Review Article



# Anemia and red blood cell transfusion in the adult non-bleeding patient

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**Abstract:** Anemia is a global health issue. It is associated with a wide variety of disease states in both medical and surgical patients. Increased morbidity and mortality are notable in patients with even mild anemia. Clinicians often consider red blood cell (RBC) transfusions as first-line therapy for patients with anemia to raise the hemoglobin (Hgb) level and increase oxygen delivery. RBC transfusion in the hemorrhaging patient can be life- or limb-saving. However, RBC transfusion may result in serious adverse events, both acute and delayed, and thus, the medical decision to transfuse in the non-bleeding, anemic patient must be carefully considered. Recent literature identifies RBC transfusion practice, in a multitude of patient populations, can be readily avoided with attention placed on proper assessment of patient symptoms, optimal diagnosis of the etiology of the anemia, and appropriate treatment thereof. This review seeks to collate the current state of the science regarding RBC transfusions in the adult non-bleeding patient. Evidence-based alternatives to transfusion will also be briefly presented.

**Keywords:** Anemia; red blood cells (RBC); transfusion

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## Introduction

Anemia is a global health issue affecting approximately one quarter of the world's population (1). Anemia in presurgical patients may be as high as 40% (2) and results in increased morbidity and mortality (3,4). Furthermore, an Australian study found more than 1/3 of non-anemic medical and surgical patients admitted to the hospital subsequently developed anemia (5). Even mild anemia, defined as Hgb 10.0–11.9 g/dL in women, 10.0–12.9 g/dL in men, was independently associated with increased mortality and length of stay (LOS).

While anemia is a formal and commonly used medical diagnosis, it should not be accepted as normal, but instead as a sign associated with an array of disease states in both medical and surgical patient populations. Anemia demands attention with proper identification of the underlying etiology(ies). Anemia may not cause overt symptoms depending on the severity and physiologic compensatory mechanisms. The critical nadir hemoglobin (Hgb) level at which symptoms arise is not clear and may vary based on the etiology of the anemia, patient comorbidities, the acute or chronic nature of the anemia, and the presence or absence of overt bleeding. Clinicians often consider red blood cell (RBC) transfusion to ameliorate symptoms of anemia or to prevent perceived pending consequences of abnormal Hgb levels.

Certainly, in the hemorrhaging patient, transfusion can be life- and or limb-saving. However, in the non-bleeding patient, formulating transfusion decisions must take a risk-to-benefit perspective into consideration, such as the potential adverse events, the lack of evidence for improved oxygenation, as well as alternative evidence-based therapies.

RBC transfusions have been associated with numerous adverse events both non-immune and immune-mediated. These include, but are not limited to transfusion associated circulatory overload, transfusion-related acute lung injury, hemolytic transfusion reactions, increased wound

**Table 1** Society Guidelines: all supporting Hgb transfusion thresholds of 7–8 g/dL

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| 2009—Society of Critical Care Medicine |
| 2011—Society Thoracic Surgeons/Cardiovascular Anesthesiologists |
| 2012—AABB |
| 2013—American Society of Hematologists |
| 2015—American Society of Anesthesiologists |
| 2016—AABB |
| 2019—The NATA Consensus Statement |
| 2019—Society of Cardiovascular Anesthesiologists |

Hgb, hemoglobin; AABB, American Association of Blood Banks; NATA, Network for Advancement of Transfusion Alternatives.

and nosocomial infections, allergic reactions, increased hospital LOS, increased thrombo-embolic events, and the possibility of transfusion-transmitted disease (6-14). There is evidence that RBC transfusions do not necessarily improve delivery of oxygen or tissue perfusion (15-17). Additional technologies to evaluate tissue oxygenation and microcirculation may ultimately become the standard of care for assessment and identification of anemic patients and the potential benefit of RBC transfusion (18).

This review will present the current evidence to identify the elusive Hgb threshold and delineate the role of RBC transfusion and non-transfusion modalities for ameliorating morbidity associated with low Hgb levels in adult non-bleeding patients.

## Clinical studies of anemia and RBC transfusion in special patient populations

Recent guidelines, systematic reviews and meta-analyses of randomized controlled trials (RCTs) have found that restrictive transfusion of RBCs provides similar if not better outcomes across a broad range of medical and surgical patient populations (19,20). This has been the impetus for numerous professional societies to advocate for the tolerance of lower Hgb levels in otherwise stable anemic patients (*Table 1*). In general, the use of a specific transfusion "trigger" should be avoided as this implies automatic RBC transfusion at a designated level as opposed to a "threshold" level above which transfusion might be safely avoided and or alternative interventions could be employed. This concept is emphasized in the recent Patient Blood Management Frankfort Consensus Conference (21).

### *Critically ill patients*

By day three in the intensive care unit (ICU), up to 90% of patients will become anemic (22). Acute or chronic blood loss, poor nutrition, comorbid conditions, excessive phlebotomy, coagulopathy, and drug interactions may all contribute to anemia in the critically ill. Transfusion is performed frequently in the ICU with between 30 to 70% of patients receiving RBC transfusion based on case mix (23). The majority of these transfusions are in non-bleeding patients. A systematic review of 45 cohort studies of anemic ICU patients receiving RBC transfusion found 42 of 45 studies identified the risk of transfusion to outweigh the benefit (24).

The first RCT comparing restrictive versus liberal transfusion thresholds was published in 1999. The Transfusion Requirements in Critical Care (TRICC) trial showed a Hgb threshold of 7.0 g/dL with maintenance Hgb between 7.0–9.0 g/dL was equally effective in terms of patient outcomes, when compared to a threshold of 10.0 g/dL and higher maintenance levels of 10.0–12.0 g/dL (25). Patients with acute myocardial infarction (AMI) and unstable angina (UA) were disproportionately excluded by participating physicians, thus the TRICC investigators cautioned against extrapolating to Hgb thresholds less than 8.0 g/dL in these patients.

### *Patients with acute coronary syndromes (ACS)*

Concerns regarding restrictive RBC transfusion in patients with ACS or with underlying significant coronary artery disease (CAD) are understandable given the need for high basal oxygen extraction by the myocardium, the limited tolerance to anaerobic metabolism, and the decreased flow through stenotic vessels. Data is conflicting in this population due to the heterogeneity among patients, for example, ST-elevation versus non-ST-elevation, lack of clear definitions for "significant", yet "chronic" CAD, as well as the varied comorbidities which accompany these patients (26-33). The recent REALITY Trial randomized greater than 660 patients with AMI and anemia. The RBC transfusion threshold paradigm was ≤8.0 g/dL versus ≤10.0 g/dL. Those within the restrictive group had no increases in major adverse cardiac events (MACE) after 30 days when compared to the liberal group (34). Ongoing trials continue (35), but, at this time, available evidence

implies the potential for improved outcomes in patients with ACS with a Hgb threshold of 8.0 g/dL (36-38).

### *Patients with sepsis or septic shock*

Trials in critically ill patients with sepsis have also found a lack of evidence that RBC transfusion improves outcomes (39,40). The Transfusion Requirements in Septic Shock (TRISS) trial included over 900 patients with randomization to Hgb thresholds of 7.0 versus 9.0 g/dL (41). This trial also included a single-unit transfusion strategy with assessment after each unit. No differences in 90-day mortality, need for vasopressors, duration of mechanical ventilation or occurrence of ischemic events were noted. *Post-hoc* analysis of a subgroup of patients from the TRISS trial showed no benefit to a liberal transfusion strategy in patients with significant comorbidities such as chronic lung disease, hematologic malignancies or metastatic cancer (42). Recent guidelines for management of sepsis and septic shock do not recommend transfusion to maintain a specific Hgb level as first-line treatment (43).

### *Mechanically ventilated patients*

Expectations regarding the need for higher Hgb levels in mechanically ventilated patients have been steeped in anecdotal and historical experience often without definitive data. A subgroup analysis of mechanically ventilated patients in the TRICC trial showed no differences in duration of mechanical ventilation between the restrictive versus the liberal group (44). A retrospective cohort study of greater than 4,300 patients necessitating prolonged mechanical ventilation (≥96 hours), found an increased risk of death associated with Hgb levels greater than 10 g/dL and receipt of at least one unit of RBCs (45). A pilot RCT of adult patients on mechanical ventilation ≥4 days revealed no differences in duration of ventilation or cardiovascular events when randomized to 7.0 versus 9.0 g/dL (46). This study showed a trend toward increased mortality in the liberal group. The recent Transfusion Requirements in Cardiac Surgery III (TRICSIII) trial contained greater than 2,400 patients with available data regarding duration of mechanical ventilation and found no differences in median days (47). Data surrounding Hgb levels required as part of weaning protocols are somewhat limited, however, current evidence points to restrictive thresholds, Hgb <7.0 g/dL (23,36,48,49).

## Transfusion in cardiac surgery

The previously mentioned TRICSIII trial is the largest trial to date, including over 5,200 patients (47). This trial captured intra-operative and post-operative transfusions after randomizing to a 7.5 versus 9.5 g/dL Hgb strategy. No differences were noted between the groups for outcomes including all-cause mortality, AMI, new-onset renal failure, stroke, LOS or infections. Subsequent analysis from this trial found no differences in long-term outcomes six months after discharge, specifically mortality, AMI, stroke, or renal failure (50). Two recent meta-analyses recognized restrictive RBC transfusion is not inferior to liberal transfusion practice in cardiac surgery patients (51,52).

The Clinical Practice Guidelines on Patient Blood Management for Cardiovascular Surgery has been recently published (53). This publication supersedes the prior 2011 guidelines (54) and has several significant modifications, not the least of which is the specific change from "blood conservation" to "patient blood management" guidelines. There is also an expanded collaboration of the Society for Thoracic Surgeons and the Society of Cardiac Anesthesiologists with the American Society of Extracorporeal Technology and the Society for the Advancement of Patient Blood Management. As such, the intent of the authors was to stress the importance of a multidisciplinary evidence-based approach to the care of cardiac surgery patients. The concept of blood as a liquid organ is also emphasized, thus one must extrapolate that transfusion represents a fluid/liquid transplant. The guidelines include the above-mentioned studies regarding restrictive RBC transfusion and incorporation of goal-directed transfusion algorithms. Class and level of evidence are delineated for anemia management, optimization of coagulation, minimizing bleeding and blood loss, and multimodal interventions to conserve the patient's own blood. These concepts all align with a patient-centered approach as a pillar of Patient Blood Management (PBM). Previous studies underscore the relevance of PBM to the cardiac surgery arena to limit transfusion exposure and provide better quality of care (55,56).

Of note, the expanding interest for anemia management in this population has been driven by recent evidence that the prevalence of pre-operative anemia in cardiac surgery patients is as high as 31% (57). Anemia and transfusion are independently associated with worse clinical outcomes (57). Iron deficiency is the most common cause of anemia in this population and studies indicate laboratory evaluation

of iron status and subsequent iron repletion can decrease transfusion rates as well as the incidence of persistent anemia post-operatively (58). A recent expert panel, using a modified RAND Delphi method, recommends all patients preparing for cardiac surgery be evaluated for iron deficiency whether or not overt anemia is present (59).

## Other surgical and medical patients

Limiting unnecessary RBC transfusion in other surgical patients is likewise important. The American Society of Anesthesiologists (ASA) practice guidelines for perioperative management advocates for thorough assessment of bleeding risk, diagnosis and treatment of anemia and use of pharmacologic adjuncts to decrease blood loss; all techniques which will minimize the need for allogeneic RBC transfusion (60). Restrictive transfusion practice is evidence-based, well-tolerated, safe, and applicable for orthopedic, burn, and surgical oncology patients (61-64). There remains some question as to the adequate Hgb level for patients undergoing major vascular surgery. Data is limited. A small pilot study of 58 patients showed higher death rates and major vascular complications with lower Hgb, <8.0 g/dL (65). The authors called for further trials prior to extrapolating general restrictive thresholds to these patients.

A recent consensus statement regarding post-operative anemia management after major surgery has been published, helping to clarify interventions which furnish continuity of care for surgical patients before and after discharge (66).

Hematology/oncology patients may have significant transfusion needs, particularly during episodes of high-dose or ablative chemotherapy, radiation therapy, or after stem cell transplantation. Transfusion reactions are frequent in these patients, as well as the increased risk of alloimmunization and transfusion-associated graft versus host disease. Current evidence speaks to the safety and efficacy of restrictive transfusion in varied hematologic patient subgroups (67-73). The American Society of Hematology (ASH) Choosing Wisely® Campaign stresses a restrictive approach with RBC transfusions considered when Hgb levels drop below 7.0–8.0 g/dL (74).

There remains some uncertainty in chronic transfusion-dependent hematologic patients, particularly in the outpatient (OP) setting. Liberal RBC transfusions come with the increased incidence of the afore-mentioned risk of acute transfusion reactions with the added risk for transfusion-related iron overload. Patients with myelodysplasia (MDS) represent a significant number of those in the OP arena and have been found to receive the most RBC transfusions when compared to other patients with hematologic conditions (75). MDS is predominantly a disease of older patients, many of whom have co-morbid cardiac disease coupled with the dysregulated iron metabolism which may cause further cardiac injury and, thus, place them at risk for ACS (76). The OP setting also raises the question of RBC transfusion to maintain a more constant or stable Hgb level as opposed to the potential fluctuations with a more restrictive transfusion strategy i.e. lower Hgb thresholds and single-unit transfusion. This may be a more significant issue for patients who are demographically farther removed from their care team. The current REDDS-2 pilot study will address issues associated with OP transfusion (77).

## Single-unit transfusion

Single-unit RBC transfusion has historically been discouraged with double-unit transfusion favored, assuming more effective oxygen delivery and correction of anemia. This practice rested on opinion and was not evidence-based. In the late 1980s, the National Institute of Health (NIH) published recommendations for single-unit RBC transfusion primarily driven by the concern for patient exposure to transfusion-transmitted diseases (78). The double-unit transfusion rate, however, still remained at >98% in 1998 (79). Recent literature shows a move to more broad acceptance of single-unit RBC transfusion practice with a "treat-to-target" clinical assessment and lab-driven correlation (80,81). A 2008 survey by the College of American Pathologists (CAP) found the percent of single-unit transfusion in 124 hospitals, 6518 total transfusions, to be 60% (82). The United Kingdom National Institute for Health and Care Excellence (NICE) Guidelines implemented a single-unit policy in general medicine patients with overall reduction in RBC transfusions of 50% and an increase in single-units transfusion rate from 30% to 53% over six months (83).

Single-unit transfusion strategies have been shown to be safe and effective even in high-risk patients (84,85). Coupled with evidence that adverse outcomes are associated with even a single unit of RBCs, this sends a clear message to limit transfusion when possible (86,87). ASH and AABB strongly advocate for the use of single-unit RBC transfusion as part of restrictive practice (74,88). See comment in the previous section regarding

consideration for SUT in OPs.

## Competing strategies/non-transfusion alternatives

RBC transfusion may be avoided through proper diagnosis and management of anemia. Iron deficiency is the most common etiology (89). Other nutritional deficiencies and chronic gastrointestinal or gynecological blood loss are also frequently identified. Comorbid inflammatory conditions, such as autoimmune disorders, congestive heart failure (CHF), and chronic kidney disease (CKD) induce functional iron deficiency as a result of increased hepcidin, the primary regulator of iron metabolism and absorption. Increased hepcidin limits iron absorption and thus effective erythropoiesis, even in the face of adequate total body iron stores (90).

Anemia is common in patients with CHF. This is often a result of iron deficiency. Transfusion may result in circulatory overload and thus transfusion avoidance should be encouraged when other treatment options are available. Recent study results encourage the use of iron supplementation for patients with CHF and show significant improvement in New York CHF classification and outcomes (91,92). The European Society of Cardiology recommends the use of intravenous iron in symptomatic CHF patients with low ferritin or transferrin saturation as this can improve symptoms, capacity for exercise and general quality of life (93).

Chronic blood loss causes iron deficiency in patients with inflammatory bowel disease (IBD) and these patients are much less tolerant of oral supplementation. A recent systematic review and meta-analysis found intravenous iron, when compared to oral agents, more effectively increased Hgb levels and repleted iron stores in these patients (94).

Parenteral iron in patients with CKD has been found to more rapidly increase iron stores and Hgb levels, while reducing the need for erythropoiesis-stimulating agents (ESAs) (95). A large RCT reported scheduled infusions of intravenous iron reduced mortality and comorbid cardiovascular events (96). The discovery of hypoxia-inducible factor (HIF) and its role in erythropoiesis in CKD has opened the door to development of HIF-prolyl hydroxylase inhibitors, such as roxadustat and vadadustat. These oral medications stimulate endogenous erythropoiesis by stabilizing HIF (97). Phase III trials are currently ongoing in the U.S. and some agents have been approved for both non-dialysis dependent (NDD-CKD) and dialysis-dependent (DD-CKD) patients (98). Efficacy for anemia treatment has been shown in recent RCTs, however some questions remain as to safety (99,100).

ESAs, given either intravenously or subcutaneously, stimulates RBC production. A recent review and meta-analysis of 32 RCTs using pre-operative ESAs in surgical patients identified significant reduction in the number of peri-operative RBC transfusions without significant risk (101). Even single-dose and ultra-short (between 1–2 days) provision of ESAs in cardiac surgery patients can decrease RBC requirements (102,103). Management of cancer-associated anemia with ESAs has been recently reviewed by the American Society of Clinical Oncology (ASCO) and ASH (104). Recommendations are to consider use of ESAs in patients with chemotherapy-induced anemia without curative intent and with Hgb levels <10 g/dL. Of course, when using ESAs there should be provision of concomitant iron therapy for full repletion of iron stores which allows for the lowest dose of this agent to avoid Hgb concentrations >11.0 g/dL. This prevents hyperviscosity and the risk of thrombosis. Studies indicate no benefit for use of ESAs for patients with pre-treatment Hgb >10.0 g/dL (105,106).

Operative blood loss exacerbates pre-existing anemia and, thus, pharmacologic agents that minimize bleeding can play an active role in the overarching management of the anemic patient. The incorporation of anti-fibrinolytic agents such as tranexamic acid (TXA) or aminocaproic acid, can reduce blood loss, anemia, transfusion risk and mortality (107-111). The use of antifibrinolytics and the possibility of thrombosis have been historical safety concerns, however, a recent systematic review and meta-analysis of 216 relevant studies using TXA showed no increase for any thrombo-embolic event including deep venous thrombosis, pulmonary embolism, AMI or stroke irrespective of dosing (112).

Additionally, topical hemostatics may also contribute to control or prevention of bleeding and thus provide some mitigation from worsened anemia. An excellent review has been published by Huang *et al.* (113).

Excessive phlebotomy should be discouraged as this contributes to anemia in the hospital setting. Diagnostic testing can result in >40 milliliters of blood loss every day with a median of 200 milliliters during hospital admission (114). Best practices have been published by the Center for Disease Control (CDC) Laboratory Medical Best Practice Group, the American Society for Clinical Pathology (ASCP) Choosing Wisely® Campaign and are echoed in the Choosing Wisely® statements from the

 

Society for the Advancement of Patient Blood Management (SABM) (115-118).

Intra-operative blood conservation strategies such as autologous cell salvage and acute normovolemic hemodilution also reduce the need for, and the exposure to allogeneic RBCs. Timely reviews are available (119,120).

## Future research needs

A recent review by Mo *et al.* highlights the need for continued study of transfusion practices in specific patient subgroups where equipoise remains, as well as suggesting other outcome measures as both necessary and appropriate (121). These could include improved tools for assessment of quality of life, attention to the patient experience, both physical and psychosocial, and study of the economic ramifications of transfusion and competing strategies. These concepts are clearly aligned with the patient-centered approach advocated in the proposed "global definition" for Patient Blood Management (122).

## Conclusions

Anemia represents a global health issue. Whether acute or chronic, the signs and symptoms are myriad and etiologies are not mutually exclusive. While RBC transfusion may be life- and/or limb-saving in the actively bleeding patient, RBC transfusion should not be the default in the non-bleeding medical or surgical patient. Transfusion remains, however, one of the most commonly performed procedures in healthcare (122). As presented in this review, the preponderance of the data support restricting transfusion when Hgb is >7.0 g/dL. based on current RCTs, multiple retrospective, observational and cohort studies, along with numerous systematic reviews and meta-analyses. Transfusion may be necessary in specific patient populations, such as those with ACS, with a threshold of 8.0 g/dL and perhaps within a range of 7.0–8.0 g/dL in Hematology/Oncology patients who are chronic transfusion-dependent and clearly symptomatic.

Clinicians must address competing strategies based on the etiology(ies) of anemia, patient comorbidities, and critically consider the risks of transfusion with the notable, often poorer outcomes. The concept of blood as a fluid organ must be recognized and become part of our healthcare lexicon. Acknowledging Hgb "thresholds", not "triggers', clinically relevant symptoms, and active reassessment of patients after any-and-all treatments for anemia is key to quality patient-centered care.

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