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Appendix

Resources for Additional Information on Blood Conservation

The following organizations and their associated websites are excellent sources for blood-conservation information. They both have active memberships and offer updated reviews of the current literature, newsletters, and continuing education meetings.

1. Society for the Advancement of Blood Management, www.sabm.org
2. Network for Advancement of Transfusion Alternatives, www.nataonline.com

Anemia: Risks, Tolerance, and Pharmacologic Adjuvants for Treatment

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Learning Objectives: 1) To understand the physiology of anemia, the reserve of the oxygen-delivery system, the clinical risks of anemia, the impact of directed therapy of anemia, the risks of red blood cell transfusions, the pharmacology of pharmaceutical agents used to treat anemia, and 2) to review clinical outcome measures in blood conservation techniques.

Abstract

Anemia has been identified as a risk factor for poor outcomes across diverse populations of medical and surgical patients. Even in low-risk, community-dwelling adults, anemia imparts a survival disadvantage. Red blood cell transfusions are still commonly used to correct anemia in many clinical situations, but evidence is emerging that transfusions may confer an additional risk rather than provide a benefit. In clinical practice, consistency is lacking with regard to hemoglobin thresholds that trigger the administration of transfusions; moreover, transfusions are often administered without sufficient justification. Because of the potential for risk, transfusions should be avoided whenever possible, but the degree of acute anemia that may be tolerated without negative impact on morbidity and mortality is still uncertain and varies by clinical circumstance. Consideration of therapy with erythropoietic agents and supplemental iron to reverse declining hemoglobin levels instead of transfusions may be a reasonable alternative. Several studies in high-risk patients indicate that this approach has the potential to provide clinical benefit. Prospective and well-designed clinical trials are needed to identify the ideal hemoglobin concentration and confirm that outcomes are improved when that concentration is achieved. Other strategies to limit blood loss and preempt the development of anemia and anemia-related morbidity are also needed.

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The degree to which anemia can be tolerated without exacerbating morbidity or increasing the risk of mortality is a complex clinical question currently without a generalizable answer. A patient's body mass, primary illness and severity, comorbidities, fluid status, anemia severity and rate of onset, surgical status, and anticipated blood loss are among the factors determining the window of hemoglobin (Hb) needed to deliver adequate oxygen. When intervention is required to correct anemia, the choice of therapy may depend on all these variables, as well as blood availability, the patient's prior transfusion history, and the patient's religious convictions.

The 1999 study by Hébert and colleagues,¹ in which a restrictive transfusion policy (Hb <7 g/dL) was as effective as a liberal policy (Hb <10 g/dL) in a variety of critically ill patients, raised fundamental questions about the need for blood transfusions to correct moderate anemia in critically ill patients. Subpopulation analyses have since suggested that restrictive transfusion policies are justified in trauma and mechanically ventilated populations.^{2,3} Even patients who were once believed to benefit from liberal use of blood transfusions (e.g., those with severe cardiac disease⁴) have recently been found to have higher mortality and myocardial infarction rates if they receive red blood cell (RBC) transfusions when their nadir hematocrit (Hct) is higher than 25%.⁵

Banked blood is limited in supply and is costly,⁶ and although safer than ever with regard to viral transmission,⁷⁻⁹ blood products are associated with risks beyond the spread of infection that cannot be eliminated with current donor screening.¹⁰ Each transfusion is said to be associated with a 20% chance of producing an adverse event of some kind.¹¹ Given these odds, the potential for anemia-related morbidity should be carefully considered; that is, does it pose a similar risk to that of a transfusion? One systematic review of the literature relating to anemia in surgical patients acknowledged that uniform definitions of anemia, anemia prevalence estimates, and information about the impact of anemia on outcomes are lacking or inconsistent.¹²

Medical consensus concerning tolerable Hb/Hct levels, or an appropriate algorithm for anemia intervention, does not exist. In addition, lessons about tolerance of acute severe anemia have emerged from experimental observations, clinical experience in Jehovah's Witnesses,¹³ and contemporary movements that promote bloodless medicine and surgery.^{14,15} This article reviews the risks of anemia and transfusions, the variability of transfusion practices, current evidence on the lower limits of anemia tolerance, and pharmacologic alternatives to transfusions for managing anemia.

Anemia Risks

Anemia has been implicated as a risk factor for poor outcomes in a variety of diseases and patient types (Table 1). The impact of chronic anemia has been particularly well studied in patients with kidney disease, heart disease, or other chronic conditions, but less is known about the risks associated with acute anemia. For example, increased cardiac morbidity and mortality have been observed in anemic patients with end-stage renal disease,¹⁶ and in patients with advanced heart failure, declining Hb levels and poor prognosis have been strongly correlated ($P = 0.00001$).¹⁷ A large prospective study found that even low-risk community-dwelling adults ($n = 14,410$) were at increased risk of mortality from cardiovascular disease (CVD) if anemia, defined as Hb <13 g/dL in men and <12 g/dL in women, was present.¹⁸

The impact of acute anemia, occurring as a result of blood loss following surgery, trauma, or with acute inflammation that occurs in critical illness, is not as clearly documented with regard to outcomes.

Carson et al¹⁹ performed a retrospective cohort study of surgical patients who declined transfusions for religious reasons and demonstrated that low preoperative Hb or acute blood loss was more likely to result in death in patients with preexisting CVD than those without CVD. Patients undergoing both noncardiac and cardiac surgery tended to fare worse if they were anemic prior to, during, or after the procedure; the critical Hct associated with increased risk, however, varies among different studies and populations.²⁰⁻²³

In a retrospective study of 78,974 Medicare patients aged 65 years or older with acute myocardial infarction,²⁴ 30-day mortality rates were highest among patients with the lowest Hct values at hospital admission, and mortality steadily declined with increasing Hct values (Fig. 1). Blood transfusions provided clear benefit in patients whose Hct on admission was $\leq 30\%$ (4.2% of the population under study), but the benefit was not as clear when the Hct was 30% to 33%, and there was no evidence that blood transfusions were beneficial in patients whose Hct was higher than 33%. Although the authors adjusted for other contributing factors (e.g., do-not-resuscitate orders, no primary reperfusion therapy, less frequent use of aspirin or beta-blockers) when accounting for transfusion benefits, these factors may have also influenced the relationship between anemia and lower survival. As is the case with many reports of anemia risk and transfusion benefit,¹² interpretation of these results is subject to limitations inherent in the retrospective design.

An examination into the consequences of acute severe anemia in nine volunteers revealed that subtle changes in cognitive function (delayed and immediate memory and reaction time) were apparent when Hb was experimentally reduced to 5.0 g/dL, but no impairment was seen when the Hb was reduced to 7.0 g/dL.²⁵ A second study found that breathing oxygen to increase Pao₂ to 350 mm Hg or greater reversed the memory impairment and reaction time increases caused by the very low Hb concentration.²⁶ To further investigate the mechanism of the impairments, a third study in which somatosensory-evoked potentials were measured revealed that the cognitive and reaction time impairment resulting from acute anemia was not the result of reduced central afferent neural conduction velocity.²⁷ Peripheral nerve conduction velocity actually increased by 4.4% when the nadir Hb concentration was lowered to 5 g/dL, but conduction velocity was unchanged by breathing oxygen. The authors attributed the decreased latencies to elevated limb temperature rather than to acute anemia. Method issues resulting from the acute induction of hypoxia, for example, lack of equilibration, make these findings difficult to interpret.

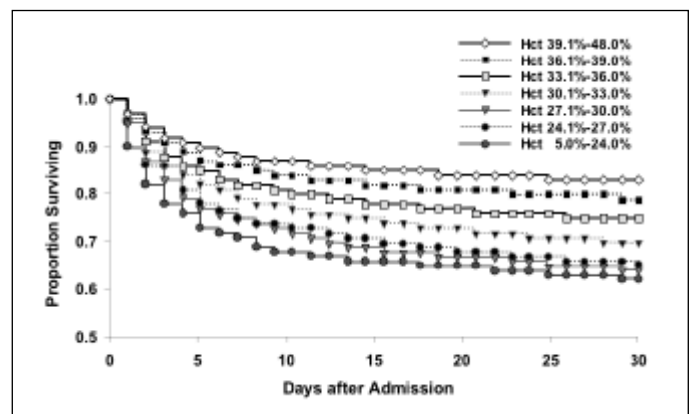


Figure 1. Impact of anemia on survival in individuals 65 years of age and older who were hospitalized for acute myocardial infarction. (Reprinted with permission from Wu W-C, et al. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001;345:1230-6.)

Table 1. Selected Studies Demonstrating Morbidity and Mortality Risks of Anemia^a

Population	Study Description	Anemia Definition	Anemia-Associated Risk	Source
Low-risk, community-dwelling adults 45-65 years old; no CVD at baseline (n = 14, 410)	Prospective, cohort study	Hb below WHO criteria ^b	Adjusted HR for de novo CVD = 1.4 (95% CI: 1.01,1.95; <i>P</i> = 0.040); risk factor for survival in men (<i>P</i> = 0.212) and women (<i>P</i> = 0.045)	Sarnak et al, ¹⁸ 2002
Advanced heart failure (n = 1,061)	Prospective, cohort study	Hb below WHO criteria ^b with stratified quartile analysis of Hb <12.3 g/dL, Hb 12.3-13.6 g/dL, Hb 13.7-14.8 g/dL, and Hb >14.8 g/dL	1-year survival by Hb quartile = 55.6%, 63.9%, 71.4%, and 74.4%, Adjusted RR of mortality = 1.131 (95% CI: 1.045, 1.224) for each 1 g/dL decrease in Hb	Horwich et al, ¹⁷ 2002
End-stage renal disease (n = 432)	Prospective cohort study	Stratified tertile analysis of Hb >9.5g/dL, Hb 8-9.5 g/dL, and Hb ≤8 g/dL	For each 1 g/dL decrease in Hb, adjusted RRs of de novo cardiac failure = 1.28, <i>P</i> = 0.018; recurrent cardiac failure = 1.20, <i>P</i> = 0.042; mortality = 1.14; <i>P</i> = 0.024; left ventricular dilatation (OR) =1.46, <i>P</i> = 0.018	Foley et al, ¹⁶ 1996
Surgical patients (excluding open-heart surgery) ^c who refused transfusions, stratified by CVD, no CVD (n = 1,958)	Prospective cohort study	Reference Hb ≥12 g/dL, logistic regression performed with Hb as a continuous variable	Mortality was 33.3% vs. 1.3% in patients with preoperative Hb <6 g/dL and ≥12 g/dL, respectively. Risk of death associated with low Hb was higher in patients with CVD (<i>P</i> = 0.03)	Carson et al, ¹⁹ 1996
Critically ill stratified by cardiac disease, noncardiac diagnoses (n = 4,470)	Subanalysis of randomized, controlled study	Stratified analysis of Hb >12.5 g/dL, Hb 9.5-12.5 g/dL, and Hb <9.5 g/dL	Trend toward increased mortality for patients with cardiac disease and Hb <9.5 g/dL, mortality was 55%, vs. 42% in patients with noncardiac diagnoses (<i>P</i> = 0.09)	Hébert et al, ⁴ 1997
Post-CABG or valvular surgery (n = 2,661)	Retrospective database analysis	Logistic regression performed on nadir Hb concentration 24 h postextracorporeal circulation as a continuous variable	Major morbidities (length of stay, renal and abdominal complications) significantly associated with low Hb	Hardy et al, ²³ 1998
CABG surgery (n = 6,980)	Prospective, multicenter, consecutive series, observational study	Logistic regression performed across 5 categories of nadir Hct (≥25, 23-24, 21-22, 19-20, and <19) achieved during bypass	Adjusted hospital mortality rates significantly associated with lower Hct (1.6% vs. 3.9% in ≥25 and <19 Hct categories, respectively; <i>P</i> _{trend} < 0.001)	DeFoe et al, ²⁰ 2001
Cardiopulmonary bypass surgery (n = 5,000)	Retrospective analysis	Rolling decile subgroup analysis, i.e., lowest Hct to highest	Hct below 22% was significantly associated with stroke, MI, low cardiac output, cardiac arrest, renal failure, prolonged ventilation, pulmonary edema, reoperation, sepsis, and multiorgan failure	Habib et al, ²² 2003
Cardiopulmonary bypass surgery (n = 2,738)	Prospective, sequential enrollment	Logistic regressions performed on nadir Hct during bypass	Increased probability of risk-adjusted mortality with Hct ≤14% (OR = 2.70, <i>P</i> = 0.002) in all patients; Hct ≤17% (OR = 2.20, <i>P</i> = 0.017) in high-risk patients	Fang et al, ²¹ 1997
Elderly (aged 65 and older) with MI (n = 78,974)	Retrospective study of Medicare database	Hct values stratified into 7 categories: 5-24%; 24.1-27.0%; 27.1-30.0; 30.1-33.0%; 33.1-36%; 36.1-39%, and 39.1-48.0%	Crude 30-day mortality correlated with decreasing admission Hct	Wu et al, ²⁴ 2001

^aCVD, cardiovascular disease; WHO, World Health Organization; HR, hazard ratio; RR, relative risk; OR, odds ratio; CABG, coronary artery bypass graft; MI, myocardial infarction.

^bHb <13 g/dL in men and <12 g/dL in women.

^cThe authors noted a limitation of the study was that estimated blood loss was not consistently collected and was poorly correlated with the decline in Hb.

Given that the functional alterations were reversible, it is unknown whether they were the result of a pathophysiologic process or compensatory autonomic changes that serve to protect against acute hypoxia, analogous to syncope in the case of acute hypovolemia.²⁸

Overall, there is no shortage of evidence that anemia, at some level of severity, is associated with risks and poor outcomes on a population level. However, the Hb/Hct threshold necessary to achieve an acceptable outcome for any individual patient is not known. When blood transfusion is factored into the mix of variables that have potential impact on morbidity and mortality, it becomes increasingly difficult to isolate and estimate anemia tolerance and risks. Moreover, studies of the risks of acute anemia are, for the most part, retrospective database reviews. Patients with the lowest Hb/Hct are typically transfused at significantly higher rates and have higher morbidity and mortality. To sort out whether the poor outcomes are attributable to anemia, transfusions, or both, prospective, randomized, and appropriately stratified trials are needed.

Transfusion Risks

In the last several decades, the world has witnessed a dramatic decline in the risk of viral transmission (human immunodeficiency virus [HIV], hepatitis B virus, and hepatitis C virus) through blood transfusion.⁷⁻⁹ Nevertheless, bacterial infections (1 in 2,000 units transfused), transfusion-related acute lung injury (TRALI; 1 in 5,000 units transfused), and clerical error (1 in 12,000 units transfused) still account for adverse events related to blood administration.⁷ Other risks, of numerous type and severity, have been documented.^{8,29-47} As mentioned earlier, Walker¹¹ estimates that, overall, there is a 20% chance of sustaining an adverse event following a transfusion.

Considerable variability exists in published data relating to transfusions and their contribution to mortality. One meta-analysis of 17 studies⁴⁸ noted substantial heterogeneity in mortality risk estimates, failing to detect what many others have asserted,^{5,36,49} which is that mortality is higher in transfused patients and a that causal relationship linking transfusions to fatal outcomes is possible.

Immune modulation by blood transfusions is another topic replete with conflicting data, speculation, and debate.^{8,45,50} Downregulation of T-cell proliferation in orthopaedic surgical patients,⁵¹ enhancement of tumor recurrence following colorectal cancer resection and allogeneic transfusion,⁵² and occurrence of bacterial infection and pneumonia in the postoperative setting⁵³ are representative evidence that blood transfusions modulate immune function. Whether these effects can be attributed to the storage time of RBC units,⁵⁴ the presence of leukocytes in allogeneic blood,⁸ or a combination of these factors is incompletely understood.⁵⁰ Opposing regulatory positions with regard to leukoreduction of red blood cell units reflect the lack of consensus about the mechanism and clinical significance of immune modulation following blood transfusion.⁸ At the present time, the U.S. Food and Drug Administration (FDA) has not mandated leukoreduction for the U.S. blood supply. In contrast, the Canadian Blood Service⁵⁵ and many countries in Europe⁵⁶ have adopted leukoreduction as the de facto standard.

TRALI is a complication of allogeneic blood transfusion that, until recently,⁵⁷ has gone underrecognized and underreported.⁵⁸ Characterized by the presence of bilateral pulmonary edema, dyspnea, hypoxemia, fever, and hypotension in the presence of normal cardiac function,⁵⁹ the syndrome is nearly identical to acute respiratory distress syndrome (ARDS) but does not confer as high a mortality risk. Lung damage also tends to be transient compared

with ARDS.⁴² TRALI is so named because it is known to be a direct consequence of blood product transfusion; although random-donor or whole-blood-derived platelets are most commonly associated with TRALI, it can occur following administration of most blood products.⁶⁰ The syndrome has only recently been defined,⁵⁷ and its pathogenetic mechanism is still under investigation. Donor and recipient factors involving lipids, cytokines, and antibodies participating in a two-event sequence of TRALI development have been hypothesized. Deferral of donors whose blood is at high risk of triggering the syndrome has been recommended⁶¹; however, because of the uncertainty that still exists regarding its mechanism, transfusion avoidance may be the only guaranteed way to prevent TRALI.

Justification for Transfusions

Because clinicians must balance the risks of anemia with those of transfusions, one might expect that transfusion indications would be clearly defined, but that is not the case. In the often-cited single-center observational study of Corwin and colleagues,⁶² an indication was not specified for nearly one-third (29%) of the transfusions given to critically ill patients. Only 19% of the transfusions were administered because of a low Hct, defined for study purposes as <25%. For the other indications noted (including surgery/bleeding, low cardiac output, myocardial ischemia, and oxygen transport), the pretransfusion Hct averaged 27%. In a multicenter cohort study of transfusion practices in intensive care units (ICUs), RBCs were most frequently administered for acute bleeding or to improve the delivery of oxygen (35% and 25% of 758 transfusion orders, respectively).⁶³ Based on another survey designed to evaluate the quality of transfusion practices in two teaching hospitals, an alarming 42% of transfusions administered were not justified.⁶⁴ In the latter study, the amount of transfused products inversely correlated with physicians' knowledge about transfusion indications. Other studies have reported inappropriate transfusion rates of 18% to 57%.⁶⁵

Variability in Transfusion Practices and the Evolution of Transfusion Triggers

Transfusion practices are known to vary widely across institutions. In a survey of ICUs, pretransfusion Hb levels averaged between 8.1 ± 1.1 and 9.0 ± 1.2 g/dL at six participating institutions, and 35% of all transfusions were administered at Hb levels from 9.5 to 10.5 g/dL.⁶³ In patients who were undergoing coronary artery bypass graft surgery at 18 centers, RBC usage varied from 0.4 to 6.3 units per patient, plasma was given to 0% to 97% of patients, and 0% to 80% received platelets.⁶⁶ Unnecessary blood product transfusions accounted for some of the variability that these authors observed. Heterogeneity in transfusion practices during orthotopic liver transplantation was examined by Ozier et al⁶⁷ across eight institutions (Fig. 2). Controlling for individual patient preoperative and intraoperative characteristics, the variation was explained by differences in blood loss estimates, intravascular hydrostatic pressures in the surgical field, fluid management strategies, perioperative coagulopathy management, and transfusion triggers.

A hemoglobin level of 10 g/dL (~30% Hct), the "10/30 rule," was once the accepted threshold for administration of a RBC transfusion.⁶⁸ Practice guidelines of the American Society of Anesthesiologists (ASA)⁶⁵ as well as many investigators have

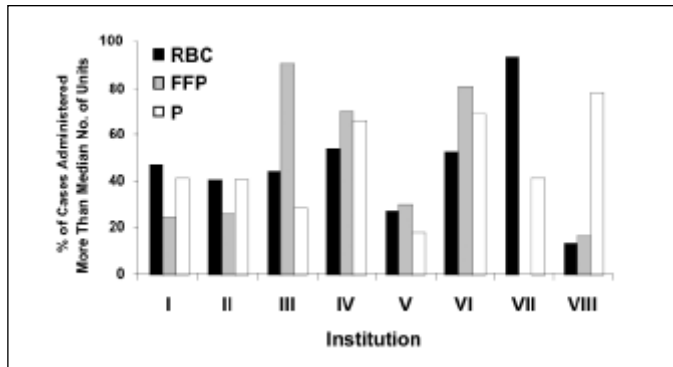


Figure 2. Institutional variability of transfusions of red blood cells (RBC), fresh-frozen plasma (FFP), and platelets (P) at institutions I-VIII. Bars represent the percent of cases who were administered more than the median number of units of specified component. (Ozier et al.⁶⁷ Institutional variability in transfusion practice for liver transplantation. *Anesth Analg* 2003; 97:671-9. Copyright ©2003, Lippincott, Williams & Wilkins. All rights reserved. Used with permission.)

indicated that this trigger is outdated. Recommendations have been trending toward lower Hb levels (Table 2). Clinical practices to lower transfusion triggers have, however, lagged behind evidence-based recommendations such as those first articulated by Hébert and colleagues.¹ Despite evidence that transfusions should be withheld for the majority of patients until Hb falls below 7.0 g/dL, some recently published reports indicate that pretransfusion Hb levels still average from 8.2 to 8.7 g/dL (i.e., 1.2 to 1.7 g/dL higher than may be necessary) in general populations of critically ill patients.^{47,69,70}

At one medical center that has adopted a multimodal blood conservation program, Moskowitz and colleagues⁷¹ studied transfusion risk factors in patients (n = 307) undergoing major cardiac surgery. RBC mass, surgery type and urgency, number of diseased vessels, serum creatinine ≥ 1.3 mg/dL, and preoperative prothrombin time were significant risk factors for allogeneic transfusions. These factors were further validated using a derived equation to predict transfusion requirements. Informed transfusion decisions, reduced transfusion rates, conservation of blood resources, and better outcomes are possible using this approach. Recently, this center (Englewood Hospital and Medical Center) has been cited to have the lowest risk-adjusted patient mortality (1.23%; 95% confidence interval [CI]: 0.14, 4.45) as a result of cardiac bypass surgery in the state of New Jersey.⁷² Thus, cardiac surgical patients may still have reserve to tolerate anemia for short periods. Transfusions, because they carry their own risks, can be avoided in this population, although further study is needed.

According to the 1996 analysis and report of the ASA,⁶⁵ one universal “trigger” for transfusion is inappropriate for all clinical circumstances. The ASA task force concluded that “transfusion is rarely indicated when the Hb concentration is >10 g/dL and is almost always needed when it is <6 g/dL, especially when the anemia is acute,” and that transfusion decisions in patients whose Hb lies between these levels “should be based on the patient’s risk for complications of inadequate oxygenation.” The ASA’s recommendation spans an enormous range of Hb values that are probably too broad to be useful. Additionally, their guidelines fail to address the following important questions:

1. How should the risk of transfusion itself be factored into the trigger equation?

Table 2. Transfusion Thresholds from the Medical Literature^a

Transfusion Threshold	Basis of Observation	Relevant Population	Possible Exceptions	Source
Hb = 7 g/dL	Randomized, prospective study	Critically ill (n = 838)	Acute MI, unstable angina	Hébert et al, ¹ 1999
Hct $\leq 25\%$	Post hoc analysis of 3 large international trials	Patients with acute coronary syndromes (n = 24,112)	Unstable patients	Rao et al, ⁵ 2004
Hb = 9 g/dL factors (n = 99)	Randomized, prospective study	Patients undergoing major arterial reconstruction; most with high incidence of cardiac risk factors (n = 99)	None specified	Bush et al, ⁷⁹ 1997
Hb = 8 g/dL	Consecutive enrollment into randomized groups	Patients undergoing elective CABG surgery (n = 428)	High-risk patients with excessive bleeding	Bracey et al, ⁸⁰ 1999
Almost always transfuse when Hb <6 g/dL; if Hb is 6-10 g/dL, consider risk of inadequate oxygenation before transfusion; rarely transfuse when Hb >10 g/dL	Systematic review using controlled and uncontrolled observational studies and expert opinion	Applies to most patients (number of patients not given)	None specified, but consider underlying disease if Hb 6-10 g/dL	ASA, ⁶⁵ 1996
Hb >5 g/dL was proposed to be safe since it was not associated with increased risk of death	Retrospective, systematic review of medical literature	Medical or surgical Jehovah’s Witness patients (n = 4,722)	Consider underlying disease	Viele and Weiskopf, ⁸¹ 1994
Hb <7 g/dL	Evidence-based review and consensus panel	Patients with sepsis (n = 140)	Acute instability, coronary artery disease, low cardiac output, pulmonary disease that leads to severe arterial hypoxemia, organ or tissue ischemia	Zimmerman, ⁷⁸ 2004

^a MI, myocardial infarction; CABG, coronary artery bypass graft.

2. To what extent will the RBC transfusion improve oxygenation, especially when older blood is used that may have a storage lesion?
3. What is the incremental short-term risk to patients of transfusing at a lower Hb/Hct threshold? Asked another way, to what degree can acute anemia be tolerated without incurring additional risk?
4. What alternative measures can be used to help avoid transfusions and the adverse consequences of anemia?

The first two questions will require further study to answer; thus, the remainder of this article will be limited to a discussion of anemia tolerance and pharmacologic support to help achieve transfusion avoidance.

Tolerance of Anemia and Physiologic Limits of Compensation Mechanisms

The lower limit of tolerance to acute anemia is not known. Weiskopf et al⁷³ studied the effects of acute, severe, isovolemic anemia in conscious, healthy, resting volunteers. Experimental reduction of Hb from 13.1 to 5.0 g/dL (corresponding oxygen transport [To₂] of 10.7 mL O₂ kg⁻¹ min⁻¹) was tolerated without evidence of inadequate oxygen transport as assessed by oxygen consumption and plasma lactate concentrations. In these volunteers, systemic vascular resistance decreased and heart rate, stroke volume, and cardiac index increased. Compensatory mechanisms for falling arterial oxygen content—that is, increased cardiac output—were well tolerated in these healthy individuals, agreeing with earlier experimental evidence in dogs and baboons.^{74,75} In a subsequent study in which a β-adrenergic antagonist (esmolol) was used to reduce heart rate,⁷⁶ acute reduction of Hb was to 4.7 g/dL (corresponding Do₂ = 7.3 mL O₂ kg⁻¹ min⁻¹) yet systemic oxygenation was still adequate. These subjects were acutely and severely anemic for approximately 1 hour. Thus, for short periods in otherwise healthy individuals, very low Hb levels can be tolerated as long as perfusion is maintained.

In conditions of low Hct, flow in the microcirculation is accelerated because of improved rheologic properties of blood. These properties involve plasma viscosity, shear stress, cellular deformability, and aggregation. When plasma viscosity is reduced along with the Hct, below some point capillaries tend to collapse from the lack of shear stress factors; functional capillary density then becomes too low for oxygenation to occur. Thus, for optimal lowering of the transfusion trigger, a high-viscosity colloid fluid should be infused instead of a crystalloid to maintain perfusion.⁷⁷

Healthy subjects typically are not candidates for transfusion, however, and the degree to which a sick individual is able to compensate for anemic hypoxia is likely to be more limited. Tolerance of anemia is thought to be affected by cardiac status, and is affected by the level of anesthesia, pharmacologic agents, hypothermia, or other conditions such as sepsis⁷⁸ in which physiologic function may be impaired. A randomized, prospective study in patients undergoing major arterial reconstruction surgery was conducted to determine whether an Hb threshold of 9 g/dL (restrictive) versus 10 g/dL was sufficient to prevent myocardial ischemia. As the authors hypothesized, the restrictive transfusion strategy was well tolerated. Reduced oxygen delivery was compensated by increased oxygen extraction in the peripheral tissues rather than by increasing myocardial work.⁷⁹ Using a blood conservation technique to augment the return of blood from a bypass circuit during coronary artery bypass graft surgery, Bracey and colleagues⁸⁰ determined that a transfusion threshold of 8 g/dL was safe and conserved blood resources in low-risk patients. Recent

evidence from Rao et al⁵ indicates that anemia can be tolerated to an Hct of 25% (Hb ~8.3 g/dL) without RBC transfusions in patients with acute coronary syndromes.

Additional information about anemia tolerance may be found in literature describing experiences with Jehovah's Witnesses. These are patients who, because of religious beliefs, refuse blood transfusions even when the consequences may be dire. One review described 1,404 major operations that were conducted without transfusions in Jehovah's Witness patients.¹³ Mortality attributed to lack of blood was the primary cause of death in 8 patients, and anemia contributed to death in 12 others. Anemia-related deaths totaled 1.4%. Although Hb/Hct levels were not reported for all the cases included in this review, intraoperative Hct levels of 15% during normovolemic hemodilution were said to be typical and well tolerated. Compared with the 20% of patients (n = 281) who hypothetically avoided transfusion risks, the authors implied that the added mortality risk of 0.5% to 1.5% from withholding transfusions was a reasonable tradeoff. Viele and Weiskopf⁸¹ also reviewed 61 reports from 4,722 moderately or severely anemic (Hb ≤8 g/dL or Hct ≤24%) medical or surgical Jehovah's Witness patients who were not transfused. Some survived with very low Hb concentrations (as low as 1.4 g/dL), and 5 g/dL was identified as a threshold below which mortality increased sharply. In the 23 of 50 deaths reportedly related to anemia, Hb had fallen below 5 g/dL; nevertheless, 25 survivors were identified with Hb <5 g/dL.⁸¹ A statistically based study noted that Hb became an independent predictor of mortality only when it fell below 3 g/dL.⁸²

Recently, perhaps the worst single case of traumatic injury in a Jehovah's Witness was reported, that of a 67-year-old man involved in a motor vehicle crash who had an Injury Severity Score of 29.⁸³ The patient's Hb on admission was 9.7 g/dL, and following intubation and surgery, a nadir Hb of 3 g/dL was recorded (Fig. 3). Crystalloids and hetastarch were used to maintain circulation volume, and norepinephrine was administered to maintain organ perfusion. Therapy with iron, folate, vitamins B12 and K, and epoetin alfa (48,000 units/day) was initiated. Despite a complicated ICU stay resulting from respiratory failure, the patient survived and was discharged to rehabilitation after 47 days of hospitalization; the discharge Hb level was 7.9 g/dL. The authors also reviewed 16 other trauma cases representing 13 survivors with nadir Hb levels ranging from 1.6 to 7.9 g/dL (mean Hb 4.2 ± 1.8 g/dL for 11 cases where Hb was reported). Three nonsurvivors had nadir Hb levels of 0.9, 1.8, and 6.5 g/dL.⁸³

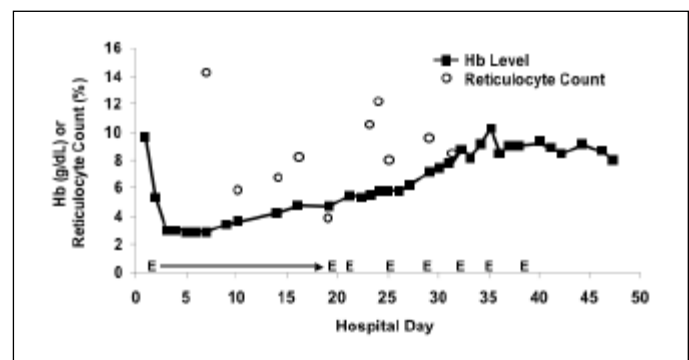


Figure 3. Hemoglobin concentration and reticulocyte count in a 67-year-old man who was injured in an automobile crash and who refused transfusion with blood products for religious reasons. E, dose of erythropoietin (48,000 units) given; → = daily doses of erythropoietin.⁸³ (Kulvatunyou N, Heard SO. Care of the injured Jehovah's Witness patient: case report and review of the literature. *J Clin Anesth* 2004; 16:548-53.⁸³ Copyright ©2004, Elsevier. All rights reserved. Used with permission.)

Chronic anemia may allow further tolerance of acute anemia because of adaptive increases in 2,3-diphosphoglycerate levels that facilitate oxygen transport.⁶⁵ Tolerance of Hb levels less than 3 g/dL has been described in hemodynamically stable, chronically anemic children treated within the extremely low transfusion threshold guidelines at the Uganda AIDS control program in Kenya.⁸⁴ Unfortunately, little else has been published about adaptations and tolerance limits in cases of chronic anemia, presumably because most conditions characterized by very low Hb (e.g., sickle cell anemia, congenital dyserythropoietic anemias, chronic renal disease, HIV) are treated with transfusions and/or erythropoietic agents.⁸⁵⁻⁹⁰

Pharmacologic Adjuvants for Anemia Management

Erythropoietins and Iron. Therapy with erythropoietic agents and concomitant iron therapy represent the mainstay of adjuvant therapy for anemia. The case of the 67-year-old man described in the previous section illustrates the utility of an erythropoietic agent plus iron, folate, and vitamin B12 to stimulate red cell production and increase Hb. There are currently three available erythropoietic agents: epoetin alfa, epoetin beta, and darbepoetin alfa. As a class, these agents inhibit apoptosis of erythroid precursors in bone marrow and allow proliferation and differentiation of erythroid cells, leading to an increase in RBC mass.^{91,92} Stimulation of erythropoietin receptors may also inhibit apoptosis in nonhematopoietic tissues, including heart, brain, and retina, and at least theoretically have the capacity to exert cytoprotective effects.^{93,94}

Epoetin alfa has long been used to reduce the need for allogeneic blood transfusions in anemic patients about to undergo elective, noncardiac, nonvascular surgery; numerous studies have documented its use prior to cardiac surgery to augment RBC production and minimize the use of RBC transfusions.⁹⁵⁻⁹⁷ During a course of erythropoietic therapy, RBC production is stimulated, but a transient imbalance between iron availability and requirements, known as functional iron deficiency, may ensue.⁹⁸ Concomitant use of a small amount of iron, given orally or intravenously, is necessary to prevent the formation of microcytic hypochromic RBCs. The hepatic protein, hepcidin, recognized as a regulator of iron homeostasis through its effects on the intestinal absorption of iron, may play a role in iron availability in anemia and during erythropoiesis, but further study is required to fully understand these complex processes.^{99,100}

Epoetin alfa with parenteral or oral iron has also been shown to reduce transfusion requirements in critically ill patients in two randomized, placebo-controlled studies.^{101,102} The first study (160 patients) used an epoetin alfa dose of 300 units/kg beginning on ICU Day 3 and continuing for 5 days, with subsequent reduction of the dose to 300 units/kg every other day to reach a Hct >38%. Dosing continued for a minimum of 2 weeks to a maximum of 6 weeks. In the second, larger study (1,302 patients), weekly epoetin alfa (40,000 units per dose) was administered beginning on Day 3, for a total of three to four doses depending on the length of the ICU stay. Both studies demonstrated that treatment with epoetin alfa significantly reduced the number of RBC transfusions compared with placebo; however, Hb or Hct levels were increased despite fewer transfusions. Neither study demonstrated significant improvement in mortality in epoetin alfa-treated patients compared with placebo.

Five studies have been performed to date with erythropoietins in patients with congestive heart failure (CHF), and all five have demonstrated increases in Hb and treatment benefits. Silverberg and colleagues¹⁰³⁻¹⁰⁶ conducted four of these studies using epoetin beta: an uncontrolled pilot study (n = 26),¹⁰³ a randomized controlled study (n = 32),¹⁰⁴ a nonrandomized open-label study of predialysis patients

with severe CHF (n = 179), half of whom also had type 2 diabetes,¹⁰⁵ and, recently, an open-label nonrandomized study in symptomatic patients (n = 78) with CHF.¹⁰⁶ In the pilot study, patients with severe CHF were administered intravenous iron and epoetin beta (starting dose of 2,000 units weekly, which was increased or decreased as necessary to achieve and maintain a target Hb of 12 g/dL) for a period of intervention averaging 7.2 months. Mean Hb increased from 10.16 ± 0.95 g/dL at baseline to 12.10 ± 1.21 g/dL (*P* < 0.001). Mean left ventricular ejection fraction (LVEF) increased 27.8% (*P* < 0.001) and the New York Heart Association (NYHA) functional class improved from 3.7 to 2.7, on average (*P* < 0.05). Furosemide use dropped from 201 to 78 mg/day. Compared with a similar period of time before the onset of the anemia treatment, the mean number of hospitalizations per patient was 2.72 ± 1.21. Following anemia treatment, hospitalizations fell to an average of 0.22 ± 0.65 per patient (*P* < 0.05), a decrease of 91.9%. The authors concluded that anemia correction was associated with an impressive improvement in cardiac function reflected in a marked improvement in the NYHA functional class and a striking reduction in hospitalizations.

The randomized trial of intravenous iron and epoetin alfa versus no treatment for anemia in 32 patients¹⁰⁴ demonstrated similar results to the pilot study, with reduction in NYHA functional status, improved LVEF, dramatically reduced frequency of hospitalizations, and reduced diuretic use. In the nonrandomized, uncontrolled open-label study,¹⁰⁵ clinical improvement was noted in both diabetic and nondiabetic patients following epoetin alfa, reflected in NYHA status, hospitalizations, and slowing of renal disease progression.

Following the first three studies by Silverberg and colleagues, Mancini et al¹⁰⁷ compared epoetin alfa starting at a dose of 5,000 units three times weekly plus oral iron and folate (treatment group) to placebo in a single-blind trial in CHF patients. In the treatment group, Hb levels, peak oxygen uptake, and exercise duration were significantly increased over baseline. The placebo group showed no significant increases. Blood volume analysis was conducted in a subset of the epoetin alfa-treated patients, which showed an increased volume of RBCs over baseline. Portoles and colleagues¹⁰⁸ also demonstrated increased Hct in a small series of predialysis patients (n = 11) treated with epoetin beta that correlated with significant reductions in left ventricular mass index and left ventricular hypertrophy (LVH). The reduction in LVH occurred without improved blood pressure control, confirming the role of anemia among the multiple factors leading to LVH. The most recent study by Silverberg et al¹⁰⁶ in CHF patients demonstrated that correction of the anemia with epoetin beta, together with initial iron supplementation (iron sucrose), results in significant improvements in Hb levels, NYHA class, LVEF, and hospitalization rate and stabilizes renal function.

Other Pharmacologic Considerations for Adjuvant Anemia Management. In addition to erythropoietic support for prevention and management of anemia, clinicians who practice blood conservation, transfusion avoidance, and bloodless medicine and surgery have recognized other classes of drugs as part of their strategy. Table 3 provides a list of these agents and the rationale for use, most of which have been available and used for decades. Recombinant activated factor VII (rFVIIa) is one such agent that warrants brief mention. This relatively new drug enhances thrombin generation and is currently indicated only to treat bleeding in individuals with hemophilia who have developed neutralizing antibodies to clotting factors. Not yet approved by the FDA for nonhemophilia-related applications, rFVIIa is being used off-label to control hemorrhage, with mixed results.^{109,110} Policies are now beginning to emerge that will help clinicians understand its potential place in therapy, benefits, risks, and dosing.¹¹¹

Table 3. Pharmacologic Adjuvants for Prevention/Management of Anemia or to Improve Anemia Tolerance

Agent(s)	Rationale for Use
Aprotinin, desmopressin, aminocaproic acid, tranexamic acid, vasopressin, conjugated estrogens, norethisterone, medroxyprogesterone, recombinant factor VIIa, topical hemostatic agents, tissue adhesives, H2-blockers, sucralfate	Reduce bleeding
Epoetin alfa (see text), epoetin beta (see text), darbepoetin alfa, iron, androgen therapy (only if no response to erythropoietin), vitamin C, vitamin B12, folic acid	Increase RBC mass
Vitamin K, recombinant factor VIIa, factor VIII, factor IX	Correct clotting factor deficiencies
Recombinant or artificial hemoglobin, perfluorocarbon solutions	Augment delivery of oxygen
Crystalloid or colloid solutions	Maintain normovolemia
Norepinephrine	Maintain end-organ perfusion

Data adapted from Martyn et al¹⁵ (from Tables 2-4).

As a final note, drugs that increase the tendency to bleed (e.g., nonsteroidal anti-inflammatory agents, aspirin, anticoagulants, certain antibiotics, some cardiovascular and psychotropic drugs, some herbal medications) should be avoided or carefully monitored.¹⁵

Conclusion: Lessons from Blood Conservation and Bloodless Surgery

Clinicians are faced with the task of balancing the risks of transfusions with the risks of anemia. When an appropriate approach to the anemic patient is taken, transfusion of RBCs will become the last resort, requiring intensive assessment of all risks and benefits to patients. There are important lessons to be learned from institutions that employ blood conservation practices and/or bloodless surgery. The fundamental aims of successful bloodless surgery programs articulated by Martyn and colleagues¹⁵ are as follows:

1. Optimize the patient preoperatively
2. Maximize hematopoiesis
3. Minimize blood loss
4. Maximize oxygen delivery

Although these are simple principles, they are commonly ignored. An integrated approach with a coordinated team of surgeons, anesthesiologists, hematologists, pathologists, nurses, administrators, technicians, pharmacists, and blood bankers is needed to achieve these goals. Many tasks are involved in mitigating or improving tolerance to anemia. These tasks include a careful preoperative assessment of anticipated blood loss and risk factors, pharmacologic intervention to stimulate RBC production and minimize blood loss, judicious choice and use of fluids to maintain normovolemia, and implementation of autotransfusion options, as well as performing controlled hypotension during surgery, minimizing metabolic demand, maintaining adequate oxygen support, and employing surgical techniques that minimize blood loss. Applying any or all of these practices to critically ill and trauma patients will help to minimize transfusions and transfusion risks.

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