# Approaching a Safe Last Resort

## *Triggers for Perioperative Blood Transfusion*

W. Scott Beattie, M.D., Ph.D., F.R.C.P.C., Duminda N. Wijeysundera, M.D., Ph.D., F.R.C.P.C.

ANESTHESIOLOGISTS and perioperative physicians often face the challenging decision between transfusing or not transfusing an anemic patient. This decision implicitly requires balancing the risks of anemia *versus* the risks of red cell transfusion in an individual patient. Anemia affects more than 30% of patients undergoing elective surgery, and is associated with increased perioperative morbidity and mortality.[1,2] Conversely, the risks of perioperative red cell transfusion are also well described.[3,4] Observational studies have found that administration of just 1 to 2 units of erythrocyte concentrate to surgical patients is associated with increased morbidity and mortality. Nonetheless, it must be acknowledged that observational studies will likely never be able to adequately adjust for the inherent confounding by indication associated with perioperative transfusion. Stated otherwise, clinicians preferentially transfuse patients who are undergoing extensive risky surgery or have more severe comorbidity, especially cardiovascular disease. These confounders are almost always inadequately captured in observational datasets, therefore precluding adequate risk adjustment when assessing the association between transfusion and outcomes.

***"[There are] context-specific differences in appropriate transfusion triggers...[and this research] provides important guidance on how best to transfuse anemic surgical patients."***

Given the clinical importance of identifying appropriate circumstances to transfuse anemic surgical patients and the limitations of observational research methods to address this question, current "best evidence" comes from so-called "transfusion trigger trials." In these randomized controlled trials, patients are randomized to have either a high hemoglobin concentration threshold for triggering a transfusion (*i.e.*, "liberal" transfusion strategy) or a low hemoglobin concentration threshold (*i.e.*, "restrictive" transfusion strategy).

While widely viewed as considerably less biased than equivalent observational studies, the transfusion trigger study design has been criticized.[5] For example, these trials cannot be blinded and typically lack a control group representing usual clinical practice. The definition of "restrictive" and "liberal" across trials has been heterogeneous. Most importantly, the design entails imposing fixed standardized thresholds to *all* patients within an arm of the trial. By comparison, in clinical practice, physicians individualize a patient's transfusion threshold based on concomitant comorbidity. Thus, most perioperative physicians would specify different transfusion triggers for an otherwise healthy 35-yr-old patient compared to a 65-yr-old individual with long-standing cardiovascular disease.[6] Subgroup-specific differences in the efficacy and safety of transfusion trigger thresholds are both physiologically plausible and consistent with physicians' usual clinical practice.

In this issue of ANESTHESIOLOGY, Hovaguimian and Myles[7] present a meta-analysis of previous transfusion trigger trials that seeks to account for these important context-specific differences in appropriate transfusion triggers. While several previous meta-analyses of transfusion trigger trials have been published,[8–11] the study by Hovaguimian and Myles is superior in several important respects. *First*, they included every trial evaluating two transfusion thresholds in patients more than 18 yr of age. *Second*, they evaluated the compliance to the transfusion protocol, the erythrocyte-sparing effect, and the absolute difference in hemoglobin concentrations achieved between study arms. *Third*, these analyses evaluated outcomes separately within five *a priori* defined "context-specific" strata chosen to minimize the patient and procedural heterogeneity.

The results are important, and point to the importance of considering context when determining an appropriate transfusion trigger. In the younger noncardiac population, it is clear that a restrictive strategy (transfusion when hemoglobin concentration decreases below 70 g/l) is superior. In our view, this should be the policy *for this population*. Conversely, application of a restrictive strategy (transfusion when

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hemoglobin concentration decreases below 80 g/l) during cardiovascular surgery did not increase ischemic events or infections, but was associated with a disturbing trend toward increased mortality. Ongoing studies, such as the Transfusion Requirements in Cardiac Surgery III trial (Clinicaltrials.gov NCT 02042898), will better inform any policies with respect to appropriate transfusion triggers in cardiac surgery.

Finally, in noncardiac surgery, a restrictive strategy (transfusion when hemoglobin concentration decreases below 80 g/l) increased ischemic events, but surprisingly did not affect the mortality rate. The current guidelines in this patient population are largely based on, and consistent with, the restrictive transfusion strategy employed in the Functional Outcomes in Cardiovascular Patients Undergoing Hip Fracture Repair trial.[12] In this randomized controlled trial comparing transfusion triggers in high cardiac risk, predominately elderly female, patients after hip fracture surgery, the restrictive transfusion threshold was 80 g/l. Importantly, the Functional Outcomes in Cardiovascular Patients Undergoing Hip Fracture Repair trial incorporated a provision to transfuse at any time if there were "symptoms." Notably, the trial found that rapid bleeding, heart failure, hypotension, and tachycardia occurred frequently and more often in the restrictive strategy arm. But when these hemodynamic symptoms were treated, there were no differences in postoperative myocardial injury or deaths at either 30 days or 3 yr.[13] Thus, on the basis of this trial at least, a practice of administering erythrocyte concentrate when the hemoglobin concentration decreases to 80 g/l with the provision for earlier symptomatic transfusion appears both safe and economical. Whether this treatment plan is generalizable to other populations requires further study.

While the study by Hovaguimian and Myles provides important guidance on how best to transfuse anemic surgical patients, transfusion is just one component of a comprehensive strategy to mitigate the perioperative risks of anemia. There is a critical need to study preoperative interventions, such as iron and erythropoietin, to potentially reduce preoperative anemia.[14] In addition, an overall strategy must incorporate methods for minimizing perioperative blood loss, such as appropriate fluid administration protocols, protocols for managing long-term preoperative anticoagulants[15] or antiplatelet agents,[16] appropriate thromboprophylaxis regimens,[17] maintenance of normothermia,[18] targeted use of antifibrinolytics,[19] and careful surgical technique. In this scheme, transfusion is considered the "last resort" in anemia management, further restricting exposure to the risks of blood products.

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## Correspondence

Address correspondence to Dr. Beattie: scott.beattie@uuhn.ca

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## ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

# Choleric Temperamental Education for 1893 Classes by "Masters of Anaesthesia"


Flemish artist Maerten de Vos' spear-wielding *Cholericus* (1583) reminds us that a **fire**-like patient of "choleric" temperament commanded the hot, dry "yellow bile" humor linked by ancient Greeks with elemental **fire**. By 1893 at Chicago's Post-Graduate School of Anaesthesia (PGSA), professors were tutoring future "Master of the Science of Anaesthesia" candidates to anticipate that a choleric patient's anesthesia might comprise—what today's anesthesiologists would characterize as—(1) a swift induction, (2) a risk for heart-depressing anesthetic overdosage (termed "concussion" by the PGSA), and (3) a stormy emergence. PGSA founder and secretary, Professor Samuel J. Hayes, D.D.S., M.S.A., taught that choleric patients might resist preanesthetic calming. Dr. Hayes also used the journal that he edited, *The Dental and Surgical Microcosm*, as a primer for teaching PGSA students about the dangers of cardiovascular "concussion" from anesthetic overdose. 

*George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.*