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## Blood Transfusion and Outcomes Research

**Bruce D. Spiess, MD, FAHA**

*Department of Anesthesiology*

*Professor and Vice Chairman*

*Director of VCURES*

*Virginia Commonwealth University Medical Center*

*1200 East Broad Street*

*Richmond, VA 23298-0695 USA*

BDSpiess@HSC.VCU.EDU

**Learning Objectives:** 1) To learn of the contemporary risks of blood transfusion. 2) To understand that no prospective randomized trials were involved with the development of blood transfusion. 3) To appreciate that contemporary outcomes research has shown that patients receiving blood transfusion have worse outcomes compared with those who receive less blood. The only relative large randomized trial shows that patients receiving more blood did worse or no better than those who were transfused less. Other smaller randomized trials have not shown any advantage to transfusion.

### Abstract

Modern blood banking is approximately 105 years old, dating back to the first description of the ABO-rH system. Since that time no prospective trials of efficacy of blood transfusion have been mandated as they would for the approval of a new drug. The only trials that exist show that either blood transfusion makes no difference to outcome or that in some subgroups of patients it is linked with a higher death rate than in those patients receiving less blood. Data-based research cannot prove cause-and-effect, but a consistent finding is the association of blood transfusion to more infection, immunosuppression, longer hospital stays, more multisystem organ failure, transfusion-related acute lung injury, and other dysfunctions. Clearly, an appropriate or best practice for blood transfusion must exist. In massive blood loss cases, transfusion surely saves lives. A lot of research is yet to be conducted in many different subgroups of patients before we have a clear guidance for the practitioner for when it is best to transfuse.

Transfusion of allogeneic blood is now 105 years old in the modern era. Its use grew throughout the 20th century, with major changes in practice surrounding the conflicts of the First and Second World Wars.<sup>1</sup> Blood banking has focused on supply as a major problem. Indeed, supply continues to be one of the biggest challenges facing the blood banking industry today.<sup>2</sup> Shortages of stored red cell products in the United States may approach 10% to 15% this year alone, and regional short-term crises result when blood is not available.<sup>3</sup> Costs of blood products are rising faster than other medical care costs. It is expected that a unit of red blood cells may cost more than \$500.00 in the next 3 to 5 years. The United States Congress is aware of these critical issues, as are the organizations governing the collection and distribution of blood.

In the 1970s it became widely known that allogeneic blood transfusion carried a high risk of viral disease transmission.<sup>1,3</sup> Hepatitis C (at that time known as non-A, non-B) was present in about 1% of all units transfused, but because of the relatively large number of units that each transfused patient received, the risk of seroconverting after transfusion was widely quoted to be at 10%. The prevailing transfusion practice did not ever question whether transfusion improved patient outcome. It was simply accepted that blood transfusion was good, and the risk of hepatitis was therefore accepted. When the acquired immunodeficiency (AIDS) crisis was felt in the Western World, the lay press focused on viral disease transmission in the blood supply. With such public pressure the medical profession refocused their thinking and began a number of safety steps to reduce viral transmission. Not only were donor criteria made stringent and paid donors outlawed, eventually nucleic acid testing for portions of viral DNA led to very effective detection of possible infectious units. Today, the scourge of hepatitis and AIDS has been almost eliminated from the blood supply. The risk of contracting hepatitis C is probably in excess of 1/1,000,000 units transfused, and the risk of contracting AIDS is approximately 1/1.5-2.5 million units transfused. Hepatitis B may be more common at approximately 1/150,000-500,000 units transfused.<sup>4,5</sup>

In the 1970s a national study followed more than 300,000 patients who had contracted hepatitis through blood transfusion.<sup>6</sup> Approximately 1,000 of these patients died every year, and many others developed chronic active hepatitis leading to cirrhosis and hepatomas. No researcher in that very large National Institutes of Health-sponsored series of studies asked the important question if the medical profession knew whether transfusion was improving outcome.

Although today we have largely defeated the risks of hepatitis and AIDS from blood transfusion, the laymen still focus on these viral pathogens. It is the responsibility of the medical community to shift public opinion and understanding to contemporary appropriate risks and outcomes from transfusion. Modern blood banking tests only for certain viruses, but many more are present in most transfusions. Transfusion-transmitted virus is present in a significant number of units tested (8-82%).<sup>7-10</sup> Debate continues as to whether

this virus is capable of causing a catastrophic hepatic failure in immunocompromised hosts. Epstein-Barr virus is present in approximately 0.5% of transfusions, and this virus has been associated with non-Hodgkin lymphoma.<sup>11,12</sup> It appears that this lymphoma is far more prevalent in patients who have been transfused. Cytomegalovirus (CMV) appears in a large number of transfusions. In patients who are CMV-negative and immunocompromised, CMV can cause deadly encephalitis. New viruses are emerging or becoming known to us in Western medicine. There is no doubt that SARS (severe acute respiratory syndrome) and the avian flu virus will eventually show up in our blood supply. Therefore, although we have largely defeated hepatitis and AIDS in the blood supply, all other viruses should still be considered present and dangerous.

What remains amazing is that during the height of the hepatitis epidemic from blood transfusion, no large blood banking or national health consortium asked the most important question of all: "Does transfusion actually improve patient outcome?" When anesthesiologists and surgeons discuss outcomes, they focus on mortality and major morbidities such as myocardial infarction (MI), stroke, infections, congestive heart failure, renal failure, pneumonia, acute respiratory distress syndrome, multisystem organ failure, as well as length of hospital stay and intensive care unit (ICU) admissions. It has long been thought (without confirmatory research) that blood transfusion treats or makes many of these conditions better. Only in the last few years have relationships between some of these outcomes and transfusion been investigated.

Most of the research published on outcomes of blood transfusion has been retrospective and uses databases. Even with the best and most controlled multivariate analysis, only statistical associations can be proven from databases. Cause-and-effect relationships require prospective, randomized research to definitively prove outcomes. Multiple prospective studies with similar findings cement the cause and effect. One would think that blood transfusion has undergone rigorous, randomized prospective trials for efficacy, but this is not the case. Instead, the focus of study has been on viral transmission prevention and storage and/or supply. There are fewer than five randomized trials of transfusion of size greater than 100 patients per group. These trials have been assessed in several meta-analyses that show either a slight worsening of outcome with transfusion or no difference in outcomes.<sup>13-15</sup> Only one study is of substantial size with a wide enough separation of transfusion trigger to adequately assess differences in outcome.<sup>16</sup> Clinicians are therefore often perplexed in making the decision of when it is most appropriate to transfuse. Today we simply do not have the science to understand when it is best to transfuse.

### Prospective Randomized Trials

The single largest trial of transfusion was recently published from a cooperative effort in Canada known as the TRICC (Transfusion Requirements in Critical Care Investigators) trial.<sup>16</sup> Eleven major academic institutions cooperated in their medical ICUs by randomizing patients to receive a transfusion of red cells at one of two hemoglobin triggers. The liberal trigger was at 10 g/dL and the restrictive trigger was 7 g/dL. The patients who entered into this study had acute respiratory distress syndrome, gastrointestinal bleeding, pneumonia, or vascular failure, and a major subgroup had known severe coronary artery disease. To put this study into perspective, the reader should imagine what it would require to do such a study in one's own institution, wherein critically ill patients are prospectively randomized to receive blood at a widely and historically accepted transfusion trigger versus a more aggressive and lower level. Many United States ethics committees might well have had trouble agreeing to the protocol, and for that reason the Canadians should be congratulated for the science that was bravely undertaken.

Hébert et al<sup>16</sup> found some astonishing things (Tables 1 and 2). Perhaps the most astonishing result is what they did not state in their findings. Nowhere in any outcomes were critically ill patients statistically better by having a more liberal transfusion trigger. The study did follow the protocol well, and the hemoglobin levels were significantly lower in those patients who were supposed to be in the restrictive group. All patient mortality was not different between groups ( $P = .1$ ), but the in-hospital mortality was less in patients who received fewer transfusions and were allowed to bleed or be hemodiluted to a lower hemoglobin ( $P = .05$ ). In patients with overall known cardiac disease, the mortality rates were not different in patients who received more and less blood ( $P = .69$ ). In patients who were relatively young and in those patients with relatively low prehospital APACHE scores, the use of blood transfusion was associated with increased mortality ( $P = .03$  and  $.02$ , respectively). There were significantly fewer MIs reported in the group that received fewer red cell transfusions, and there was less congestive heart failure and acute respiratory distress syndrome in those with less transfusion. In a subset of 375 patients with known coronary artery disease, of which 257 had severe coronary atherosclerosis, there was no overall difference in mortality.<sup>17</sup> It should be noted that this study was neither powered nor focused on testing the efficacy of transfusion in patients with evolving MI. Although there were no differences in mortality and fewer MIs in the group with less transfusion, there was also less multisystem organ failure in the group that received less transfusion. This study<sup>16,17</sup> is the largest and best-performed randomized,

**Table 1. Mortality Rates Among Critically Ill Patients Receiving Either Liberal or Restrictive Transfusion Triggers in the ICU**

Patients	Restrictive (7 g/dL)	Liberal (10 g/dL)	P
All patients	18.7	23.3	.10
APACHE II	8.7	16.1	.03
<55 years old	5.7	13.0	.02
Cardiac disease	20.5	22.9	.69
Death (hospital)	22.2	28.1	.05

Adapted from data from Hébert et al.<sup>16</sup>

**Table 2. Percent of Patients Encountering Specific Morbidities by Liberal Versus Restrictive Transfusion Triggers in the ICU**

Patients	Restrictive (7 g/dL)	Liberal (10 g/dL)	P
MI	0.7	2.9	.02
Pulmonary edema	5.3	10.7	<.01
Angina	1.2	2.1	.28
ARDS	7.7	11.4	.06
Infectious	10.0	11.4	.38

ARDS, acute respiratory distress syndrome. Adapted from data from Hébert et al.<sup>16</sup>

prospective study of transfusion that has been completed to date. In a substudy, it was found that transfusion of red cells did not improve patient's abilities to be weaned from respirators.<sup>18</sup>

Two other studies of approximately half the size of the study by Hébert et al<sup>16</sup> do exist for cardiac surgery.<sup>19,20</sup> Both of these studies were performed in coronary artery bypass grafting (CABG) in the 1980s and 1990s. The studies randomized patients to one of two different red cell transfusion triggers. In neither study were the transfusion triggers profoundly different. There was no advantage shown by more liberal transfusion.

## Jehovah's Witness Experience

The Jehovah's Witness religious sect believes in the strict interpretation of the Bible with regard to certain passages in the book of Leviticus. Accordingly, they routinely do not accept blood transfusions. There is a large series of patient study on this sect.<sup>21</sup> From this series it is possible to judge the effect of withholding blood transfusion on morbidity and mortality. Unfortunately, none of the series has any randomization and there are a number of varied surgical procedures, so there may not be large numbers of many particular surgical procedures. However, what can be generalized from the data is that patients tolerate anemia well. Mortality does not rise in comparison with other groups, or in comparison with groups with higher hemoglobin until the hemoglobin falls to approximately 5 g/dL or below.<sup>22</sup> Only at that point does mortality double, and only if the patients have not only a low hemoglobin, but continued and severe or massive blood loss. Perhaps it is the low hemoglobin in the face of other systemic instability, such as hypovolemia, that leads to the increased death rate in this group of patients. It is difficult to draw a conclusion that 5 g/dL might be an appropriate transfusion trigger, but the level seen in the Jehovah's Witness patients is not too much above the hemoglobin found at critical oxygen delivery in mammals and humans.

Critical oxygen delivery ( $DO_{2crit}$ ) is an important physiologic concept in shock medicine.<sup>23,24</sup> All mammals have a point at which either cardiac output, regional blood flow, or hemoglobin oxygen transport becomes critical. Above this point, there is flow that is independent oxygen delivery. Below that point, oxygen delivery becomes flow-dependent, and aerobic metabolism shifts to anaerobic metabolism. With such a shift, metabolic acids are produced and lactate begins to build up. The longer an animal stays below  $DO_{2crit}$  or undergoes some other type of instability, the more likely it is that death will result. One can think of this concept in terms of a climber going up Mount Everest: the longer he stays in "the killing zone" or above an altitude where  $DO_{2crit}$  is present, the more his physiology suffers and the more unlikely he is to return alive. It has been discovered in a number of animal research studies that a hemoglobin level of 3 to 3.5 g/dL corresponds to  $DO_{2crit}$ .<sup>24</sup> Some variability from animal to animal does exist, but the level is well preserved across species. In one study of anesthetized humans, it was found that  $DO_{2crit}$  was at approximately 4 g/dL hemoglobin.<sup>25</sup> That is not far below the level found at which the Jehovah's Witness patients have increased mortality rates. In animal models of transfusion, it has been found that  $DO_{2crit}$  is higher in animals that received stored blood as compared with those that were not transfused.<sup>26</sup> When one thinks about it, that means that shock,  $DO_{2crit}$ , comes earlier or at higher hemoglobin. There may be at least two reasons why this occurs. Banked blood has almost no intracellular 2,3-diphosphoglycerate (2,3-DPG), and banked red cells lose their ability to flex and distend, and therefore are unable to move well through the microcirculation.<sup>27,28</sup> They take on bizarre shapes such as rounded and speculated forms. Transfusion of allogeneic blood therefore simply does not supply the tissue with oxygen.<sup>29-32</sup>

## Immunomodulation

Transfusion of allogeneic blood carries a number of immune-mediated compounds and activated cell lines.<sup>33</sup> White cells harvested at the time of centrifugation and separation are found both within the platelet concentrates and red cell concentrates. Recent use of various white cell filtration systems can eliminate over 99% of these white cells. However, leukodepletion in the United States is not universal, and data regarding the effects and outcomes from universal leukodepletion to date do not support its universal application. Canada and Western Europe have adopted universal leukodepletion. Immunosuppression still exists, even if transfusions do not transmit white cells.

Transfused white cells infect the recipient and develop cell lines living within the recipient's bone marrow. Acutely, these donor cells compete with the recipient's helper T-lymphocytes and there is acute immunosuppression for a number of days. Donor DNA has been isolated from the recipient for up to 1 year after the date of a transfusion. In the 1970s and 1980s, transfusion was the standard of care at the beginning of solid organ transplantation (i.e., renal transplant).<sup>34</sup> Transfusion of patients who received renal transplants improved acute and chronic rejection through immunosuppression.

The effects of immunosuppression have been widely investigated in cases of colon cancer. If a patient is transfused during the period of colon resection, the incidence of metastasis and early death is increased between 1.5-fold and twofold.<sup>35-37</sup> Other cancer operations have been investigated, but the data are not as strongly in agreement as they are in colon cancer. It is possible that patients with more advanced cancers may have the tendency to bleed more or have more extensive operations, and therefore the increased risk of metastasis is from other covariants of disease rather than transfusion alone. However, when multivariate analysis is performed carefully, the association of transfusion with metastatic disease remains highly significant.

Perioperative risks of major infection appear associated with transfusion as well. A number of orthopaedic surgery studies have prospectively randomized patients to receive autologous or allogeneic blood when it was transfused.<sup>38-43</sup> The risk of infection is increased with allogeneic blood between 1.3-fold and 3.5-fold over autologous blood. There are some studies in which no difference has been shown between autologous and allogeneic blood, but by far the largest number of studies show immunosuppression.

Vamvakas and Carven<sup>44-46</sup> have published a number of studies looking at various databases regarding CABG surgery. They have demonstrated that postoperative pneumonia is highly associated with the number of non-white cell-reduced red blood cell units or platelets transfused. In one study they noted that the risk of pneumonia was increased 5% per unit of red cells transfused.<sup>44</sup> However, in later work they retreated a bit from statements in their earlier work by noting that transfusion alone could not be singled out above all the other potential confounding variables as causing infection.<sup>46</sup>

Blumberg,<sup>33</sup> who has published widely on the effects of transfusion on immunomodulation, has stated: "We estimate that the death rate from allogeneic transfusion related infection and cancer recurrence combined may exceed the death rate due to all other transfusion related risks combined." Categorically, immunomodulation is today the most important adverse event and outcome effect of transfusion. Persons discussing transfusion risks with patients should take this to heart and realize that viral transmission is not the number-one risk. Of interest, Hébert et al<sup>16</sup> did not show an increased risk of infection with their randomized prospective study of transfusion. Their study was not of surgical patients but was of medicine patients, some of whom already had severe infections, including pneumonia. The surgical patient entering

the operating room without infection may well be a different group of patients than those critically ill in a medical ICU.

The study by Hébert et al<sup>16</sup> showed that multisystem organ failure was increased in patients who received more transfusion, especially those patients in the subgroup that had significant coronary artery disease.<sup>16,17</sup> Multisystem organ failure is probably an immune-mediated function, although it could also be related to microcirculatory oxygen delivery and reduced flow-through capillaries resulting from cell clogging of banked blood. Multisystem organ failure has been shown to be more common in trauma patients who received largest amounts of allogeneic transfusion.<sup>47-49</sup> Once again, the covariant of severity of disease or injury might seem difficult to separate from those patients who receive the most blood transfusions. However, the studies performed report multivariate analysis in which covariates are weighted. The results show that transfusion remains an independent predictor of adverse outcome even when all confounding variables are accounted. In these models that take into account the covariates, blood transfusion always has a strong association with the adverse outcome of multisystem organ failure.

### Transfusion of Patients with Cardiovascular Disease

It is a widely held belief that patients with coronary artery disease or other vascular disease may benefit from a higher transfusion trigger than otherwise healthy surgical patients. This belief does have some support in the literature.<sup>50,51</sup> In a small series of patients having peripheral vascular surgery, better outcomes have been noted if the hemoglobin or hematocrit is held at higher levels. One of these studies, although widely quoted, has only 27 patients.<sup>51</sup> Again in the work of Hébert et al,<sup>16,17</sup> MI levels were lower in patients who received less transfused blood. There was no increase in strokes by patients who tolerated lower hemoglobin levels.

In a study of elderly orthopaedic patients, there appeared to be no advantage to transfusing at a higher trigger versus a lower trigger.<sup>52</sup> Two major studies done from retrospective databases have attempted to establish the best transfusion behavior for patients with known coronary artery disease or evolving MI.<sup>53,54</sup> In one of these studies, from a Medicare database, the records of all patients who entered an emergency room (ER) to rule out a diagnosis of MI were examined over a 1-year period.<sup>53</sup> Approximately 250,000 patients were originally included in the database; hemoglobin levels, when available at the time of entrance to the ER, were provided. Some patients received transfusion and others did not. Mortality was the main outcome, and the authors segmented the group into different ER-entry hemoglobin levels. Most patients were eliminated from the database for a wide range of reasons; approximately 75,000 patients were analyzed. Only patients over 65 years of age were included in this group of 75,000 patients. The different entry hemoglobin levels were then examined by Kaplan-Meier survival curves; in patients who had less than 33% hematocrit on entry to the ER and who were transfused, there was an increase in survival rate. This study was published in one of the United States' most prestigious medical journals and was accompanied by an editorial noting that we finally knew when to transfuse, and it was at the standard 10 g/dL of hemoglobin that people had practiced for years. Many cardiologists embraced this major article and used it to confirm that patients must receive a blood transfusion at or about 10 g/dL.

Unfortunately, the study's conclusions should not be as widely embraced as one is led to believe by the editorial. Of the original 250,000 patients, there were only approximately 3,500 patients in the group that had less than 33% hematocrit on entry to the ER. If one compares the group with a low hematocrit, and who were therefore thought to benefit from transfusion, with the groups that were not

anemic, some very important differences stand out. Those who were anemic had over twice the frequency of "do not resuscitate," as well as more diabetes, congestive heart failure, and other measures of high risk. Furthermore, those anemic patients were treated far less aggressively. Almost half as many in the low hematocrit group received cardiology consultation, immediate percutaneous coronary intervention (PCI), or thrombolytic therapy as similar patients in the normal hematocrit group. Also, patients in the anemic group had less than half as many surgical interventions with CABG as did those with normal hematocrit. Because mortality was the major outcome, it is very important to normalize the groups as much as possible. It is not surprising that patients who entered the ER severely anemic (<30% hematocrit) and with evolving MIs were helped by transfusion. Only those patients who might have benefited from such a transfusion were likely transfused. The do-not-resuscitate patients and other potentially unsalvageable persons were probably not transfused. Therefore, a bias exists.

This study did use multivariate analysis to control for potential covariates. Also, there are no data on when patients were transfused. All that is known from the database is that patients were transfused at some time during their hospitalization. Of interest is the contrapositive conclusion that is present in the article, but not discussed. If a patient had a transfusion and had a hematocrit of 33% or greater, he or she was far more likely to die than if there was no transfusion. That is an astounding and significant finding. Therefore, although this study was widely heralded, it certainly does not settle once and for all the question of whether a higher transfusion trigger (10 g/dL) improves outcome in patients with either evolving MI or known coronary artery disease.

Recently, another very large database study, a retrospective examination of transfusion and outcome in evolving MI, was published in another prestigious medical journal.<sup>54</sup> This study used data from three prospective pharmaceutical PCI trials. Approximately 25,000 patient records were examined; there were excellent data, not only on transfusion but also on adverse events including bleeds, MIs, and death. Overall, the Kaplan-Meier survival curves showed that patients who were transfused during PCI or immediately afterward were far more likely to die than those who were not transfused. The authors did try to control for potential confounders by doing exhaustive multivariate and propensity analyses. After all of the statistical examinations, they found that if a patient was transfused during PCI, the risk of mortality increased by 3.9-fold.

Engoren et al<sup>55</sup> examined approximately 2,000 CABG patients in one group's series. They not only looked at mortality immediately after surgery, but more importantly they focused on the effect of perioperative blood transfusion on long-term outcome. They followed their patients for up to 60 months after CABG surgery. They found that patients who were transfused had twice the risk of death, even up to 60 months after hospital discharge. They performed propensity analysis, which involves the use of a multivariate analysis, to create a score for potential confounders. Each patient was assigned a numerical risk score based on the prior analysis. Patients with like risk scores were examined as groups with and without the dependent variable transfusion. The effect of transfusion on the long-term mortality rate held up, even with this rigorous propensity analysis. Why would transfusion at the time of surgery affect long-term mortality? It may be related to the effects of inflammatory mediators. Transfused blood carries large loads of cytokines and inflammatory messengers, as well as activated white cells. The endothelium of the coronary bed is made particularly susceptible to inflammatory events when ischemia and reperfusion occur during CABG surgery. The use of transfusion then insults such susceptible endothelium with tremendous loads of inflammation. Further research needs to be done, not only to confirm the work of Engoren et al,<sup>55</sup> but to further understand the mechanism for this effect.

Researchers at Duke University have examined renal failure after CABG surgery.<sup>56</sup> Not surprisingly, they found that relative anemia during CABG surgery is related to increased postoperative creatinine levels. It could well be expected that transfusion would mitigate or make this risk of elevated creatinine better, but the findings from their study were exactly the opposite. Transfusion did not make renal function better or preserve it. The more blood transfused, the worse the renal failure, and the rise in creatinine levels paralleled at ever higher levels of renal dysfunction compared with the effects of anemia alone. Adverse outcomes are increased with anemia, but trying to treat the anemia makes the outcomes even worse.

## Hematocrit and Outcome

There are many reports in the literature of studies showing that low hematocrit is associated with increased adverse outcomes. At least three studies of CABG surgery outcomes have noted that low hematocrit at various times during and after surgery are associated with increased morbidity and mortality.<sup>57-59</sup> One study examined the hematocrit level on entry to the ICU, and contradicts the other studies.<sup>60</sup> That study examined the patient's hematocrit (the sum total of the patient's hematocrit, anemia, volume replacement, and transfusion in the operating room) on leaving the operating room. There were some controls for transfusion. The ICU entry hematocrit was the only hematocrit associated with outcome. Patients entering the ICU with the lowest hematocrit levels had the best outcomes. In the other studies in which hematocrit was associated with adverse outcomes and increased mortality, there was no assessment of transfusion.<sup>57-59</sup> However, most of these studies called for liberalization of the transfusion triggers.

One study of patients with congenital heart disease conducted at Children's Hospital of Boston was stopped when the oversight board found the data so compelling as to halt further research.<sup>61</sup> This study looked at psychomotor and mental development levels in patients who had undergone repair for congenital heart disease. Those patients with higher hematocrit levels during the surgeries had better psychomotor index scores at age 1 year. The design of this randomized study was such that bypass-priming volumes were calculated for a bypass hematocrit of 20% or 30%. Priming solutions were made up of whole blood and Plasmalyte (Baxter Healthcare, Deerfield, Illinois). At age 1 year, Bayley scales of infant development were used for psychomotor and mental development indexes. Of note, the mental development index scores were not different between groups. One may interpret these data to mean that it was most appropriate to transfuse the patients to a higher hematocrit. However, the use of blood products in transfusion was not different between groups (median, 168 vs. 165 mL per patient). The outcome of increased neurologic development was based only on better maintenance of the patient's own hematocrit, or the fact that the patients with the higher hematocrit had less edema and other free fluids. Native red cells function much better than do transfused cells, and this study essentially shows these effects. Ultimately, the explanation for the differences in outcome on one of the developmental tests needs to be further investigated.

## Platelet Transfusions

This article thus far has discussed the adverse outcomes associated with red cell transfusions. Platelet concentrates contain the highest concentration of live white cells of any blood product. During centrifugation, the buffy coat contains highly concentrated platelets and white cells. A retrospective research study looked at the

database records of more than 1,700 patients who underwent CABG surgery.<sup>62</sup> The data were prospectively collected as part of the clinical trials for Food and Drug Administration (FDA) approval of the use of aprotinin in cardiac surgery. These trials had excellent data regarding blood loss and transfusion use. Because of the nature of their FDA phase III trial, the study contained very accurate and blinded data on adverse outcomes. From these combined data it was found that patients receiving platelet transfusions are at particularly high risk for respiratory dysfunction, difficulty supporting the circulation (requiring more than two catecholamines), infections, stroke, and death. When both multivariate and propensity analyses were applied to the data, there remained a statistically significant relationship between platelet transfusion, stroke, and death. Indeed, the risk of stroke was threefold to fivefold increased, and death was as high as sevenfold higher in patients who had received a platelet transfusion. In the latest multicenter study of perioperative ischemia (McSPI) database, it has been shown that early postoperative use of aspirin decreases the MI and death rate. In the fine print of the study, one learns that those patients who did receive platelet transfusions had almost the same death rate as was found in the database of platelet research on the use of aprotinin.<sup>63</sup>

## Conclusion

When one realizes that blood banking and transfusion are over 100 years old, it is perhaps a bit difficult to believe that we really know little about when to transfuse. Historically, the transfusion trigger has moved considerably. In the very earliest days of transfusion, the trigger was close to the  $Do_{2crit}$  (3.5 g/dL). Around the time of World War I, the trigger moved up to 5 to 7 g/dL with the belief that it was perhaps unhealthy to wait until the heart failed or the patient became acidotic before transfusing. In the 1930s to 1947, John Lundy's opinion was that transfusion should be at 10 g/dL, and that opinion was reprinted until the hepatitis and AIDs crisis.<sup>64,65</sup> Dr. Lundy was a pioneer in anesthesiology, developing the intravenous agent pentothal and working at the Mayo Clinic to help establish blood banking there. He used the best-available data at the time and his experiences in the operating room to promote that patients should receive blood if the hemoglobin dropped below 10 g/dL. No large-scale outcome research study had ever been performed until the study by Hébert et al,<sup>16</sup> which is the largest and best study of its kind.

What is badly needed is an active, prospective research study on outcomes in a wide range of different clinical situations. To date, no national health agency has sponsored the necessary trials, which speaks to a cultural bias that blood transfusion is good. Ideally, we deserve the prospective studies of transfusion in many different disease states and under different surgical scenarios. Only after perhaps several hundred studies will we know better when it is advantageous to transfuse and when it is better to tolerate anemia. At the present time, there are no scientific data to back up that societal belief that blood transfusions are good and save every person to which they are given.

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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

**Andrew Gettinger, MD**

Department of Anesthesiology  
Dartmouth Hitchcock Medical Center  
Dartmouth Medical School  
One Medical Center Drive  
Lebanon, NH 03756 USA  
Andrew.Gettinger@Dartmouth.edu

**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."<sup>1</sup> 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.<sup>2</sup>

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