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Transfusion in the Perioperative Period: A Consideration of the Risks and Benefits as a Guide to Determine When and Who to Transfuse

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Learning Objectives: 1) To understand the risks and benefits of transfusion at the perioperative stage, and 2) to learn not only when to transfuse, but who to transfuse.

Abstract

The decision to transfuse allogeneic red blood cells is complex and requires consideration of multiple factors, many of which are poorly defined. This review focuses on the risks and benefits of allogeneic transfusion, based on existing data. Consideration of these risks and benefits provides a basis for a clinician to make an informed decision regarding transfusion of allogeneic red blood cells.

The simple answer to the question about when to transfuse allogeneic red blood cells is when the benefits of the transfusion exceed the risks. The rest of this article will explore issues of both the benefits and risks for the perioperative patient. In many ways, physicians have assumed benefits from allogeneic red blood cells and have not appreciated, or have underappreciated, the risks of those transfusions. It is likely that if red blood cell transfusion as a new biologic intervention were to be presented to the Food and Drug Administration (FDA) today, it would have a particularly difficult time winning approval from the agency.

All physicians caring for the patient in the perioperative period routinely make decisions regarding the administration of allogeneic blood. Traditionally, triggers for transfusion had been set at hemoglobin of 10 g/dL and a hematocrit of 30%. These recommendations are derived from animal experiments in the late 1930s and early 1940s that confounded the two issues of hypovolemia and anemia. Despite the poor scientific foundation for these recommendations, they can be found in textbooks published as recently as the 1980s. During the 1980s, for the first time, the medical community became concerned about allogeneic transfusions and the associated risks resulting from the introduction of human immunodeficiency virus (HIV) in the blood supply. Careful re-review of indications revealed a paucity of scientific data supporting the hemoglobin trigger of 10 and 30. The FDA convened an expert consensus conference that opined that transfusion was likely to be necessary when the hemoglobin level dropped below 7 g/dL and unlikely to be necessary at a hemoglobin level greater than 10 g/dL. This expert consensus group came to these conclusions not on the basis of objective data, but on clinical impressions.

Since the change from an accepted level of hemoglobin trigger from which to transfuse the patients, clinicians making these decisions have experienced what Dr. Leon Festinger called "cognitive dissonance."¹ This is a concept proposed first in 1957 by Festinger, a psychologist. Cognitive dissonance is a psychological phenomenon that refers to the discomfort felt at a discrepancy between what you already know or believe and new information and interpretation. In this case, the decision to forego or hold off on allogeneic transfusion to levels progressively lower than a hemoglobin of 10 g/dL or hematocrit of 30% can create a sense of discomfort on the part of the clinician. There continues to be a paucity of "generalizable" triggers that are evidence-based to definitively guide the decision to initiate allogeneic transfusion.

Transfusion decisions can also be influenced by external factors. In the 1980s and early 1990s, it was commonplace for transfusion decisions to be reviewed by hospital-based transfusion committees. One criterion for review was that the patient received a single unit of red blood cells for transfusion. This was intended to identify transfusions that were unnecessary. These reviews did not distinguish between a 50-kg female patient and a 110-kg male patient, or that a single-unit transfusion might be all that was necessary to reestablish adequate red cell mass. Clinicians, recognizing that their decisions would be reviewed, frequently would administer a second unit of packed red cells, not necessarily because of indicated need, but because of the knowledge that, with a second unit transfused, post hoc review of their decision-making would be eliminated, i.e., there would not be an audit. It is heartening that recent information coming from Canada that documents transfusion behavior has indicated an increase in single-unit transfusions in 2002 versus a previous review in 1993.²

It is useful to consider the magnitude of allogeneic transfusion to understand the importance of this issue. Each year in the United

States, approximately 14 million units of packed red blood cells are collected. Of these 14 million units, 12 million are actually transfused to approximately four million patients per year. Two-thirds of these transfusions occur perioperatively in the surgical patient or our intensive care units (ICUs). The supply of these 14 million units is threatened by a number of factors, one of which is that the donor population is aging. Younger populations of patients do not donate with the frequency that the World War II, Korean War, and even Vietnam veteran-era populations of patients have donated to the altruistic blood supply. At the same time, the efforts on the part of the blood banking community to increase the safety of the blood supply has resulted in significantly increased donor deferral criteria, and new populations of patients (European travel, exposure to high risk) are now precluded from entering the donor pool.

The fragility of the altruistic blood supply is challenged even further by the increasing number of surgical procedures that require blood availability, a circumstance that is projected to increase as the baby boomer population enters its late adulthood and elderly years of life. This increasing demand has been partially offset by conservation efforts by the blood bankers. Blood bank products are now aligned to treat specific conditions for which they are indicated. Packed red blood cells are now available to treat anemia. Frozen plasma is used for factor deficiency and coagulopathy. Cryoprecipitate is indicated for the treatment of low fibrinogen levels, and platelet concentrates are indicated for conditions with low or dysfunctional platelets.

The management of the blood supply is optimized to increase the proportion of donated blood that is actually transfused to patients. This works as follows: freshly donated blood is tested for markers of disease and, when cleared, is distributed to outlying institutions that transfuse with less frequency. The fresh blood is inventoried and remains on the shelf of those low-volume blood banks until it starts to approach its outdate, which is currently 42 days, using CPDA₁ (citrate-phosphate-dextrose-adenine)-ADSOL preserved blood. As the blood approaches its outdate, it is redistributed to blood banks in settings in which transfusion is more common, and where it is more likely to be transfused to patients. This method maximizes the conservation and use of a limited resource, but results in a generalized transfusion practice of administering red blood cells that are closer to their expiration date in those settings that handle large populations of critically ill patients, such as level-one trauma centers or academic medical centers that use large numbers of packed red blood cells. Concern has been raised regarding this practice because of recent issues regarding the decreased efficacy of blood as it ages. These concerns will be explored in more detail subsequently. The cost of blood has varied from approximately \$400 to estimates of \$1,250 per unit. These costs are variable as they take into account the cost of testing and the cost of the administration, and the labor necessary to manage the freely donated, altruistic blood.

Risks of Transfusion

When most clinicians consider the risks of transfusion they focus on the infectious risks associated with allogeneic blood. In recent years, efforts on the part of the blood bank community, such as donor deferrals and more sophisticated testing, have resulted in an altruistic blood supply that is increasingly safe. Current estimates for the risk of HIV is 1 in 900,000 donated units, the risk of hepatitis C is 1 in 600,000 units, and the risk of hepatitis B is 1 in 108,000 donated units. Other infectious etiologies (West Nile virus, Chagas disease, babesiosis, malaria) occur even less frequently, but are influenced by geographic patterns of disease. Bacterial contamination of red blood cells is rare, and this is observed more frequently in platelet

concentrates that are maintained at room temperature. Additional concerns have been raised about prion disease (mad cow, human T-cell lymphotropic virus, type-1). These are long latency diseases, which are poorly characterized in terms of their risk as it relates to the blood supply. Because of this uncertainty, the blood banking community has taken a conservative posture by deferring donors with potential exposure to these diseases.

Less frequently considered risks are the risks of volume overload. In a surgical patient with acute blood loss, volume overload is not typically a problem. The issue that is more commonly addressed is the rate of resuscitation and the capacity of the cardiovascular system to respond to rapid administration of both blood products and fluids to keep up with significant surgical or traumatic blood loss. The use of inotropes in the setting of rapid transfusion may be necessary if cardiac contractility cannot be maintained because of excessive volume loading. More typically, acute abnormalities of electrolytes, including citrate intoxication with rapid infusion of frozen plasma, and other citrate-containing solutions, including packed red cells, can create transient myocardial dysfunction.

Another complication of transfusion that is not commonly considered is that of transfusion-related acute lung injury (TRALI). This condition presents with a syndrome of respiratory distress, hypoxemia, hypotension, and moderate-to-low grade fever. It typically occurs within 4 to 6 hours of receiving blood products. Although plasma is the most common blood product associated with TRALI, it can also occur with platelets or packed red blood cells. Antihuman lymphocyte antibody or antigranulocyte antibodies are a causative factor in more than 80% of TRALI cases in women. It is now understood that this is significantly underreported as it is difficult to diagnose because it is indistinguishable from other conditions associated with respiratory insufficiency in the postoperative period. One review, published by Kopko and colleagues,³ focused on an incident case that resulted in a donor-linked fatality in the recipient. Thirty-six other recipients of blood products from this one donor were identified, and their clinical courses were reviewed retrospectively. The study documented a spectrum of variable presentation of TRALI from very mild conditions to the incident case fatality. The observation was that TRALI was underdiagnosed and underreported, with 7 of 15 cases reported to the transfusion service and only 2 of 15 reported to the regional blood collection service. Despite this underreported status, the FDA has identified TRALI as the third most common cause of transfusion-associated fatality from their drug database. In 2001, the FDA issued a "Dear Doctor" letter to all physicians, alerting them to this previously unacknowledged complication of transfusion.⁴

Although the rate of transfusion-associated infectious disease has plummeted over the past decade, the risk of fatal hemolytic reactions resulting from clerical error continues to plague the clinical community. Linden and colleagues⁵ reviewed transfusion reactions in New York State and identified 104 clerical errors. The wrong unit was administered 1 in 12,000 times, with an ABO incompatibility of 1 in 33,000 transfusions. The mortality reported was between 10% and 50%, depending on the volume of mislabeled blood that was received by the unintended recipient. Patients who are more at risk include those in the operating room who are anesthetized and unable to alert the care team to the immediate symptoms associated with mislabeled blood and patients who are critically ill in the ICU. Recognition of this issue and its persistence despite improvements in other areas of transfusion safety has prompted some medical centers to introduce technologies to decrease its frequency. One such technology is the Bloodloc system (Novatek Medical, Inc., Greenwich, CT). When blood is drawn from a patient for typing and screening, the sample is identified with a three-letter code (the Bloodloc code). As blood is distributed from the blood bank to the clinical setting, the clinician reviews the Bloodloc code on the

patient's name band and uses it to "unlock" the blood product that has been delivered. Although this is not a foolproof method (errors at the time of specimen collection can still occur), it is believed that this supplemental technology increases the safety of blood administration.

Immune Suppression

The medical community has long understood that the transfusion of allogeneic blood results in immune suppression. In the early days of renal transplantation, allogeneic blood transfusion was used as an immunosuppressant to decrease the incidence and frequency of transplant rejection in the postoperative period. More recently, however, additional concerns have been raised as this issue has been reexamined. Blumberg et al⁶ demonstrated an increased frequency of cancer recurrence following curative operation for colon cancer in patients who were transfused (56 of 129 versus 6 of 68 patients who were not transfused). This was highly statistically significant ($P < 0.0001$). In addition to the issue of recurrence, the time to recurrence after adjustment for baseline factors was also statistically significant. Similar observations have been made in patients having surgery for head and neck malignancies and in patients having surgery for urologic malignancies.

Of even more concern are the clinical associations with infection as a consequence of transfusion of allogeneic red cells. Koval et al⁷ documented an increased incidence of postoperative infection in 687 geriatric patients undergoing open reduction and internal fixation of hip fractures. Twenty-seven percent of the transfused patients, versus 15% of the nontransfused patients, developed infection. The transfusion effect was present on a multivariate analysis in trying to identify other causes for these increased infections in the transfused population. A similar finding was identified in patients undergoing surgery for colorectal cancer. Houbiers and colleagues⁸ reported on 697 patients; 39% of the transfused patients versus 24% of the nontransfused patients developed bacterial infections in the postoperative period. The observation was also made that the relative risk increased with the total number of units that were transfused. The relative risk was 1.6 times for a one- to three-unit transfusion, and 3.6 times for more than three units. This supports the beliefs that incremental transfusions do increase the risk of these complications and that each unit of blood should be considered as a separate risk factor. Laboratory investigations in which the magnitude of the surgical insult and the extent of that insult can be controlled rigorously have supported the findings from the clinical literature.

Additional support for these concerns has surfaced from analysis of the Project Impact database. Taylor and colleagues⁹ reported that the nosocomial infection rate was greater in critically ill patients who were transfused than not, and that the association of increased frequency of infection is persistent when the population of patients studied was adjusted for probability of survival and age. In addition to the frequency of infection, mortality rates, length of intensive care, and hospital stay were significantly increased in patients who were transfused as compared with the nontransfused group. Although these associations are not definitive proof of causality, they provide strong circumstantial evidence for the adverse effect of allogeneic blood.

Oxygen Transport Function of Blood

The purpose of allogeneic transfusion is to increase oxygen delivery at the tissue level. Throughout the 1980s and 1990s, there was a significant body of work that investigated the efficacy of different strategies to increase oxygen delivery by increasing perfusion

and oxygen transport during critical illness. William Shoemaker was one of the leading proponents of this important physiologically based treatment approach. Shoemaker and his colleagues¹⁰⁻¹⁹ demonstrated improvements in outcome when septic and other populations of critically ill patients had augmented oxygen delivery. The delivery of oxygen and the calculation of oxygen delivery are heavily influenced by the level of hemoglobin. The other major determinant is cardiac output. Studies in which oxygen delivery was enhanced by increasing the hemoglobin available for oxygen delivery demonstrated increases in "calculated" delivery of oxygen but not in oxygen consumption. This is in direct contrast with comparable studies that used inotropes to increase cardiac output. Those studies demonstrated an increased effect on oxygen consumption.

The explanation for these findings is complex and is likely the result of the biochemical abnormalities associated with stored red blood cells. The red cell itself is a biconcave membrane that has important rheologic properties of deformability as the red cell traverses the capillary bed. Stored red blood cells have decreases in membrane flexibility and are less deformable, and therefore more likely to result in tissue bed sludging and impaired oxygen carriage. Additionally, metabolic changes develop over time as a component of the storage lesion that is a consequence of blood preservation. Oxygen may not be released at the tissue level because of a shift in the O₂ dissociation curve mediated by decreasing amounts of 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP).²⁰ The inability of banked blood to efficiently unload oxygen is reversed in 4 to 12 hours as a consequence of 2,3-DPG and ATP repletion (Table 1).

Table 1. Biochemical Changes to Blood over Time

Storage Day	pH	K+ (meq/L)	2,3-DPG and ATP (mmol/g Hgb)
0	7.16	3.3	13.3/4.18
14	6.93	17.6	
21	6.87	21.7	
35	6.73	17.2	0.7/2.40

Hgb, hemoglobin.

As the limitations of allogeneic blood as a method to improve oxygen delivery were being better understood, an important contribution was made by Marik and Sibbald.²¹ They reported findings from 23 patients in whom they had concurrently measured pHi, a surrogate for visceral perfusion. These measurements were made before and after the transfusion of allogeneic blood. Their findings were startling in that they associated a decrease in pHi with the age of the blood being transfused. They subsequently confirmed that pHi always decreased if blood was >15 days old. In a follow-up study, Fitzgerald, a researcher in Sibbald's laboratory, created an investigation replicating these critical findings.²² In a cecal-perforation rat sepsis model with supply dependency created by progressive hemodilution, rats were found to have increased consumption with fresh blood (1- to 3-day-old red blood cell transfusion), but not with older blood (stored for 28 days or longer).

There appears to be clinical support for these findings. Keller et al²³ reported an 18-month review, focused on the transfusion of allogeneic red blood cells, of all trauma patients admitted to Boston Medical Center. This retrospective review focused on 86 patients receiving from one to four units within the first 48 hours after admission to the trauma center. Blood was preserved with CPDA₁-

ADSOL with a 42-day outdate shelf life. They reported on the average age of all units, the age of the oldest unit, and the average age of the two oldest units and examined the data based on blood shelf life of 7, 14, 21, and 28 days. There were an insufficient number of infections in the population to comment on the frequency of infectious complications following the transfusion of stored blood. They did find, however, that patients who had been transfused with allogeneic blood that was stored for >14 days had an increased hospital length of stay ($P = 0.01$). This effect persisted after multivariable analysis controlling for injury severity. Hospital length of stay increased 2 days per unit transfused.

A randomized trial of fresh versus aged allogeneic blood will be required to definitively address the issue of whether duration of storage is deleterious to blood. One such trial was attempted by the group at the Ryder Trauma Center at the University of Miami School of Medicine. This high-volume trauma center cares for 8,000 trauma patients a year, 3,600 of whom are severely injured. The researchers implemented a study randomizing patients to young blood (<11 days old) versus old blood (>20 days old) if the blood bank was able to supply adequate amounts of the randomized target. After 1 year, the study was abandoned because of the difficulty enrolling patients and having the appropriate randomized blood product available in the blood bank. During that year of study, only 24 patients were actually randomized. The authors suggest that, for the question to be definitively answered, a large-scale, multicenter trial would be required. The feasibility of such a trial has been demonstrated by Hebert and colleagues²⁴ from the Canadian Critical Care Trials Group.

Clinical Tolerance of Anemia

Despite the ongoing efforts by the blood banking community to successfully increase the safety profile of allogeneic red blood cell transfusions, there is an evolving agreement among experts in the field that the indications for transfusion can be much more conservative than had been the case previously. Weiskopf and colleagues²⁵ at the University of California, San Francisco, have done a series of studies defining the physiologic tolerance to anemia. In their first work, the group studied the acute, short-term, normovolemic hemodilution in healthy patients and volunteers down to hemoglobin levels of 5 g/dL. With normovolemia maintained, these subjects tolerated the anemia without any clinical consequence. In a subsequent study that was published in June 2000,²⁶ this same group documented cognitive changes at hemoglobin levels below 7 g/dL using the same experimental model of normovolemic hemodilution in healthy patients. Further work, published in April 2002,²⁷ demonstrated that the cognitive changes previously identified were reversible with supplemental oxygen in addition to the protocol that was not part of the first study. Observers have suggested that it is possible that, for longer periods of time, such levels of anemia might not be tolerated as effectively. Others have suggested that, with additional time, adaptation to lower levels of hemoglobin would result, providing the opportunity for extended periods of time at low hemoglobin and hematocrit levels without physiologic consequences.

Acute normovolemic hemodilution has been employed clinically in a variety of settings in the operating room. Matot et al²⁸ randomized patients having liver resection to a protocol of hemodilution versus conventional management. They found no differences in hemodynamics, morbidity, or postoperative laboratory tests, including hemoglobin level, in the population that underwent hemodilution. What they were able to document was a substantial decrease in the percentage of patients transfused, with the conventional therapy group being transfused >30% of the time and

the hemodilution group being transfused <10% of the time. A frequent commentator on the evolving conservatism regarding transfusion triggers is Jean-Francois Hardy. He recently opined that "the quest for a universal transfusion trigger, i.e., one that would be applicable to patients of all ages under all circumstances, must be abandoned. All RBC [red blood cell] transfusions must be tailored to the patient's needs, at the moment the need arises."²⁹

Carson et al³⁰ reported on transfusion triggers in a systematic review of the literature. They concluded that, of the nine studies reviewed and over 1,600 patients reported, the overall outcome was one favoring more restrictive transfusion triggers than more liberal transfusion triggers, a finding that was statistically significant. In that same review article they noted that, despite more restrictive transfusion triggers and therefore fewer units transfused, there was no increase in cardiac events. Additionally, the 30-day, all-cause mortality analysis favored the more restrictive management of patients.

In a landmark study, the Canadian Critical Care Trials Group published a randomized controlled trial in the *New England Journal of Medicine*.³¹ This was a multicenter randomized trial of transfusion requirements in critically ill patients. Twenty-five ICUs from the trials group contributed 838 patients who had a hemoglobin of <9 g/dL within 72 hours of ICU admission. They were randomized to a restrictive transfusion limb with a trigger of 7 g/dL versus a conventional limb with a transfusion trigger of 10 g/dL. After each transfusion, the hemoglobin was checked. In the restricted transfusion group, the hemoglobin averaged 8.5 versus 10.7 g/dL in the liberally transfused group. In the restricted group, there were 54% fewer allogeneic blood transfusions, and 33% of these patients received no transfusions at all. All of the outcome measures favored the group with the restricted transfusion protocol. There was a trend toward decreased 30-day mortality, hospital mortality, ICU mortality, and organ failure score. These findings have had a significant impact on the transfusion decisions of critical care physicians in Canada. The Canadian Critical Care Trials Group conducted a scenario-based national survey that confirmed a change in reported transfusion triggers as compared with an earlier study.³² Currently, Canadian physicians are using lower transfusion triggers and are much more comfortable with single-unit transfusions. When questioned, these physicians were influenced by the large-scale Canadian study and institutional guidelines. In an accompanying editorial by Corwin,³³ the challenge of distributing new knowledge across populations of physicians and slow adoption was noted.

Despite widespread acknowledgment that more conservative transfusion triggers should be adopted, there appears to be ongoing controversy regarding this issue in patients with concurrent cardiac disease. In a retrospective study by Wu et al,³⁴ patients who had had an acute myocardial infarction had a better outcome when they were transfused if their hematocrit was <33%. Also favoring a more aggressive transfusion trigger is the work by Nelson and colleagues³⁵ that documented that ST segment changes increase as the hematocrit drops in vascular surgery patients starting with hematocrits of <30%. In contrast, the Canadian Critical Care Trials Group did not demonstrate an increase in mortality among patients with cardiac disease who were randomized to the conservative protocol. This was a prospectively randomized trial, but the cardiac subgroup was a post hoc subgroup and may not reflect a truly randomized population. In addition, concerns have been raised regarding entry into the protocol and the potential exclusion of patients at high risk of coronary disease by their treating physicians.

In an attempt to further understand the influence of transfusion concurrently with patients with acute coronary syndromes, Rao et al³⁶ analyzed the results of three large observational cohorts of patients (these three studies were titled GUSTO IIb, PURSUIT, and

PARAGON). Together, these three studies reported on over 24,000 patients. Transfused patients had a 10% higher mortality. Rao and colleagues used the Cox proportional hazards model incorporating transfusion as a time-dependent covariable. The 30-day mortality was almost four times higher with an increased mortality, with nadir hematocrits of greater than 35%. The authors concluded that this finding presented a strong recommendation for randomized controlled trials. In the accompanying editorial, Hebert and Ferguson³⁷ noted that "observational studies do not provide unbiased estimates of the benefits of therapy when the degree of anemia is directly related to the administration of red blood cells." They joined the authors' recommendation for a randomized controlled trial in different populations of patients with ischemic heart disease.

Consent and Deferral

Explicit consent for transfusion is becoming more normative in the United States. Many institutions have incorporated transfusion as part of the elective surgical consent process in both surgical consent forms and anesthesia consent forms. Additionally, consent to transfusion for an episode of care is becoming the norm in most other clinical settings outside the operating room. As is the case in the context of emergencies, or in the circumstance when the patient is unable to consent personally and does not have a surrogate decision-maker identified, general consent is valid or can be waived by a treating physician. Of interest is the population of patients who refuse blood products on religious grounds. There is an increasing experience with surgical programs specifically agreeing to manage these patients without blood transfusion. Outcome data from those environments suggest that, with careful attention to hemostasis, even very complex cardiac and orthopaedic procedures can be accomplished with minimal physiologic consequences. These findings offer support for the emerging practice of more conservative transfusion thresholds being applied more generally.

Conclusions

Allogeneic blood transfusion continues to increase in safety as donor populations are more effectively screened and laboratory testing continues to decrease the risk of infectious disease. Despite these improvements in blood safety, increasing concerns have been raised about the efficacy of allogeneic blood. Healthy patients without comorbidity have been demonstrated to tolerate anemia to a much greater extent than previously had been considered. Many believe that patients with coexisting disease (cardiac, pulmonary, and neurologic) may have circumstances that require higher levels of hemoglobin, but there is little objective evidence to support those beliefs. Red blood cells, or allogeneic blood, may be harmful even in circumstances in which the prevailing wisdom is that a higher hemoglobin is necessary. Clearly, there is no universal transfusion trigger. Each transfusion should be considered individually in the context of the patient's condition, with appropriate consideration for the real and meaningful risks associated with allogeneic blood cells.

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Instructions for Authors

ITACCS welcomes the submission of manuscripts for publication in its journal, *TraumaCare*. Reports on airway management; new equipment; new drugs or new applications of old drugs; training programs for technicians, nurses, and physicians in trauma care; and trauma care in developing nations are encouraged. Reports of disaster management, original research in any aspect of trauma care, and case reports of difficult problems are also of interest. Topics related to injury prevention, prehospital care, improvements in hospital management of injured patients, long-term rehabilitation, and ultimate outcome after injury will be considered as well.

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