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How to guide transfusion decision-making? (that is the question)

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Red Blood Cell (RBC) transfusion is indicated to improve oxygen (O_2) delivery to tissue, and for no other purpose. Although RBC transfusion increases hematocrit (Hct) and thereby blood O_2 content, it does not necessarily follow that tissue O_2 delivery is likewise increased - unless blood O_2 content, itself, is rate-limiting in transfer of O_2 from lung to tissue. This important distinction is clearly illustrated in the paper by Fiser, et al. in the current issue of the *Journal* [1], in which efficacy was retrospectively evaluated for administered to 45 children on ECMO. Efficacy was defined as a 5% increase in mixed venous HbO_2 % (SvO_2) or in 'tissue' O_2 saturation (near infra red spectroscopy, NIRS StO_2). In this single institution retrospective analysis, 617 RBC transfusions were administered to 45 children, with a median per-individual exposure to 10.9 donor units. In this population, the median Hct maintained during ECMO was 37%. Notably, only 5% or 9% of transfusions were efficacious in improving measures of tissue oxygenation (by SvO_2 or StO_2 , respectively); this striking lack of efficacy was uniformly observed across the full range of pre-transfusion Hct values (~ 25–45%), RBC unit storage duration (~ 0–30 days), and regardless of ECMO indication (cardiac or respiratory). As such, this paper instructs us how *not* to guide transfusion decision-making (assuming we wish our decisions to be efficacious > 10% of the time).

The practice evaluated in this report (transfusion to maintain ~ 'normal' Hct) is consistent with the Guideline published by the Extracorporeal Life Support Organization (ELSO)[2] and with reports by other ECMO centers[3], though some now target a lower Hct (30%)[4]. The strategic basis for this approach is to maintain an 'adequate' RBC mass well above a threshold that may critically limit tissue O_2 delivery. This approach is not limited to caring for patients on ECMO and is a component of guidelines for sepsis, trauma, stroke, respiratory failure and etc. However, with improved understanding of vascular signaling and gas transport by RBCs[5, 6] and of the full array of defects comprising the RBC 'storage lesion'[7, 8], we now appreciate that this strategy must be balanced by consideration that:

(1) processed/stored donor and native RBCs do not exhibit similar physiology and (2) RBC transfusion may cause harm (beyond transfusion reactions and transmission of infection) – and that this harm appears progressive with transfusion volume and frequency. Specifically, RBC transfusion loads tenuous systems for clearing free Hb and Fe, impairs physiologic control of regional vascular tone, negatively impacts coagulation, immune function and antioxidant systems – in fact, a series of acronyms have been coined to describe these protean complications of RBC transfusions (TACO, TRIM, TRALI, and etc.). As such, newer ‘restrictive’ Hct thresholds for transfusion (e.g. ~ 21%) are now appreciated to be at least non-inferior (and in many cases, to be superior) to more ‘liberal’ Hct thresholds (e.g. ~ 30%) for a broad array of conditions [9–15], even in actively bleeding patients [16].

Moreover, while traditional thresholds for transfusion are currently undergoing a broad ‘reset’, a comprehensive paradigm shift is emerging in our approach to transfusion for the critically ill, with re-consideration of the transfusion ‘Hct trigger’ strategy, itself. Clearly, it is not feasible to define specific Hct boundaries across the complex interaction of developmental-, condition- and stress-specific situations encountered in the ICU. Ideally, the decision to transfuse should be based upon individual and context-specific consideration of the degree to which anemia contributes to tissue O₂ delivery constraint (and/or reserve)[17–20]. This distinction is exemplified by the targeting ‘physiologic’ triggers (e.g. transfusing only to rectify abnormal measures of perfusion sufficiency, rather than to maintain a specific Hct, irrespective of context)[21, 22]. However, in considering the best means to define and execute such a strategy, we must improve current means to assess functionality of the circulating RBC mass and its specific relationship to tissue O₂ delivery, perhaps through novel use of current technology[23, 24]. Hopefully, this excellent paper by Fiser et al.[1] will stimulate further effort in this ‘vein’.

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