Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Hematol Oncol Clin N Am 21 (2007) 185–200
HEMATOLOGY/ONCOLOGY CLINICS OF NORTH AMERICA

Red Cell Transfusions and Guidelines: A Work in Progress

Bruce D. Spiess, MD[a,b,*]

[a]Department of Anesthesiology, Virginia Commonwealth University Medical Center, 1200 East Broad Street, Richmond, VA 23298-0695, USA
[b]Virginia Commonwealth University Reanimation Engineering Shock Center, Box 980695, Virginia Commonwealth University Medical Center, 1200 East Broad St., Richmond, VA 23298-0695, USA

Approximately 14 million units of whole blood are collected and transfused each year, predominately as packed red cell units [1,2]. Other components are manufactured as well, but the actual use of red cells comes dramatically close to all the blood that is collected. Because of economic and social changes in the United States, there exist continual regional shortages of blood [1,2]. These shortages will get worse, and the economics of blood transfusion are rapidly changing. They are not the focus of this paper.

Transfusion was first performed in 1666 to 1667 with animal blood transfused to humans. In the early 1800s human to human blood transfusions were developed, but it was not until 1900 when Landsteiner discovered the ABO histocompatibility system that modern blood transfusion really began [3]. In 1914, the citrate added to blood made it possible to store blood for some period of time anticoagulated.

The First and Second World Wars, saw increased use of both plasma and whole blood [3]. Actually, it was the Spanish Civil War that saw the first large scale use of blood transfusion with whole blood preserved using citrate. It was around the time of the Second World War that component separation became possible. During that conflict (World War II), however, most of the blood transfused in the operating room, was collected often from a soldier, nurse, or volunteer nearby. Plasma was collected in the United States and shipped to the war front, but rarely was banked blood sent over because it had to be constantly refrigerated. The Korean and Viet Nam Wars saw a shift from whole blood to packed red cell units. The Viet Nam War was significant in that it was the first time that blood components were collected in the continental United States, stored, and shipped to the front line field hospitals treating

*Corresponding author. Department of Anesthesiology, Virginia Commonwealth University Medical Center, 1200 East Broad Street, Richmond, VA 23298-0695. *E-mail address*: bdspiess@hsc.vcu.edu

0889-8588/07/$ – see front matter
doi:10.1016/j.hoc.2006.11.006

casualties with massive blood loss. Of interest, it was during the Viet Nam War that adult respiratory distress syndrome (ARDS) was first described. Today, the United States Food and Drug Administration lists transfusion-related acute lung injury (TRALI) as one of the top three risks of transfusion. Was the description of ARDS due in part at least to the use of stored blood?

From 1933 until 1947 John Lundy, MD, was providing revolutionary leadership at the Mayo Clinic by commanding the division of anesthesia. One of his most visionary undertakings was the establishment of a blood bank to support the rapidly expanding surgical and anesthesia services. He published his opinions, based on large experiences, that 10 g/dL of hemoglobin (Hgb) and or a 15% circulating volume loss constituted the appropriate levels at which to trigger a transfusion. These opinions were not based on a long history of animal or human oxygen supply demand research. Furthermore, there was no outcome research performed in a rigorous manner. His opinions were, however, formed from years of experience in the operating rooms of the Mayo Clinic.

It had generally been accepted that blood transfusions saved lives, from the experiences of the two World Wars. Such belief came out of the World Wars and was clearly driven by the popular advertising campaigns creating a patriotic duty to donate blood. Such patriotism and the societal beliefs regarding transfusion were not just limited to the United States. Advertising campaigns reflecting the patriotism can be found in the Soviet Union as well as Britain and throughout the allies [3]. In 1940, the American Red Cross dramatically increased the advertising as well as industrialized the collection of blood for plasma [3]. As early as 1943 the first reports of transfusion-transmitted hepatitis arose.

Transfusion-transmitted hepatitis was rampant and a major problem from 1943 until 1996. In the United States, sera conversion from a blood transfusion to hepatitis-positive status ran somewhere between 7% and 17%. The most widely quoted statistic is that approximately 10% of patients receiving blood did become hepatitis positive. In 1972, the National Post Transfusion Hepatitis study was published [4]. That one study followed up with 300,000 patients who had known posttransfusion hepatitis for up to 10 years to discover how many required rehospitalization, complications, costs, and how many died per year. Approximately 1000 patients per year died of cirrhotic problems from this cohort of 300,000 patients. Of interest, in Australia the sera-conversion rate was less, approximately 3% to 5%, but in Japan before the human immunodeficiency crisis (HIV/AIDS), as many as 45% of patients receiving a unit of blood became hepatitis positive. No mention of whether patients needed or benefited from a transfusion arose in either the National Post Transfusion Hepatitis Study or as a response to its publication.

The transfusion trigger, established by Lundy's leadership, was followed with no real research on either transfusion outcome or oxygen carrying capacity until 1987 when the HIV/AIDS crisis refocused the lay public's attention on blood transfusion and infectious risks. During the time from the 1940s until the late 1980s no one asked the most basic question of blood transfusion: does transfusion improve outcome? As we look back today, it is obvious that red

cell transfusion has never undergone prospective randomized testing in the fashion of that of a new drug. Through the late 1980s and into the mid 1990s the establishment of more rigorous donor elimination (deferral) and new testing (surrogate markers for hepatitis C virus [HCV], and nucleic acid testing) have largely eliminated the risks of hepatitis and HIV/AIDs [1,5,6]. The use of nucleic acid testing (NAT) pooled, and now individual NAT testing, have been able to find segments of viral DNA in blood so that it can be eliminated from the transfusion pool. Even with the most advanced NAT testing, today a small but present window of infectivity exists for donors if they have been exposed and have not yet had high enough viral titer values for NAT testing to detect the virus. It appears that a 3- to 6-week window still exists. For some viruses, the window of infectivity is longer than that for other viruses. That being said, today, the risks of contracting hepatitis or HIV/AIDS from blood transfusions in the United States is probably approximately one in two million units transfused. Still, the most commonly discussed risks of blood transfusion are the infectious risks [1,5,6]. This chapter will turn its focus away from infectious risk, of which many still remain, and hone in on whether red cell transfusions improve oxygen delivery to tissues and whether blood transfusions actually improve patient outcomes.

OXYGEN DELIVERY

The delivery of oxygen to tissues is the primary function of the erythrocyte. Transfusion of banked red cells must be to improve tissue oxygen delivery (not oxygen carrying capacity). Other excuses for transfusion (eg, volume expansion, support of blood pressure, and wound healing) have been promoted; however, all contemporary guidelines specifically are couched in oxygen availability and delivery.

Hemoglobin is housed inside the erythrocyte as the primary oxygen storage molecule. The metalloprotein of hemoglobin uses an iron moiety as the binding site for oxygen and, as we are all taught in medical school, the relationship of one binding site to another causes a progressive decrease in the ability of hemoglobin to release oxygen. As oxygen leaves a heme protein, the next oxygen molecule is more tightly bound. Hemoglobin is a profound oxidizer and is highly toxic to endothelial cells as well as other tissues. In the 1930s it was thought that a "blood substitute" could be easily created by lysing red cells, thereby creating a stroma-free hemoglobin solution. Experiments in animals worked well for the first 12 to 24 hours, but the animals succumbed to multiple organ dysfunction and failure by 48 to 72 hours. Not only were the solutions not truly stroma free, but it was thereby proven that free hemoglobin is itself highly toxic. Endothelial cells pinocytose free hemoglobin, which leads to dramatically increased endothelial cell dysfunction exhibited as reperfusion injury and oxidative stress. Such cells, rather than being naturally anti-inflammatory, become pro-inflammatory and highly thrombotic. Evolution must therefore have favored the enclosure of hemoglobin inside of a cell envelope. If one looks at the cytosol of the erythrocyte, it contains a very high concentration of antioxidants.

Hemoglobin also binds nitric oxide, and the concentration of red cells is to a great extent a regulator of flow and systemic vascular tone. Nitrosohemoglobin has unique properties that are just today being studied. It may well be that the evolutionary advantage for the "normal hemoglobin" level experienced in our population today is the result of an advantage for the best blood pressure versus capillary flow, rather than a strict oxygen delivery situation.

Inside the red cell also is found a stable concentration (20-25 μmol) of 2, 3 diphosphoglycerate (2,3 DPG). 2,3 DPG regulates the oxyhemoglobin dissociation curve and right shifts the curve. With normal 2,3 DPG the P_{50} or partial pressure of oxygen at which hemoglobin is 50% saturated is approximately 26 mmHg. Other metabolic byproducts have dramatic effects on the oxyhemoglobin dissociation curve as well. Hydrogen ion drives the curve to the right, increasing the release of oxygen as does carbon dioxide. Acidosis, therefore, increases the movement of oxygen off of hemoglobin. Under normal conditions, because of the oxyhemoglobin dissociation curve, it is possible for erythrocytes to unload at maximum 26% of their total oxygen load. For erythrocytes stored as banked blood, the maximum release of oxygen is considerably less (probably about 6% or less). The P_{50} of stored blood depends on how long it has been stored and the intracellular 2,3 DPG. Within 24 hours of harvest and separation, the 2,3 DPG has decreased rapidly in stored blood. By 48–96 hours, the levels are almost zero [7]. Unfortunately, the addition of 2,3 DPG to stored banked blood is ineffective, because the stored cells will not take up the 2,3 DPG, and plasma esterase enzymes rapidly degrade it. Once a unit of banked blood is infused, the erythrocytes rewarm and begin ATP production as well as repletion of 2,3 DPG. However, by 24 hours after transfusion, the levels are only back to slightly less than half of normal.

The P_{50} of stored blood at 28 days is about 6 to 11 mm Hg [8]. Of interest, the P_{50} of myoglobin, a target for oxygen delivery by the red cell, is 5 mm Hg [8,9]. The oxygen affinity of stored red cells is therefore so high that certainly they give little of their stored oxygen to tissues and may well act as an oxygen sink pulling oxygen away from plasma, normal red cells, and other sources. Within one pass through the lungs, these banked red cells will oxygenate and therefore no longer be an active sink for oxygen. But, the banked blood cells do not unload their oxygen at tissue sites. What we do not know is what small amount of increased oxygen delivery is necessary or critical for tissues in need.

The concept of critical oxygen delivery (DO_{2crit}) is important to the understanding of cellular shock [10,11]. Tissue oxygen delivery is determined by oxygen-carrying capacity (hemoglobin concentration and oxyhemoglobin dissociation curve) and cardiac output. Decreases in cardiac output can lead to cardiogenic shock if the cardiac output falls low enough that DO_{2crit} or supply-independent oxygen delivery to tissues is not met.

If the cardiac output is maintained or allowed to increase in response to dilutional anemia, and if the cardiac preload is maintained, anemia is surprisingly well tolerated. Compensatory mechanisms for progressive euvolemic anemia

include not only an increase in cardiac output (increased left ventricular emptying and tachycardia) but a change in oxygen extraction ration from the erythrocyte itself. The red cell capillary transit time increases, but a little known fact is that in striated muscle (the only place it has been studied), capillary hematocrit is stable. Capillary hematocrit value is 12% to 15% with very little variation [12].

Even if the patient has a normal hematocrit of 40%, the capillary hematocrit level is stable at 12% to 15%. Standard physiology experiments have found that there is a calculated increase in oxygen delivery as euvolemic hemodilution progresses. The increase in cardiac output outstrips the relatively small decrease in oxygen-carrying capacity from a progressive loss of red cell concentration. At approximately 30% to 33% hematocrit level, the highest calculated oxygen delivery can be seen on a graph (Fig. 1) [13]. Such a graph has often been used as justification for the 10 g/dL trigger of transfusion. Basing transfusion therapy on such a graph, however, is fraught with several fallacies and has led to probably an overly liberal use of red cell transfusions. Foremost, is the realization that the microcirculation, where the oxygen is delivered, is carefully regulated to a 12% to 15% hematocrit level, and whatever the hematocrit level is in the larger arteries may be of relatively little importance to the microcirculation except to increase blood pressure and therefore capillary driving pressure. Second, a fallacy of this argument is the widespread belief that banked blood functions as well as native red cells in delivering oxygen.

The concept of flow-independent and flow-dependent critical oxygen delivery is now one of the key concepts for understanding contemporary shock

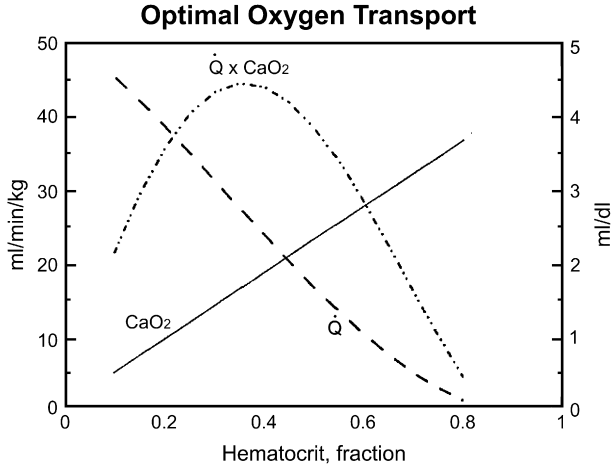

Fig. 1. As euvolemic hemodilution proceeds, cardiac output goes up because of increased left ventricular emptying. This leads to a calculated maximum oxygen delivery at a hematocrit level in the mid 30s. However, this calculated event may not actually take place in the microcirculation. (*From* Winslow RM. Hemoglobin-based red cell substitutes. Baltimore (MD): Johns Hopkins University Press; 1992. © Copyright 1992 Robert M. Winslow, MD; with permission).

research. There is a flow-independent oxygen delivery in which most tissues function at most times. When either cardiac output or hematocrit level decreases sufficiently, then flow-dependent critical oxygen delivery is encountered. To the left of the critical cliff of the curve, tissues develop a progressive oxygen deficit. This is analogous to climbing Mount Everest. The longer one spends above a certain altitude, the killing zone, the more likely it is that tissue damage or death will occur. When tissues switch to flow-dependent oxygen delivery, they switch to anaerobic glycolysis with consequent lactate production and NADPH shifts. Metabolic acidosis can be the end result. The point of shift from flow-independent to flow-dependent oxygen delivery, critical oxygen delivery (DO_{2crit}), is the ultimate definition of shock. Cardiogenic cellular hypoxia is caused by a decrease in cardiac output. Anemic cellular hypoxia is caused by loss of red cells, hemorrhage, or hemodilution. Septic shock leads to high output hypoxia in that capillaries are closed, leading to shunts and lack of oxygen delivery. Hypoxic hypoxia is caused by decreased oxygen-carrying capacity either through cellular poisoning, such as carbon monoxide, or acute respiratory failure. If one simply followed the notion that increasing oxygen-carrying capacity in the face of critical oxygen delivery improves outcome, any one of these situations should and could be helped by transfusion. Perhaps only in severe anemic hypoxia can transfusion make any difference at all.

Stored red cells not only have a decrease in intracellular 2,3 DPG that leads to decreased oxygen release but as they age in storage they undergo a number of other cellular changes. Biochemical, hormonal, inflammatory, and cellular structural changes all occur. Red cells change from being a normal biconcave discoid shape to globular swollen (spherocyte) and spiculated (shistocyte) shapes. Initially, by day 5 to 10 red cells get spicules on the surface of their membranes [14]. These spicules fall off, and the cells become rounded (spherocytes) but also swell and loose their flexibility. They loose approximately 15% to 20% of their cell membrane phospholipids by day 15 to 28 [14]. As the red cells survive in their anoxic environment, they loose their Na-K ATPase function, and the cells become edematous. Cellular flexibility is what allows normal erythrocytes (7-8 μm) to transit capillaries (3-5 μm). With the cell swelling and loss of lipid membrane material, red cells become very stiff and quite friable [14]. They are prone to early destruction, and, if cytokines are present, they are rapidly sequestered and have a shortened circulating half-life.

Red cells clump together in storage [14]. The longer the blood bags are stored, the higher number of red cell clumps are present and the larger the numbers of red cells in each of these clumps [14]. The cells interact through cross linking of fibrinogen with glycoprotein IIb/IIIa binding sites. Up until several years ago, it had not been appreciated that red cells expressed these ligands. A red cell may possess only 50 to 100 of these sites, whereas a platelet expresses, when activated, up to 100,000 such sites.

The combined effects of low P_{50}, dysfunctional cell flexibility, bizarre cellular shapes, and erythrocyte clumping means that banked blood is very poor at

perfusing the capillary microcirculation. Studies examining blood flow to the microcirculation have shown that when stored red cells are used, there is a dramatic reduction of flow. In rat models of hemorrhagic shock, both the mesenteric blood flow and the hippocampal blood flow are reestablished with fresh blood only [15,16]. Using stored rat blood to resuscitate hemorrhagic shock leads to only a 10% restoration of flow. In both of the noted studies, the use of stored blood restores blood pressure beautifully. Fresh blood can cause hyperemic responses in tissues because of increased oxygen delivery, but this is not seen with stored blood transfusion. Rather, the tissues continue in an oxygen-starved environment.

In animal studies of euvolemic hemodilution, it has been shown that the hemoglobin level corresponding to DO_{2crit} is approximately 3 to 3.5 g/dL [10]. It is the same level in humans [11]. Notably that corresponds to the level at which the capillary network auto regulates its red cell flow, 12% hematocrit value. In rat studies of hemorrhagic shock, it has been shown that the level at which critical oxygen delivery is encountered is elevated if stored blood is used [17]. Critical DO_2 goes up to 4 g/dL or greater [17]. That means that after transfusion, shock comes earlier or at a higher hemoglobin level. Remember, the true definition of shock is the point at which DO_{2crit} is reached. Such a revelation, shock comes earlier with transfusion, is exactly opposite of the historical teaching regarding blood transfusion.

From some of the newest microcirculatory work in transfusion it has been shown that banked blood does not increase oxygen delivery to tissues. Indeed, it may be responsible for up to a 400% decrease in tissue oxygen delivery [16]. Importantly, not only are the blood pressures restored with transfusion, both systemic arterial and venous, but blood gases seem to show improvement whether using fresh or stored blood. Venous oxygen saturation decreases with anemic hypoxia [16]. Transfusion of either fresh or stored blood restores mixed venous oxygen saturation. This happens even though tissues may be showing no increased delivery of oxygen to tissues.

It actually makes some sense if one realizes what has already been discussed regarding P_{50} and 2,3 DPG. Stored erythrocytes take up oxygen and do not release it to tissues and therefore contribute to increased mixed venous oxygen levels. If practitioners use mixed venous oxygen saturation as an indicator of tissue anoxia, they may be misled. Using banked blood in transfusion mixed venous saturation rises. A natural satisfaction that a patient is better after transfusion can be the result, but this rise in mixed venous saturation might well be artifact and misleading. Today, mixed venous saturation is a highly regarded invasive measurement that has been thought to follow tissue oxygen demand and delivery. It is only when one follows tissue or systemic lactate that one can find that the tissues have slipped below DO_{2crit}. Clearly, we wish to transfuse to avoid lactate production and slipping below critical oxygen delivery, but the important question is how to know or predict when that may happen. Work in patients after coronary artery bypass surgery grafting (CABG) surgery showed that there was no increase in oxygen delivery to the

microcirculation with one or two units of blood [18]. Only with a change in the fraction of inspired oxygen did tissue oxygenation change. Therefore, the notion that one will increase oxygen delivery to tissues with transfusion has been shown to be not true in a randomized trial with real heart surgery patients. Furthermore, in some critically ill patients, it has been shown that transfusing banked blood actually decreases gut oxygen delivery making the tissues more acidotic [19,20].

Today, we are hampered by not having the right technology to either detect DO_{2crit} or to know how close a tissue or individual patient is to that one physiologic disaster zone. That is one of the key take-home points for this report. We really have no way to know how close any individual patient is to the point of needing more oxygen-carrying capacity, nor do we know exactly how much more oxygen-carrying capacity is required when an individual nears that critical physiologic point.

TRANSFUSION AND OUTCOMES

Transfusion has never undergone extensive prospective, randomized trials. One would think for a 105-year-old therapy, a large data subset of trials in any number of disease states would exist that could tell us when transfusion improved outcome. There are two trials of transfusion in CABG comparing different transfusion triggers [21,22]. The data from these trials show no improved outcome with a more liberal transfusion trigger. They were never analyzed the other way around. That is to say, these studies were never examined carefully to see if patients who had more transfusions did less well, in particular, with respect to infection or immune modulation. That being said, the two trials did not have very large differences between their transfusion triggers, and knowing what we know today it might well be assumed that one would not necessarily find differences in outcomes. There are several other very small randomized trials, but the individual trial sizes were so small they should not even be discussed.

In all of transfusion medicine, there has been only one large randomized trial to date. This is the Transfusion Requirements in Critical Care (TRICC) study by Hébert and colleagues [23]. In the last month, it has been named the single most important report in the history of transfusion. It was published in 1998 and is a cooperative study performed at 25 different Canadian academic institutions. The patient group studied was medical intensive care patients. Some were on ventilators with ARDS, others had gastrointestinal bleeding, some had infections, and more than 33% of them had known significant coronary artery disease. This patient cohort was certainly deemed to be at high risk for both early mortality and either organ or whole-body critical DO_2 being reached. Patients were assigned randomly to receive a red cell transfusion at either the standard 10 g/dL or 7 g/dL trigger for transfusion.

One should pause and think about what an undertaking that particular study was. Allowing a patient with known ARDS on a ventilator or with known coronary artery disease to become that anemic is certainly not standard medical practice. To do that study at 25 different Canadian institutions and to have

the backing of the Canadian government is truly groundbreaking and visionary. That study probably could not have been done and still would not be done in the United States because most hospital ethics committees would think it unsafe.

The findings of the TRICC study found no advantage to transfusion (Table 1) [23]. Overall mortality did show just how ill the group studied had been. The in-house, 30-day mortality rate did show that patients who had transfusions at the lower transfusion trigger had a statistically lower mortality rate. Those patients who were young and who entered the intensive care unit with a relatively low Acute, Physiology, Age, Chronic Health Evaluation (APACHE) score had a lower mortality rate with less transfusion. Nowhere in any subgroup analysis did patients do better with more transfusions. The overall myocardial infarction (MI) rate was low, and the rate was statistically lower in those patients who were allowed to become profoundly anemic and not have a transfusion. The occurrence of ARDS and pulmonary edema were also statistically and striking lower in the group that received less blood. Of interest, there was no overall difference in infection rate in the two transfusion groups. Others have found striking differences in infection rate with perioperative transfusion. The finding here of no difference in infection rate may well be because these were medical patients in whom a large number already had infections before they had transfusions. Those data contrast to the data from elective surgery in which patients generally do not enter the operating rooms infected before a transfusion.

Subgroup analysis by Hébert and colleagues [24] did show that in more than 300 patients with known coronary artery disease there was no advantage in survival to early or more aggressive (10 g/dL) transfusion. The mortality was not different, but those patients who had more transfusions had a higher incidence of multisystem organ failure (MOF). MOF often is the bane of the intensivist's existence as one after another critical organ system dysfunctions and fails. The fact that MOF was more common in the group that received

Table 1
Results from the TRICC study by Hébert and colleagues [23]

Category	Restrictive	Liberal	*P* Value
All patients	18.7	23.3	.10
APACHE II	8.7	16.1	.03
<55 yr	5.7	13.0	.02
Cardiac diagnosis	20.5	22.9	.69
Death in the hospital	22.2	28.1	.05
MI	0.7	2.9	0.02
Pulmonary edema	5.3	10.7	<0.01
Angina	1.2	2.1	0.28
ARDS	7.7	11.4	0.06
Infectious	10.0	11.4	0.38

Nowhere in these data did patients who had more transfusions do better. There were large differences in the rate of MI and in pulmonary dysfunctions.

more transfusions may go along with some of the problems with critical oxygen delivery just discussed. Also in another subgroup analysis the investigator looked at the commonly held belief that transfusion would improve the ability for patients to be weaned from the ventilator [25]. He found exactly the opposite or at least that there were no data to support that transfusion made separation from ventilatory support any easier. Or, it could also be a manifestation of the tremendous inflammatory load a unit of blood represents. Clearly, much more research needs to be done in this area. The need for prospective, randomized trials is overwhelming.

There is a large amount of research examining transfusion and a number of adverse outcomes. Before getting into the specific studies, one should realize the limitations of data-based analysis. These analyses are always retrospective, even if the database is collected in a prospective manner. Often the databases span a number of years with changing practice and practitioners even if only from one hospital. The data from a single practitioner might be looked on as being the "best," but often his or her surgical technique changes over time even if just from practice and maturation. Data-based research at best can find relationships between events. Cause and effect can only truly be proven by large appropriately powered prospective trials. The easiest analysis of a database is to look at a univariate analysis of a single risk factor and an outcome. However, any given risk factor may have a large number of covariates and may also have relationships to the outcome. Therefore, any relationship found by univariate analysis must be vetted with some sort of weighting of the covariate of potential confounding variables. Doing data-based research, one can either perform one of a number of multivariate analyses or a propensity analysis to control for confounders. If, after all of these statistical gymnastics are completed and a particular risk factor, such as red cell transfusion, has a relationship to an outcome, such as perioperative infection, the researcher still cannot claim cause and effect. There could always be one unsuspected and unfound covariate or confounder that was missed and was not entered into the model; therefore, that one confounder could potentially throw off any relationship. Propensity scoring is now thought to be the finest way to look statistically at relationships. It uses univariate testing to find all relationships between the primary investigated risk factor and the outcome. Other potential confounders are also investigated this way, and then multivariate analysis is used to weigh each of the potential confounders. Each patient is then examined independently and given a weighted score based on the number and type of potential confounders he or she possesses. Eventually, like patients, with matched propensity scores, are matched against each other with and without the primary risk (for example, blood transfusion). If after propensity matching the relationship of a primary risk to an outcome still exists, then the evidence is stronger but not conclusive for a cause and effect. It can also be said that the more separate data-based studies published that all find the same relationship, the evidence for cause and effect becomes more compelling. A great deal of what will be discussed next has to do with data-based publications that all

agree; hence, the story is getting more compelling. It still does not prove cause and effect, because we in medicine have simply not done the right prospective, randomized trials.

Red cell transfusion with allogeneic blood is a profoundly inflammatory mixture [25–31]. It contains high levels of a large number of different cytokines, bradykinin, serotonin, and live white cells. Leukoreduced blood has magnitudes (more than 99% reduction), fewer live white cells, and lower cytokine levels, but they do exist. A large body of literature exists showing a relationship between the infusion of red cells in transfusion and early postoperative increased rates of infection [32–40]. Such infections manifest as wound infections, higher pneumonia rates, dehiscence, and, in orthopedic joint replacements, osteomyelitis. It is beyond the scope of this report to examine each one of these studies carefully, and only a small number are noted for the reader. However, Vamvakas, a Canadian transfusionist has published reports from cardiac surgery databases examining the use of red cell transfusions and the risks of perioperative infection [38,39]. He has noted that the increased risk of pneumonia is approximately 5% per unit of non–white cell reduced blood. He has further gone on in other reports to note that the number of units of red cells transfused has the highest relationship to length of stay for a patient in the ICU. Other of his works have shown that transfusion to improve oxygen delivery during weaning from the respirator either does nothing or makes it more difficult to wean. Hébert has a similar publication, and that certainly fits with the only prospective study of transfusion.

In years past, when early renal transplantation was being developed, it was the practice of those performing renal transplants to give every patient a transfusion because they knew of the immunosuppressive effects of blood transfusion [41]. Indeed, those patients who had transfusion at the time of surgery had fewer acute and chronic rejection episodes. It has been estimated that a single unit of packed red blood cells that is not leukoreduced provides the same immunosuppression as a dose of cyclosporine.

Transfusion at, or immediately after, colon resection for colon cancer has been widely investigated [42–45]. There is a relationship between transfusion and early metastasis and also early death. The same has not been shown in other cancers such as prostate cancer, but probably the same mechanisms of immunosuppression that led to more perioperative infection may also lead to the potential implantation or growth of metastatic cell implants. Blumberg [46,47] has spent his career in transfusion medicine studying these immunosuppressive effects and has written widely about how real they are. Yet still some blood bankers debate whether a unit of red cells actually increases infection rates. A prospective, randomized trial clearly is needed.

Engoren [48] is a cardiac surgeon in Toledo, Ohio. His group has published from their database with regard to both long- and short-term death rates in relationship to transfusion. In more than 1900 CABG patients followed up for 60 months, the relationship of transfusion use to death rate was shown. Those patients who had transfusion at or near the time of their operation had at least

twice the death rate as those not having a transfusion, and the Kaplan-Meier survival curves continued to diverge all the way out to 5 years after surgery. Engoren was the first to carefully use propensity scoring, and he found the relationship between death and transfusion to be preserved even if full propensity matching was carried forward. The idea that this is a manifestation of the inflammatory effects of blood transfusion fits the models of what we know is important from the percutaneous cardiology intervention (PCI) literature. When coronary endothelium is made ischemic and then reperfused, it is at high risk for a period to have platelets and white cells adhere. If they do adhere, early growth and accelerated growth of atheroma or clot may result. The cardiologists know that they should now give drugs that either cut inflammation or block the adherence and propagation of platelet nidus. Perhaps the use of transfusions during the perioperative period sensitizes the endothelial cells to future adverse events. Once again, this is a hypothesis in need of prospective testing.

The kidney always operates on the verge of its critic DO_2. No matter what the hematocrit level, there is always an area of the kidney that is at risk for tissue hypoxia. Therefore, one would assume that it, as an organ, could be an early signaler of tissue hypoxia, and if we as doctors allowed the hematocrit level to get too low, then we could expect increased occurrences of renal failure. The group from Duke University examined renal failure in relationship to the lowest hematocrit (Hct) level on bypass [49]. They found a direct relationship between lowest hematocrit level and worsening serum creatinine value after heart surgery. However, when they went back to examine the effects of transfusion, they found transfusion did not improve outcome, it actually made it worse. Habib and colleagues [50], reexamined their database and similarly found that low hematocrit level was an accurate predictor of which patients would experience adverse renal function. But the use of transfusion only made it worse. Therefore, it would seem we as physicians are "damned if we do and damned if we don't."

Two large studies have examined whether patients with impending myocardial infarction may benefit from transfusion [51,52]. These were both data-based studies, and their conclusions could not possibly be any more opposite. The study by Wu and colleagues [51] looked at a federal Medicare/Medicaid database for patients entering the emergency room with chest pain. The database had almost 250,000 patients in it, but most were eliminated from study for one reason or another. In the end, only patients older than 65 years were segmented into different hemoglobin levels. It was found that patients who had a hematocrit level of 33% or below who had a transfusion, had an improved mortality rate if they received a transfusion. The study was accompanied by an editorial claiming that "now we know that the old standard 10 g/dL transfusion trigger was correct."

Unfortunately, the number of patients who fit this low Hgb level was only approximately 3200 of the original 235,000 patients in the database. The group that had shown the effect had twice the number of patients with do not resuscitate (DNR) orders, more diabetics, and fewer aggressive cardiology or cardiac

surgery interventions than the high Hgb groups. One has to wonder if the use of blood products, creating better mortality data, was related to a bias caused by the high number (25%) of DNR patients. No multivariate statistics were done to sort out the effect of confounders. Also, the authors paid no attention to the fact that if a patient had an Hgb of 33% or higher and had a transfusion during their evolving MI, that the mortality levels rose dramatically in relation to the transfusions. The study also has been criticized because only one Hgb level was available for each patient, and no data could relate when the transfusion was performed in relation either to the one Hgb level or the MI itself. Clearly, one should not agree with the editorial saying that at last we know when it is best to transfuse.

A second study in a large database of patients who had evolving MI was published [52]. This was a retrospective analysis of three cardiology trials using new antiplatelet drugs during PCIs. This database study involved more than 24,000 patients, and those patients who had transfusions during the time of PCI had almost a four-fold increase in mortality. They did multivariate analysis and propensity analysis to control for confounders and showed that transfusion was still powerfully related to increased risk for mortality. The question, therefore, remains open and in desperate need of prospective, randomized studies. We as physicians still believe that patients with known coronary artery disease should have transfusions at a higher Hgb trigger than those with normal physiology. It may well be that with the red cell storage lesions that occur in blood banking that transfusing at a higher trigger with atherosclerotic disease may not be the right thing to do.

SUMMARY

After more than 100 years of blood transfusions, today we know painfully little about when it is best to transfuse. What can be said is that HIV and HCV are very rare but constant threats. Variant Creutzfeldt-Jakob disease (vCJD) is capable of being transmitted by transfusion, and there certainly will be a number of emerging viral infections that will probably be found someday in the blood supply. Severe acute respiratory syndrome (SARS) seems to possess all of the characteristics of a virus that should and could be transmitted by transfusion. The effects of other viruses such as cytomegalovirus and Epstein-Barr virus are as yet unexplored but very suspicious. The red cell storage lesions lead to decreased oxygen transport and release by banked blood compared with native red cells. Further, the changes in red cell deformability and formation of microaggregates contribute to blockage of the microcirculation by banked blood. The older the unit of blood, the worse the defects leading to a higher possibility of MOF. These effects combined with some major effects of immunomodulation lead to the end effect that patients who have more transfusions seem to have worse outcomes than those with fewer transfusions. The data-based studies cannot possibly prove cause and effect, but some recent work by epidemiologists suggest that when multivariate analysis shows a two-fold or greater increase in an adverse outcome it is most likely a causal relationship.

Confounders generally have less effect than a two-fold or greater response. The data today are very sobering. A great deal of research is necessary.

For so many years the blood banking industry has focused on controlling risks caused by infectious agents as well as assuring an adequate supply of blood. Perhaps with appropriate pressure and funding, research will begin looking at providing the best quality oxygen delivery, improving red cell function, decreasing immunosuppression, and improving patient outcome in those patients receiving transfusions. At the very least, we owe it to our patients to analytically and prospectively examine who should have transfusions.

References

[1] Goodnough LT, Brecker ME, Kanter MH, et al. Transfusion medicine: blood transfusion. N Engl J Med 1999;340:438–47.
[2] Goodman C, Chan S, Collins P, et al. Ensuring blood safety and availability in the US: technological advances, costs, and challenges to payment—final report. Transfusion 2003;43(Suppl):3S–46S.
[3] Starr D. Blood an epic history of medicine and commerce. New York: Harper Collins Publishers; 2002.
[4] Grady GF, Bennett AJ. Risk of posttransfusion hepatitis in the United States. A prospective cooperative study. JAMA 1972;220:692–701.
[5] Shander A. Emerging risks and outcomes of blood transfusion in surgery. Semin Hematol 2004;41(Suppl):117–24.
[6] Stramer SL, Glynn SA, Kleinman SH, et al. Detection of HIV-1 and HCV infections among antibody-negative blood donors by nucleic acid–amplification testing. N Engl J Med 2004;351:460–8.
[7] Hogman CF, Knutsen F, Loof H. Storage of whole blood before separation: the effect of temperature on red cell 2,3 DPG and the accumulation of lactate. Transfusion 1999;39: 492–7.
[8] Woodson RD. Importance of 2,3 DPG in banked blood: new data in animal models. Prog Clin Biol Res 1982;108:69–78.
[9] Beutler E, Meul A, Wood LA. Depletion and regeneration of 2,3 diphosphoglyceric acid in stored red blood cells. Transfusion 1969;9:109–14.
[10] Torres Filho IP, Spiess BD, Pittman RN, et al. Experimental analysis of critical oxygen delivery. Am J Physiol Heart Circ Physiol 2005;288:H1071–9.
[11] Van Woerkens EC, Trouwborst A, van Lanschot JJ. Profound hemodilution: what is the critical level of hemodilution at which oxygen delivery-dependent oxygen consumption starts in an anesthetized human? Anesth Analg 1992;75:818–21.
[12] Tsai AG, Arfors KE, Intagliett A. Spatial distribution of red cells in individual skeletal muscle capillaries during extreme hemodilution. Int J Microcirc Clin Exp 1991;10:317–34.
[13] Winslow RM. Hemoglobin-based red cell substitutes. Baltimore,MD: Johns Hopkins University Press; 1992.
[14] Hovav T, Yedgar S, Manny N, et al. Alteration of red cell aggregability and shape during blood storage. Transfusion 1999;39:277–81.
[15] Fitzgerald RD, Martin CM, Dietz GE, et al. Transfusion red blood cells stored in citrate phosphate dextrose adenine -1 for 28 days fails to improve tissue oxygenation in rats. Crit Care Med 1997;25:726–32.
[16] Tsai A, Cabrales P, Intaglietta M. Microvascular perfusion upon exchange transfusion with stored red blood cells in normovolemic anemic conditions. Transfusion 2004;44:1626–34.
[17] D'Almeida MS, Gray D, Martin C, et al. Effect of prophylactic transfusion of stored RBC's on oxygen reserve in response to acute isovolemic hemorrhage in a rodent model. Transfusion 2001;41:950–6.

[18] Suttner S, Piper SN, Kumle B, et al. The influence of allogeneic red blood cell transfusion compared with 100% oxygen ventilation on systemic oxygen transport and skeletal muscle oxygen tension after cardiac surgery. Anesth Analg 2004;99:2–11.
[19] Oud L, Kruse JA. Progressive gastric intramucosal acidosis follows resuscitation from hemorrhagic shock. Shock 1996;6:61–5.
[20] Auler Junior JO, Bonetti E, Hueb AC, et al. Effects of massive transfusion on oxygen availability. Sao Paulo Med J 1998;116:1675–80.
[21] Bracey AW, Radovancevic R, Riggs SA, et al. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. Transfusion 1999;39:1070–7.
[22] Johnson RG, Thurer RL, Kruskall MS, et al. Comparison of two transfusion strategies after elective operations for myocardial revascularization. J Thorac Cardiovasc Surg 1992;104:307–14.
[23] Hébert PC, Wells G, Blajchman MA, et al. A multi-center randomized controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409–17.
[24] Hébert P, Yetisir E, Martin C, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular disease? Crit Care Med 2001;29:227–34.
[25] Hébert PC, Blajchman MA, Cook DJ, et al. Do blood transfusions improve outcomes related to mechanical ventilation? Chest 2001;119:1850–7.
[26] Aiboshi J, Moore EE, Ciesla DJ, et al. Blood transfusion and the two-insult model of post-injury multiple organ failure. Shock 2001;15:302–6.
[27] Fransen E, Maessen J, Dentener M, et al. Impact of blood transfusions on inflammatory mediator release in patients undergoing cardiac surgery. Chest 1999;116:1233–9.
[28] Innerhofer P, Tilz G, Fuchs D, et al. Immunologic changes after transfusion of autologous or allogeneic buff coat-poor versus WBC-reduced blood transfusions in patients undergoing arthroplasty. II. Activation of T cells, macrophages, and cell-mediated lympholysis. Transfusion 2000;40:821–7.
[29] Hensler T, Heinemann B, Sauerland S, et al. Immunologic alterations associated with high blood transfusion volume after multiple injury; effects on plasmatic cytokine and cytokine receptor concentrations. Shock 2003;20:497–502.
[30] Lin JS, Tzeng CH, Hao TC, et al. Cytokine release in febrile non-haemolytic red cell transfusion reactions. Vox Sang 2002;82:156–60.
[31] Seghatchian J, Krailadsiri P, Dilger P, et al. Cytokines as quality indicators of leukoreduced red cell concentrates. Transfus Apher Sci 2002;26:43–6.
[32] Fernandez MC, Gottlieb M, Menitove JE. Blood transfusion and postoperative infection in orthopedic patients. Transfusion 1992;32:318–22.
[33] Newman JH, Bowers M, Murphy J. The clinical advantages of autologous transfusion. A randomized, controlled study after knee replacement. J Bone Joint Surg Br 1997;79:630–2.
[34] Vamvakas EC, Moore SB, Cabanela M. Blood transfusion and septic complications after hip replacement surgery. Transfusion 1995;35:150–6.
[35] Vamvakas EC. Transfusion of buffy-coat depleted blood components and risk of postoperative infection in orthopedic patients. Transfusion 2000;40:381.
[36] Vamvakas EC, Carven JH. Allogeneic blood transfusion and postoperative duration of mechanical ventilation; effects of red cell supernatant, platelet supernatant, plasma components, and total transfused fluid. Vox Sang 2002;82:141–9.
[37] Vamvakas EC, Carven JH. Transfusion and postoperative pneumonia in coronary artery bypass surgery; effect of the length of storage of transfused red cells. Transfusion 1999;39:701–10.
[38] Vamvakas EC, Carven JH. RBC transfusion and postoperative length of stay in the hospital or the intensive care unit among patients undergoing coronary artery bypass graft surgery: the effects of confounding factors. Transfusion 2000;40:832–9.
[39] Carson JL, Altman DG, Duff A, et al. Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture. Transfusion 1999;39:694–700.

[40] Blumberg N. Allogeneic transfusion and infection: economic and clinical implications. Semin Hematol 1997;34:34–40.
[41] Higgins RM, Raymond NT, Krishnan NS, et al. Acute rejection after renal transplantation is reduced by approximately 50% by prior therapeutic blood transfusions, even in tracolimus-treated patients. Transplantation 2004;77:469–71.
[42] Houbiers JG, Brand A, van de Watering LM, et al. Randomized controlled trial comparing transfusion of leukocyte-depleted or buff-coat-depleted blood in surgery for colorectal cancer. Lancet 1994;344:573–8.
[43] Busch ORC, Hop WCJ, van Papendrecht MAEH, et al. Blood transfusions and prognosis in colorectal surgery. N Engl J Med 1993;328:1372–6.
[44] Heiss MM, Jaunch KW, Delanoff C, et al. Blood transfusions modulated tumor recurrence—a randomized study of autologous versus homologous blood transfusion in colorectal cancer. J Clin Oncol 1994;12:1859–67.
[45] Mynster T, Nielsen HJ. Danish RANX05 Colorectal Study Group. Storage time of transfused blood and disease recurrence after colorectal cancer surgery. Dis Colon Rectum 2001;44:955–64.
[46] Blumberg N, Kirkley SA, Heal JM. A cost analysis of autologous and allogeneic transfusions in hip-replacement surgery. Am J Surg 1996;171:324–30.
[47] Blumberg N, Heal JM, Cowles JW, et al. Leukoreduced transfusions in cardiac surgery; results of an implementation trial. Am J Clin Pathol 2002;118:376–81.
[48] Engoren MC, Habib RH, Zacharias A, et al. Effect of blood transfusion on long-term survival after cardiac operation. Ann Thorac Surg 2002;74:1180–6.
[49] Swaminathan M, Phillips-Bute BG, Conlon PJ, et al. The association of lowest hematocrit during cardiopulmonary bypass with acute renal injury after coronary artery bypass surgery. Ann Thorac Surg 2003;76:784–91.
[50] Habib RH, Zacharias A, Schwann TA, et al. Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: implications on operative outcome. Crit Care Med 2005;33:1749–56.
[51] Wu WC, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med 2001;342:1230–6.
[52] Rao SV, Jollis JG, Harringtong RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 2004;292:1555–62.