenditure of funds, personnel, and time that could have been better spent otherwise.[12] For example, a problematic retrospective analysis of patient data, investigating the efficacy and safety of transfusing erythrocytes that have been stored for more than 2 weeks *versus* less than 2 weeks[13] spawned many prospective clinical trials, all of which showed no difference between the two.[14–20] In smaller studies in healthy humans, it was previously shown that infusion of autologous fresh or stored erythrocytes did not differ in their ability to reverse anemia-induced cognitive function deficits[10] or their effects on pulmonary gas exchange.[21] The latter finding was confirmed in a small randomized trial in ICU patients.[22]

Appropriately designed, executed, and analyzed randomized trials yield the most rigorous means of testing clear hypotheses. However, they yield population-based measures of intervention effects, and do not give insights into how best to treat specific patients. As with many other fields of medicine, anesthesiologists, intensivists, and transfusion specialists treat a heterogeneous population of patients, each individual patient presenting with their own pathophysiology that may make them more susceptible to the consequences of different treatment courses. The clinician must be able to identify those who are in subpopulations for which the population-based effects do not apply. In this context, evaluation of each patient's pathophysiological response to anemia is critical to our ability to make an appropriate decision as to the need for oxygen delivery support such as erythrocyte transfusion. The trial that examined a more restrictive (8 g/dl) *versus* a more liberal (10 g/dl) hemoglobin concentration trigger in high-risk patients undergoing hip fracture surgical repair found no difference for mortality between the two groups. However, 14.1% in the restrictive group *versus* 4.8% in the liberal group were transfused due to cardiovascular symptoms referable to anemia ($P < 0.00001$), rather than having been transfused by reaching the assigned hemoglobin transfusion trigger. These issues make it difficult to comprehend that individualization of erythrocyte transfusion is debated,[23–25] with some arguing against the concept.[26] Our inability to clinically evaluate adequacy of critical organ oxygenation, and the need to prevent, rather than treat, the unacceptable consequences of anemia in a specific patient, is the genesis for the range of transfusion recommended by the American Society of Anesthesiologists.[27,28]

Waiting for clinical consequences of acute anemia may be ill-advised, as by the time of their detection, anemia may have caused irreversible damage. Accordingly, we should seek to prevent, rather than treat such consequences. To this end, markers of inadequate oxygen delivery to critical organs, and highly associated, validated changes in other parameters should be sought to identify the appropriate time for preventative intervention. Only when we can transfuse erythrocytes based on immediate or imminent physiologic need will we be able to appropriately assess the benefit to risk ratio of erythrocyte transfusion.

## Competing Interests

Dr. Weiskopf has consulted for the National Institutes of Health (Bethesda, Maryland), U.S. Food and Drug Administration (Washington, D.C.), and Department of Defense (Washington, D.C.) regarding transfusion programs. He has also consulted for sponsors of hemoglobin-based oxygen carriers, but has not received any compensation from any of these commercial entities in the past 3 yr. Dr. Cook consults with TerumoBCT (Lakewood, Colorado).

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