

Restrictive *versus* liberal transfusion thresholds: lights and shadows

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Anemia (i.e., according to the World Health Organization, hemoglobin levels <13 g/L in men and <12 g/L in women) is a common condition that recognizes several causes, including blood loss, pregnancy, cancers (and associated chemotherapy), infections, kidney disease, autoimmune disorders, chronic diseases, dietary deficiency, etc¹. As anemia reduces the oxygen content of blood supplied to the tissues, with potential deleterious consequences, its proper recognition and correction is mandatory. To manage anemia, avoiding as much as possible exposure to allogenic blood transfusion, patient-centered blood management (PBM) programs have been rapidly developed worldwide in the last two decades^{2,3}. In addition to the various strategies aimed at implementing the three pillars of PBM (i.e., the optimization of endogenous erythropoiesis, the minimization of bleeding and blood loss, and the optimization of the physiological reserve), a PBM approach must also include the appropriate transfusion of red blood cells (RBC), when all other alternatives (such as iron administration) have been excluded⁴. The optimal hemoglobin threshold for transfusing RBC is a crucial question in modern transfusion medicine, which numerous investigators have tried to answer during the last forty years^{5,6}. The issue is more complex than believed given that it is not only linked to the fact that blood is a limited resource (and as such should only be used when absolutely necessary) potentially associated with adverse reactions, but it implies a close relationship with the patient clinical outcome⁷. Although each decision on when to transfuse should be personalized and related to the patient's clinical condition and comorbidities, historically, a widely accepted clinical standard was to transfuse patients when the hemoglobin level dropped below 10.0 g/dL (or hematocrit <30%)⁸. This paradigm has gradually changed over the years with a number of randomized clinical trials (>50 have been identified through a PubMed search at the time of writing) investigating if a "liberal" RBC transfusion policy (where patients are transfused at a hemoglobin concentration of 9.0-10.0 g/dL) is superior in term of clinical primary outcome (evaluated as 30-day mortality) to a "restrictive" RBC transfusion threshold (where, typically, patients are transfused only when their hemoglobin concentration falls below 8.0 g/dL). The latest update (2021) of the Cochrane systematic review on transfusion thresholds for guiding RBC transfusion, which identified 48 trials with more than 20,000 participants across a wide range of clinical contexts, showed that, compared with a liberal transfusion strategy, a restrictive transfusion strategy did not increase or decrease day-30 mortality (risk ratio [RR] 0.99, 95% CI 0.86 to 1.15) or any of the secondary outcomes assessed (i.e., cardiovascular or infectious events) with a moderate to high-quality of evidence⁹. A recent overview of 16 meta-analyses graded as high to moderate quality indicated that in most patient populations no difference in mortality existed between patients assigned to a restrictive or liberal transfusion strategy¹⁰.

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A number of guidelines and recommendations from national or international scientific societies have been published in the last two decades with the aim of translating such results into clinical practice (*see reference number 5 for a detailed summary*). Although with different levels of evidence and variable degrees of recommendations, almost all scientific societies nowadays recommended the implementation of a restrictive RBC transfusion policy in surgical, hemodynamically stable patients. The most recent international guideline on RBC transfusion is the one issued by the Association for the Advancement of Blood and Biotherapies (AABB), published in 2023 and including information from 45 RCTs among adults (20,599 participants) and 7 RCTs among pediatric populations (2,730 participants)^{7,11}. The panel of experts strongly recommended restrictive transfusion strategies, typically with a threshold of 7 g/dL for both adult and pediatric patients. At this point, the choice of a universal RBC transfusion threshold could definitively close the debate: in reality, this is not the case as several exceptions in particular subgroups must be immediately highlighted. For instance, in patients with hematologic malignancies treated with chemotherapy or radiotherapy or undergoing hematopoietic stem cell transplantation (HSCT), the small number of published trials and of participants enrolled did not permit to highlight the superiority of neither of the two transfusion thresholds. Thus, the experts performed a conditional recommendation, with low certainty of evidence, in favor of a restrictive RBC transfusion threshold in this category of patients, advocating the need for further research to reach stronger evidence⁷. A recent Cochrane review on the same issue drew similar conclusions¹². There are also gaps in the evidence regarding the transfusion needs of individuals with myelodysplastic syndromes who are transfusion dependent. Indeed, to improve the symptoms of anemia and quality of life, such patients may require higher thresholds for RBC transfusions¹³.

Another grey area on RBC transfusion trigger policy regards anemic patients with cardiovascular disorders, in particular those with acute and chronic ischemic cardiac disease. In such patients, indeed, RBC transfusion is the most important treatment for a rapid increase of hemoglobin concentration, able to restore myocardium oxygenation with a resulting better heart functional

activity and, ultimately, improved survival⁹. While the 2023 AABB international guidelines stated that “for patients with acute and chronic ischemic cardiac disease, there remains substantial uncertainty regarding the safety of restrictive RBC transfusion thresholds”, a meta-analysis concluded in favor of liberal RBC transfusion threshold as opposed to a restrictive approach for patients with cardiovascular disorders¹⁴. A more recent meta-analysis¹⁵, however, questioned such conclusions, leaving this issue substantially unsolved and deserving of further research. Another opened investigational field is that of the transfusion support to anemic patients with neurological injury/traumatic brain injury, acute neurological disorders, and stroke, considering the high oxygen requirements of a vital organ such as the brain⁹.

In conclusion, there is robust evidence from the existing literature supporting the restrictive RBC transfusion policy over a liberal strategy. However, while this recommendation can be assumed as a general rule, there are several exceptions (i.e., hemodynamically unstable patients and those with cardiovascular or neurological disorders and other comorbidities) that must be carefully considered before deciding when to transfuse a patient. Thus, in the era of PBM and patient-centered medicine, we strongly suggest an individualized approach that evaluates case by case the appropriateness of RBC transfusion. In this context, the support of transfusionists to their colleagues of other specialties in evaluating the delicate balance between patients' blood oxygenation and deoxygenation and the consequent RBC requirements is greatly advised, to improve patients' management and, finally, their clinical outcome.

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