Why an Alternative to Blood Transfusion?

Aryeh Shander, MD[a,b,*], Lawrence Tim Goodnough, MD[c]

KEYWORDS

• Transfusion • Risk • Cost • Outcome
• Allogeneic • Complication

Apart from the Hippocratic Oath, many fail to appreciate the deep marks left by Hippocrates on medicine. For one, he is credited with applying humorism to medicine and putting forth the idea that imbalances among the humors were responsible for human diseases. Being one of the four humors, blood has mesmerized people throughout history. This preoccupation has occasionally surfaced through colorful and horrifying stories of primitive attempts at transferring blood among and between humans and animals. In many accounts, such as the renowned story of the ailing Pope Innocent VIII receiving blood from young boys to rejuvenate, it is hard to discern fact from fiction. Yet, there is no doubt that blood has always been believed to be associated with life and vitality and key to curing numerous ailments.

Old habits die hard. For many physicians, ordering allogeneic blood transfusions is a matter of little hesitation. The belief that blood transfusion is a quick and easy way to boost a patient's condition and accelerate recovery is held by many. Faced with more and more evidence on the lack of safety and efficacy of blood transfusions, however, it is becoming increasingly clear that such beliefs are largely unsubstantiated and tainted with myths. For these reasons, allogeneic transfusions should be minimized. Moreover, there are situations in which blood transfusions are simply not available or acceptable to patients. In even a greater number of cases, although allogeneic blood may be available with little objection from patients, giving transfusions may

---

Aryeh Shander has been or is currently a paid consultant for Biopure, Bayer, Hemo Concepts, NovoNordisk, OrthoBiotech, and ZymoGenetics; has received grants/research support from Abbott, AstraZeneca, OrthoBiotech, and ZymoGenetics; and has received speaking honorariums from Baxter, Bayer, Pfizer, Hemo Concepts, NovoNordisk, OrthoBiotech, and ZymoGenetics. Lawrence Tim Goodnough has been or is a paid consultant for Amgen, OrthoBiotech, American regent, Watson Pharm, and Eli Lilly.

[a] Department of Anesthesiology, Critical Care and Hyperbaric Medicine, Englewood Hospital and Medical Center, 350 Engle Street, Englewood, NJ 07631, USA
[b] Departments of Anesthesiology, Medicine and Surgery, Mount Sinai School of Medicine, NY, USA
[c] Departments of Pathology and Medicine, Stanford University Medical Center, 300 Pasteur Drive, Room H-1402, MC 5626, Stanford, CA 94305, USA
* Corresponding author. Department of Anesthesiology, Critical Care and Hyperbaric Medicine, Englewood Hospital and Medical Center, 350 Engle Street, Englewood, NJ 07631, USA.
E-mail address: aryeh.shander@ehmc.com (A. Shander).

Crit Care Clin 25 (2009) 261–277
doi:10.1016/j.ccc.2008.12.012 **criticalcare.theclinics.com**
0749-0704/08/$ – see front matter

expose them to increased risks and bring about undesired outcomes. Therefore, alternatives to allogeneic blood should be sought. This article looks at the evidence for and against the use of allogeneic transfusions and discusses why alternatives to transfusion are needed.

PHYSIOLOGY OF OXYGEN TRANSPORT, ANEMIA, AND TRANSFUSION

For over a billion years, oxygen was little more than a toxic waste product of photosynthetic reactions. Some two billion years ago, as oxygen levels in the atmosphere began to rise, organisms developed the revolutionary capability to use oxygen as the ultimate electron acceptor. Aerobic metabolism provided a much more efficient way of releasing energy compared with fermentation and paved the way for the evolution of much more complicated, multicellular organisms.[1] As the size of multicellular organisms increased, simple diffusion could not keep up with oxygen demand, and ingenious mechanisms for transporting oxygen were developed. An indicator of the importance of such mechanisms (and their development early on in evolution) is the presence of various related hemoglobin (Hb) molecules in species ranging from plants to humans.[2]

Human Hb in adults consists of two alpha and two beta chains, each harboring an oxygen-binding heme group. Thus, each Hb molecule is capable of binding up to four oxygen molecules, which would amount to 1.39 mL of oxygen binding per gram of Hb at 37°C. The binding of oxygen to Hb is cooperative, and the affinity changes depending on the oxygen saturation status of the tetramer. The result is a sigmoid Hb oxygen dissociation curve with a steep slope in lower oxygen partial pressures (PO_2; range 20–40 mm Hg) usually seen in peripheral tissues, followed by a gradual turn into a plateau as PO_2 approaches the levels present in the alveolus (**Fig. 1**). The affinity for oxygen is further affected by other factors such as pH and

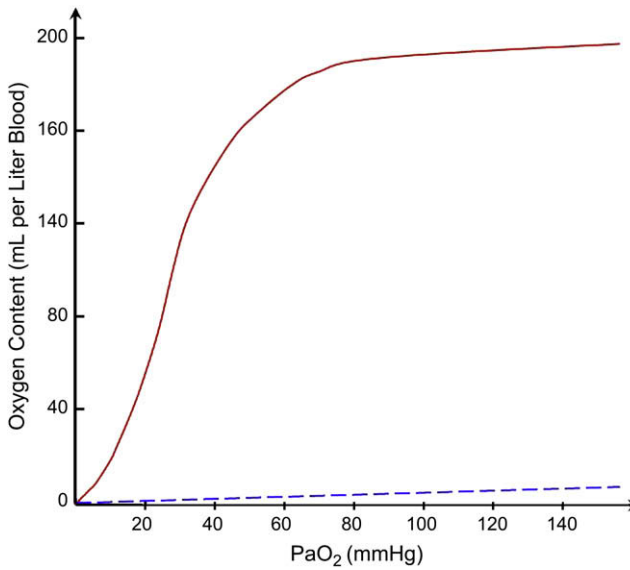

Fig. 1. Oxygen-carrying capacity of blood. The oxygen content in 1000 mL blood with 150 g/L Hb at various PaO_2 levels. Solid and dashed lines represent the Hb-bound and plasma-dissolved oxygen, respectively.

2,3-diphosphoglycerate; this is in contrast to oxygen being dissolved in a fluid (eg, plasma), which is a linear function of PO_2 according to Henry's law (see **Fig. 1**). Oxygen in blood is carried in Hb-bound and in plasma-dissolved forms, and thus the total oxygen content of arterial blood (CaO_2) is calculated as the sum of these two:

$$CaO_2 = \text{Total Hb-bound oxygen} + \text{Total plasma-dissolved oxygen} = ([Hb] \times SaO_2 \times \text{Hb oxygen binding capacity}) + (PaO_2 \times \text{plasma oxygen solubility}) \quad (1)$$

where CaO_2 is the actual oxygen content of arterial blood, *[Hb]* is the concentration of Hb in blood, SaO_2 is the arterial oxygen saturation of Hb, and PaO_2 is the arterial oxygen partial pressure.[3] At 37°C, Hb oxygen binding capacity is 1.39 mL/g and plasma oxygen solubility is 0.0031 mL/(dL·mm Hg).[4]

As evident from **Fig. 1**, within physiologic ranges of PaO_2, the amount of oxygen dissolved in plasma is negligible relative to Hb-bound oxygen and can be ignored. It should be pointed out, however, that under special circumstances (eg, treatment with hyperbaric oxygen or infusion of perfluorocarbons in the context of low Hb), plasma-dissolved oxygen can become a major source for supplying oxygen to the tissues.

Oxygen delivery to tissues (DO_2) is a product of blood oxygen content (calculated from Equation 1) and cardiac output (CO), which can be written in the following simplified equation under physiologic conditions:

$$DO_2 = \{[Hb] \times SaO_2 \times 1.39\} \times CO \quad (2)$$

Based on this equation, DO_2 appears to be directly related to [Hb] and one would deduce that any drop in [Hb] would result in reduced DO_2. Moreover, assuming that Hb is almost entirely saturated with oxygen, the easiest way to increase DO_2 appears to be to increase [Hb]. This notion has been the core physiologic justification behind giving blood transfusions to anemic patients.[5]

Such would be the case if we were considering a closed and static system of tubes and reservoirs. In reality, however, circulation is a dynamic system with far more complexity, and the relationship between [Hb] and DO_2 is anything but a direct linear one. Anemia is associated with physiologic adaptations that substantially diminish the effect of reduced [Hb] on DO_2. Studies in healthy individuals have shown that when isovolemia is maintained, an acute decrease in [Hb] to as low as 4 to 5 g/dL is well tolerated with no sign of tissue hypoxia. In these cases, circulatory response is characterized by decreased systemic vascular resistance, increased heart rate, and increased stroke volume.[6] Other changes observed in this setting include increased preload and decreased afterload due to reduced blood viscosity,[7] and inotropic sympathetic stimulation of heart.[8] All these changes result in increased COut at the level of the macrocirculation that, according to Equation 2, offsets the negative effect of reduced [Hb] on DO_2.

Furthermore, it should be remembered that normally in the microcirculation, where the blood cells pass through vessels with decreasing diameters, the de facto hematocrit becomes substantially lower than the laboratory-measured hematocrit due to more optimal alignment of red blood cells (RBCs) with the flow (the Fahraeus-Lindqvist effect).[9] This microcirculatory hematocrit stays essentially unchanged despite a significant decrease of hematocrit in the macrocirculation. Under physiologic conditions, the oxygen transported and delivered by blood (ie, DO_2) far exceeds the required oxygen actually consumed by the organs (oxygen consumption; $\dot{V}O_2$) by a factor of three to five, resulting in an oxygen extraction ratio of merely 20% to 30%. This large

reserve capacity means that $\dot{V}O_2$ is largely unaffected by a drop in DO_2 (and [Hb]) until a critical low [Hb] is reached.[4,10] In addition, hemodilution is shown to be associated with microcirculatory changes and a shift of the Hb-oxygen dissociation curve to the right, resulting in higher oxygen extraction at peripheral tissues.[11,12] It has been suggested, however, that the response to anemia at the microvascular level is organ specific, and each organ may have a different tolerance to anemia.[13] Although the lowest [Hb] below which $\dot{V}O_2$ is compromised is an elusive value dependent on many factors, for all practical purposes, this critical [Hb] level is lower (significantly, in many cases) than the arbitrary [Hb] of 10 g/dL (hematocrit of 30%) suggested as the transfusion trigger by the outdated "10/30" rule.

On the other hand, other factors may adversely affect tolerance of low [Hb]. While reduced viscosity as a result of anemia is associated with increased COut, data from studies mostly done in animal models indicate that a minimum blood viscosity is required to maintain microvascular perfusion and functional capillary density. To this end, it has been suggested that blood viscosity may be more important than its oxygen-carrying capacity in determining the critical [Hb] and the lowest RBC concentration that can be tolerated.[14] Moreover, many agents used in anesthesia can blunt the adaptive circulatory mechanisms in response to anemia,[15] although it should be pointed out that reduced activity in an anesthetized patient also reduces oxygen demand. Finally, special cases, such as patients who have heart failure and coronary artery disease and elderly patients who may have reduced tolerance to anemia, may require more vigilance.[4,16,17] This notion, however, has not been supported in studies: better ischemic outcomes in elderly patients or patients who had active cardiac disease were not seen in transfused compared with nontransfused patients, even among those who had a nadir hematocrit below 21%.[18–21]

Studies looking into the effectiveness of blood transfusions in augmenting oxygenation parameters have had mixed results. A review of 18 studies indicated that although [Hb] invariably increased following transfusion in all studies, increased DO_2 was observed in 14 studies and increased $\dot{V}O_2$ (the parameter that really matters) was detected in just five studies.[22,23] A plausible explanation might be the lack of a real need for transfusion in most of the patients in these studies, because giving additional blood is not likely to increase a $\dot{V}O_2$ level that is already within the normal range.[22]

Therefore, the question of usefulness and efficacy of blood transfusions ultimately boils down to the issue of the transfusion indications. In anemic/bleeding patients who have been adequately managed to maintain isovolemia and to avoid/treat tachycardia (and in the absence of other probable causes), evidence of organ ischemia (eg, new ST-segment depression >0.1 mV or elevation >0.2 mV, new wall-motion abnormality), inadequate blood oxygen content (eg, mixed venous partial pressure of oxygen <32 mm Hg, mixed venous oxygen saturation <60%), or compromised oxygen consumption (more than 10% decrease in $\dot{V}O_2$, oxygen extraction ratio >40%) may indicate the need for blood transfusion, although definitive data to support the positive outcome of transfusion are not available.[22] A number of criteria based on [Hb] have also been suggested to guide transfusion;[24] however, it is evident from the evidence discussed here that physiologic triggers are more accurate indicators of an individual patient need for blood, as opposed to one-size-fits-all [Hb]-based triggers. It is hoped that further research on tolerance of anemia and indicators of ischemia will provide better indicators to guide transfusion decisions and to identify patients who are most likely to benefit from blood and the far greater number who do not need transfusion and are harmed by it.

RISKS OF TRANSFUSION

Despite being considered a mundane and commonplace practice, allogeneic blood transfusion is essentially a form of organ transplantation. The risks of transfusion have been long recognized, as evidenced by the bans on transfusion in England and France in the seventeenth and eighteenth centuries. Later on, as discovery of blood groups paved the way for successful transfusions, other complications such as transfusion-transmitted jaundice began to surface. Subsequently, donor screening procedures and tests were implemented, greatly improving the safety of blood.

Transfusion risks can be categorized into infectious and noninfectious risks. Noninfectious risks are furthered grouped into immunologic and nonimmunologic risks (**Table 1**).[25] As a result of continuously improved screening and testing, the blood supply today is safer than ever from infectious risks. Nonetheless, the risk is not yet zero (and it is unlikely to be zero any time soon) because many infections have windows during which they are not readily detectable by tests. Moreover, there is always the possibility of new, emerging infections lurking around that will not be tested for until their risk is recognized and adequate testing has been developed for them.[29] Currently,

Table 1
Potential risks of transfusion

Category	Risks
Infectious	Viral infections (hepatitis A, B, C, E, and G; HIV-1 and -2; HTLV-1 and -2; HHV-8; cytomegalovirus; Epstein-Barr virus; parvovirus B19)
	Bacterial (syphilis, tick-borne infections, contamination)
	Prion (Creutzfeldt-Jakob disease, new variant)
	Parasitic (malaria, babesiosis, Chagas' disease)
	Agents not yet discovered or screened for (emerging pathogens)
Noninfectious	
Immunologic	Multiple organ failure/dysfunction syndrome attributed to cytokine release
	Postoperative infection
	Transfusion-associated sepsis
	Increased risk of cancer recurrence
	Down-regulation of macrophage and T-cell function
	HLA alloimmunization
	Transfusion-associated graft-versus-host disease
	Hemolytic transfusion reactions (immunologic)
	Allergic and anaphylactic reactions
Nonimmunologic	Transfusion errors
	Febrile nonhemolytic transfusion reactions
	Posttransfusion purpura
	Hemolytic transfusion reactions (nonimmunologic)
	Risks of old blood (storage lesion, microcirculatory occlusion, lack of effectiveness)
	Circulatory overload
	Iron overload
	Hypotensive reactions
	Metabolic disturbances (citrate toxicity, hypocalcemia, hyperkalemia, acidosis, hyperammonemia)
	Hypothermia

Abbreviations: HHV, human herpesvirus; HTLV, human T-lymphotropic virus.
Data from Refs. [9,25–28]

infective agents for which donated blood is usually tested include hepatitis B (HBV), hepatitis C (HCV), HIV-1 and -2, human T-lymphotropic virus (HTLV)-1 and -2, West Nile virus, *Treponema pallidum* (syphilis), *Trypanosoma cruzi* (Chagas' disease), and cytomegalovirus (CMV).[30] Not every test is performed everywhere and for every unit (eg, *Trypanosoma cruzi* and CMV tests). Other infective threats to blood safety not currently tested for include *Babesia*; *Plasmodium* (malaria); prions (Creutzfeldt-Jakob disease, new variant [nvCJD]); hepatitis A virus; human herpesvirus 8; and chikungunya virus.[25] Various methods of pathogen inactivation (without the need for specific testing) are under investigation and some have been implemented, but their efficacy and effect on the quality of the blood products remain to be determined.[31]

Current estimated risks of infection per RBC unit range from 1 in 100,000 to 1 in 400,000 for HBV; 1 in 1.6 million to 1 in 3.1 million for HCV; 1 in 1.4 million to 1 in 4.7 million for HIV; and 1 in 500,000 to 1 in 3 million for HTLV.[4,26,32–34] The risk of acquiring malaria through allogeneic transfusion is estimated at 1 in 4 million units. There have been seven cases of Chagas' disease and four cases of nvCJD confirmed to be transmitted through transfusions.[35–36] Finally, bacterial contamination is present in 1 in 28,000 to 1 in 143,000 units of RBCs, but it is much more common in platelets (1/2000–1/8000 units).[4,26,32–34] Of note, bacterial infections remain the leading cause of mortality due to transfusion-transmitted infections, accounting for 17% to 22% of all such cases.[37] The most common organisms in RBC units include *Yersinia enterocolitica*, *Pseudomonas spp*., and *Serratia spp*.[37] Other potential hazards include Epstein-Barr virus, leishmaniasis, Lyme disease, brucellosis, and human herpesviruses. Despite a relatively high rate of viremia in blood donors, only a few cases of anemia due to transfusion-transmitted parvovirus B19 have been reported.[38] Hepatitis G virus, SEN virus, and transfusion-transmitted virus are other infective agents commonly found in blood (1–2/100 donations), but their significance is presently unknown.[39] Specific patient populations may be at increased risk, as exemplified by the susceptibility of seronegative immunosuppressed patients to CMV, which mandates the use of leukoreduced blood products from seronegative donors for these patients. It has been suggested that leukocyte reduction may reduce the risk of other transfusion-transmitted infections, including other herpesviruses, bacteria, and protozoa.[40]

Noninfectious risks of transfusion (see **Table 1**) often receive less publicity compared with the infectious risks, but they are far more common and exceed the infectious risks by many factors when the total burden of disease (complications) is considered: the aggregate risk of transmission of major viral threads (ie, HBV, HCV, HIV, and HTLV) by way of transfusion is estimated at approximately 1 in 30,000 units or less. Moreover, not every transmission leads to a full-blown infection, and therefore, the rate of clinically significant infections may be even lower.[38,41] In contrast, a single noninfectious complication—transfusion-related acute lung injury [TRALI]—is estimated to occur in 1 out of every 5000 units of blood transfused, and possibly even more commonly because it is often unrecognized or underreported.[42] Noninfectious risks can be grouped under immunologic and nonimmunologic complications (see **Table 1**). It should be noted that this classification is somewhat arbitrary because many nonimmunologic reactions also have some immunologic components.

Allogeneic transfusion can have suppressive and stimulatory effects on the immune system. It was noticed in the 1960s that blood transfusion could prolong survival of allografts in animal models; in the 1970s, similar results were confirmed in patients receiving cadaver kidney transplantation following multiple allogeneic blood transfusions.[43] Despite the seemingly beneficial effects of transplantation in women who have multiple miscarriages, transfusion-related immunomodulation has been also reported to be associated with an increased rate of cancer recurrence and

postoperative infection in some observational studies; these associations are still being debated. Leukocytes appear to play the major role in transfusion-related immunomodulation.[44,45]

New antigen variants introduced into the body through allogeneic transfusion can stimulate the immune system to produce alloantibodies against blood cells (alloimmunization). RBC alloimmunization is one of the most frequent complications following transfusion and is more common in multiple-transfused patients (eg, patients who have sickle cell anemia).[46] Unlike long-recognized major blood groups, a large number of heterogeneous antigens (eg, various HLA classes) can cause alloimmunization. Transfusion of RBCs with such an antigen to a patient who has preformed alloantibodies against that antigen (eg, due to sensitization in previous transfusions) can result in hemolytic reactions. These so-called ''delayed hemolytic reactions'' occur in aproximately one in 1000 to one in 9000 RBC units transfused, as opposed to acute hemolytic reactions due to transfusion of ABO-incompatible blood, which are less frequent but do not require previous exposure.[22,38,44,45] Allergic transfusion complications range form mild reactions such as urticaria (occurring in 8% of transfusions) to severe deadly anaphylactic shock in immunoglobulin A–deficient patients.[47]

Transfusion-associated graft-versus-host disease (TA-GVHD) is another rare immunologic complication of transfusion in which immunocompetent, HLA-incompatible donor lymphocytes are transfused to a recipient who is immunologically incapable of eliminating them, and these cells elicit an immune response against host cells. Patients at risk of TA-GVHD include those who have cell-mediated immunodeficiencies, recipients of bone marrow transplants, and patients receiving immunosuppressive therapy. Use of irradiated blood components can eliminate the risk of TA-GVHD and should be considered in susceptible patients.[48] The condition is rare, is difficult to treat, and has a 90% mortality.[38]

Among the nonimmunologic transfusion risks, transfusion errors are estimated to occur in one in 12,000 units transfused.[49] The most obvious error is transfusion of ABO-incompatible blood, which can result in an immediate hemolytic reaction, and it remains a leading cause of fatal transfusion reactions. Other transfusion errors include erroneous transfusion of units that have tested positive for an infection and the issuance of blood for patients for whom autologous blood is available.[49]

TRALI is characterized by acute-onset respiratory distress, bilateral pulmonary edema, fever, tachycardia, and hypotension in the presence of normal cardiac function occurring within 6 hours following transfusion. TRALI can be confused with other transfusion-related or unrelated disorders and is believed to be frequently misdiagnosed and underreported.[42] Its etiology is multifactorial and likely to be related to the reaction of antibodies present in donor blood with antigens of recipient's neutrophils, leading to increased permeability of the pulmonary vessels.[44] Despite a clinical presentation similar to acute respiratory distress syndrome (ARDS), TRALI is usually transient and its mortality rate is lower at approximately 5% to 10%.[42] Transfusion-associated circulatory overload (TACO) is another complication of transfusion and presents with pulmonary edema and respiratory distress. Unlike TRALI, which is associated with increased vascular permeability, pulmonary edema in TACO is caused by increased central venous pressure and pulmonary blood volume resulting in fluid extravasation into alveolar space. TACO is estimated to occur in 1 in 3000 to as many as one in 10 transfusions depending on the patient population and definition. Distinguishing TRALI from TACO can pose a challenge; often, varying degrees of both are present together.[50]

Febrile nonhemolytic transfusion reaction is the most common cause of transfusion-associated fever, occurring in 0.1% to 1% of RBC transfusions.[38] Leukoreduction can

decrease the incidence of this complication.[51] Other causes of transfusion-associated fever (eg, hemolytic reactions, bacterial contamination, TRALI) are more serious and should be considered in febrile patients.

After removal from the body and with the added effect of storage, RBCs undergo changes (many irreversible) that adversely affect their viability and function. These adverse changes include oxidation and rearrangement of lipids, loss of proteins, and depletion of ATP and 2,3-diphosphoglycerate. In storage, RBCs continuously lose their membrane through shedding vesicles and become rigid.[52,53] Moreover, during storage, bioactive by-products and ions (eg, Hb, lipids, and potassium)—some with proinflammatory effects—are released from RBCs and accumulate in blood units whereby they can cause adverse reactions in a recipient.[54] These changes are collectively called "storage lesion."[52–54] Transfusion of blood that is stored for prolonged periods (but still within the currently accepted maximum allowed storage time of 42 days) has been linked to increased risk of complications and reduced survival in patients undergoing cardiac surgery and in other patient populations.[52–55] Some studies suggest that leukodepletion may improve the quality of stored blood products and help reduce adverse outcomes.[54]

When discussing the risks of transfusion, attention is paid primarily to the recipients of blood. It should be noted, however, that blood donation is not free of risk, and donors may experience adverse reactions and complications related to donating blood. Complications include presyncopeal symptoms, loss of consciousness, hematomas, chest pain, and allergic reactions. The incidence of donation-related complications is higher in younger donors, first-time donors, and women.[56]

Worsening of outcomes in transfused patients is a theme repeatedly observed in studies comparing transfused with nontransfused patients in various settings and populations, including critically ill patients, elderly patients, cardiac surgery cases, trauma patients, orthopedic surgical cases, and patients who have acute coronary syndrome. In these studies, patients receiving allogeneic transfusions have had higher mortality rates, higher risk of ICU admission, longer hospital and ICU stays, higher postoperative infection rates, higher risk of developing ARDS, longer time to ambulation, higher incidence of atrial fibrillation, and higher risk of ischemic outcomes compared with nontransfused cohorts (**Table 2**).[18,19,21,57–79] One caveat of most of these studies is the uncontrolled methodology and observational nature of the study. Designing a randomized controlled trial with a no-transfusion arm poses many ethical and recruitment challenges. Using the data from patients refusing allogeneic transfusions as the control arm is an option, but those participating cannot be randomized and other approaches for matching are needed. Nonetheless, randomized controlled trials comparing restrictive with liberal transfusion strategies in critically ill patients have shown that in most of the patients, outcomes of restrictively transfused patients are at least similar to their liberally transfused counterparts, if not better.[80,81]

When considering the generally unfavorable outcomes associated with allogeneic transfusion in the studies, it should be remembered that every patient has a unique oxygen delivery and consumption status and that tolerance for anemia differs among different cases. In other words, each study may include patients who have varying levels of Hb (although as discussed earlier, mere Hb level is not an accurate indicator of oxygen delivery and consumption), and some of these patients may indeed benefit from transfusion. For example, it has been reported that blood transfusion can lower the short-term mortality rate in elderly patients who have myocardial infarction and who have a hematocrit of 33 or less on admission.[71] Although several limitations (eg, retrospective nature, potential baseline differences between the groups, and consideration of admission hematocrit as opposed to more relevant nadir hematocrit

Table 2
Outcomes of transfusion

Setting/Population	Outcomes Associated with Transfusion	Study
Cardiac surgery	Increased mortality rate; longer ICU stay	Leal-Noval et al, 2001[57]
	Higher incidence of bacterial infection	Chelemer et al, 2002[58]
	Increased 5-year mortality rate; higher incidence of serious postoperative infections	Engoren et al, 2002[59]
	Higher risk of developing AF	Koch et al, 2006[60]
	Increased mortality rate; higher risk of renal failure, prolonged respiratory support, serious infection, cardiac complications, and neurologic events	Koch et al, 2006[61]
	Reduced long-term survival	Koch et al, 2006[62]
	Delayed discharge from hospital; higher risk of death within 30 d; higher risk of infection; higher risk of ischemia	Murphy et al, 2007[18]
Colorectal surgery	Higher risk of postoperative infection and intra-abdominal sepsis	Chang et al, 2000[63]
ICU/critically ill patients	Increased overall and ICU 14-d mortality rate; higher 28-d mortality rate	Vincent et al, 2002[64]
	Increased mortality rate; longer length of stay; more total number of complications	Corwin et al, 2004[65]
	Increased mortality rate; higher risk of developing ARDS	Gong et al, 2005[66]
	Higher incidence of bloodstream infections	Shorr et al, 2005[67]
	Higher risk of nosocomial infection	Taylor et al, 2006[68]
	Higher risk of developing ARDS	Zilberberg et al, 2007[69]
	Increased hospital mortality rate; prolonged hospital stay	Zilberberg et al, 2008[70]
Myocardial infarction/ischemia	Increased 30-d mortality rate if hematocrit on admission was >36%	Wu et al, 2001[71]
	Increased 30-d mortality	Rao et al, 2004[19]
	Increased risk of in-hospital mortality	Jani et al, 2007[21]
Orthopedics	Higher risk of bacterial infection; higher risk of pneumonia	Carson et al, 1999[72]
	Higher risk of infection	Innerhofer et al, 2005[73]
	Longer time to ambulation; longer length of stay	Weber et al, 2005[74]
Subarachnoid hemorrhage	Higher risk of vasospasm and poor outcome	Smith et al, 2004[75]
Trauma	Higher risk of developing infection	Claridge et al, 2002[76]
	Increased mortality rate; higher risk of ICU admission; longer ICU and hospital length of stay	Malone et al, 2003[77]
	Increased mortality rate; higher risk of ICU admission; higher incidence of SIRS	Dunne et al, 2004[78]
	Increased mortality rate; higher risk of developing ARDS	Silverboard et al, 2005[79]

Abbreviations: AF, atrial fibrillation; SIRS, systemic inflammatory response syndrome.

levels)[82] negatively affect the reliability of the observations of this study,[71] the results point to the fact that every transfusion decision is, in essence, a risk/benefit analysis. Allogeneic blood transfusions are associated with many risks, but in specific (and limited) circumstances, their benefits outweigh the risks. Under most circumstances, the benefit-to-risk ratio of allogeneic blood transfusions is not favorable, and such transfusions should be avoided or replaced by alternatives.

COSTS OF TRANSFUSION

The price tag of a unit of allogeneic RBCs represents a gross understatement of the true cost of blood. What most health care providers see as the act of transfusion (ie, ordering blood and infusing it) is just the tip of the iceberg of the numerous procedures required to procure, process, store, and distribute blood. In addition, dealing with side effects and the direct and indirect consequences of transfusion is an added cost that is usually ignored. An example is the compensation paid to the recipients of HIV-contaminated transfusions totaling billions of dollars in many countries.[83]

A number of studies have tried to estimate the true cost of blood by accounting for often-forgotten steps involved.[84] The results vary depending on the methodology of the studies, the extent and depth of the steps covered, and the perspective of the investigators, and range from $326 to $850 per unit of RBCs (adjusted for 2007 value).[85–86] It should be remembered that these figures reflect the cost of regular blood units at the time the studies were performed (ie, in the 1990s), and additional processing (eg, irradiation, deglycerolization) is associated with added costs. Another additional process, leukoreduction, has become a universal practice in many countries and its costs have not been incorporated in these figures. Finally, today's added safety of the blood supply from infectious risks has been achieved at the expense of more laborious and complicated screening and testing procedures. Although it may appear at first glance that these added costs are worth the reduced risk, it is enlightening to point out that each quality-adjusted life year (QALY) saved by adding more sensitive HIV nucleic acid testing to the serologic screening on donated blood comes at an estimated cost of over $1.5 million.[87] At the individual patient level, we may be willing to pay extra to feel safer against HIV; however, nucleic acid testing falls considerably short of the generally accepted cost-effectiveness bar set at $50,000 to $80,000 per QALY for health care interventions.[84] It is no wonder that this has been called the "price of fear."[88]

Comprehensive efforts to capture the true cost of blood are underway. The first Cost-of-Blood Consensus Conference (COBCON I) was convened by the Society for the Advancement of Blood Management (www.SABM.org) in 2003 to develop an all-inclusive model.[83] The result was a nine-step process flow model encompassing cost elements associated with blood collection (ie, donor recruitment and qualification, blood collection, blood processing and laboratory testing, blood disposal and donor notification [in case of positive test results], and blood storage and transport) and transfusion services (ie, blood service inventory and storage, pretransfusion preparation, transfusion administration and follow-up, and tracking of long-term outcomes). Societal cost elements (eg, donors' and recipients' loss of productivity) were also included. In total, over 250 cost-incurring steps were identified in the transfusion process. It was concluded that the true cost of blood was far greater than what was charged by the blood collection agencies in the United States.[83]

A newer model based on activity-based costing has been developed and efforts are underway to outline the transfusion process by breaking it into individual activities (COBCON II).[83] Preliminary results based on only a few steps of the process already

indicate an estimated cost of over $1400 per transfused unit.[84] Although the final estimated cost is expected to be significantly higher, even the current incomplete figure is twice as much as the highest previous estimate of the cost of blood. Considering the 14 million blood units transfused annually in the United States,[89] the difference amounts to $10 billion.

The true annual burden of transfusion on health care expenditure is expected to be tens of billion dollars. When all the cost elements involved in transfusion are accounted for, a more accurate picture will become available; however, even the currently available limited data are more than sufficient to provide us with an idea of the magnitude of the costs involved. Appreciation of the true cost of blood transfusions will undoubtedly promote justified used of transfusion and its alternatives.[84]

WHEN BLOOD IS NOT AN OPTION

In addition to blood units being costly, they are difficult to procure, prepare, transport, and store. Blood supply in the Unite States and many developed nations is based on voluntary donations as recommended by 28th World Health Assembly over 3 decades ago.[90] An aging population and more restrictive screening criteria has resulted in a shrinking pool of donors and has limited the supply. Currently, it is estimated that 111 million individuals in the United States are eligible to donate blood.[91] The number of actual donors, however, is significantly smaller. A survey of blood supply and demand in the United States indicated that although blood donation increased by 10.4% from 1999 to 2001, transfusion increased by 12.2%, reducing the margin between transfusion demand and supply from 9.1% to 7.9% of the total supply. It should be noted that the year 2001 witnessed a dramatic increase in donations following the September 11 terrorist attacks, and this margin is likely to be much narrower today.[92] If the current trend of increasing demand and diminishing supply continues (which is the likely scenario, as indicated by the reluctance of the ''new generation'' to donate blood),[93] the result will be an imminent shortage of blood components at the national level.

Given the complicated nature of processing, transportation, and storage of blood, local shortages are far more likely to happen. The delicate chain of supply can easily be disrupted and overwhelmed by disasters, conflicts, and mass casualty events.[94,95] Due to the increased stress and workload during such events, the probability of transfusion errors is also likely to increase.[94] More commonly, as can be seen in everyday accidents and incidences in remote areas, blood might simply not be available at the field for trauma victims. The same logistic limitations are present in combat zones. Transfusion of unscreened fresh whole blood is a controversial practice recognized by the United States military for patients who have life-threatening traumatic injuries and can expose recipients to increased risk of infection.[96]

Unlike developed countries, in many regions of the world, providing access to a safe blood supply remains a major challenge.[97–98] Many developing nations still rely largely on remunerated repeat donors who often carry a higher risk of infections.[99] Due to limited resources, donated blood cannot be and is not tested as rigorously as in developed countries: from 2001 to 2002, 6 million required tests for the markers of the four main transfusion-transmitted infections (HIV, HBV, HCV, and syphilis) were not performed on donated blood units.[100] The result is a staggering high incidence of transfusion-transmitted infections in less developed nations (eg, 5%–15% of total new HIV infections are transmitted through transfusions).[99]

In addition to logistic constraints affecting the availability of safe blood, there are certain situations in which allogeneic transfusions are not acceptable despite

availability. Some patients refuse allogeneic blood products due to religious reasons.[101] Blood transfusion is not an option in some cases of autoimmune hemolytic anemia because the transfused RBCs are targeted and lysed by the immune system. In these cases and in circumstances of unavailability of blood, the use of alternatives to transfusion is often the only option to save the lives of severely anemic patients.

SUMMARY

Chronic anemia is an independent predictor of mortality and morbidity, and it should be screened for, properly diagnosed, and treated.[102] Several adaptive mechanisms are activated in response to anemia to maintain oxygen delivery to the tissues. As a result, significant drops in Hb level can be well tolerated in most patients. In fact, in most cases, anemia is much better tolerated by patients than by their attending physicians who rush to order blood at first drop of Hb. As [Hb] decreases below a critical level, tissue oxygen consumption is compromised and signs of ischemia may appear. At this point, aggressive treatments to improve the oxygen-delivery capacity of blood are required.

Allogeneic blood transfusions are associated with a long list of infectious and noninfectious risks. A multitude of studies have demonstrated worse outcomes in patients who have been transfused, and randomized trials indicate that outcomes in restrictively transfused patients are similar to or better than outcomes in liberally transfused cases. Blood is costly and it cannot be made available or used in many situations. Recommended global strategies include restricting allogeneic blood transfusions and limiting their use to specific patients who are expected to benefit from transfusion based on objective criteria.

Alternatives to transfusion that can perform the oxygen-carrying function of blood without all the risks associated with transfusion are promising options, and they can be life-saving agents in many patients for whom blood is not available or not an option. Safer and more effective alternatives to blood are warranted to replace allogeneic blood altogether in the (limited) indications of transfusion. Elimination of infectious risks, immunologic interactions, compatibility issues, and specific storage requirements are just some of the incentives of developing such modalities. This is an exciting field with enormous potential to save millions of lives and change the face of transfusion medicine forever. Soon, blood will return to its place next to the three other humors in the books of history and we will begin using real therapeutic agents with defined safety and efficacy profiles specifically developed for transporting oxygen to tissues.

ACKNOWLEDGMENTS

The authors thank Mazyar Javidroozi, MD, for his contribution to the editing of this manuscript. He declares no conflict of interests.

REFERENCES

1. Alberts B, Johnson A, Lewis J, et al. Molecular biology of the cell. 4th edition. New York: Garland Science; 2002. p. 3–45.
2. Hardison RC. A brief history of hemoglobins: plant, animal, protist, and bacteria. Proc Natl Acad Sci U S A 1996;93(12):5675–9.
3. Shander A. Anemia in the critically ill. Crit Care Clin 2004;20(2):159–78.

4. Madjdpour C, Spahn DR, Weiskopf RB. Anemia and perioperative red blood cell transfusion: a matter of tolerance. Crit Care Med 2006;34(Suppl 5): S102–8.
5. Marshall JC. Transfusion trigger: when to transfuse? Crit Care 2004;8(Suppl 2): S31–3.
6. Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA 1998;279(3):217–21.
7. Fowler NO, Holmes JC. Blood viscosity and cardiac output in acute experimental anemia. J Appl Physiol 1975;39(3):453–6.
8. Habler OP, Kleen MS, Podtschaske AH, et al. The effect of acute normovolemic hemodilution (ANH) on myocardial contractility in anesthetized dogs. Anesth Analg 1996;83(3):451–8.
9. Barbee JH, Cokelet GR. The Fahraeus effect. Microvasc Res 1971;3(1):6–16.
10. Chapler CK, Cain SM. The physiologic reserve in oxygen carrying capacity: studies in experimental hemodilution. Can J Physiol Pharmacol 1986;64(1):7–12.
11. Morisaki H, Sibbald WJ. Tissue oxygen delivery and the microcirculation. Crit Care Clin 2004;20(2):213–23.
12. Hebert PC, Van der Linden P, Biro G, et al. Physiologic aspects of anemia. Crit Care Clin 2004;20(2):187–212.
13. van Bommel J, Siegemund M, Henny ChP, et al. Heart, kidney, and intestine have different tolerances for anemia. Transl Res 2008;151(2):110–7.
14. Cabrales P, Tsai AG, Intaglietta M. Is resuscitation from hemorrhagic shock limited by blood oxygen-carrying capacity or blood viscosity? Shock 2007; 27(4):380–9.
15. Ickx BE, Rigolet M, Van Der Linden PJ. Cardiovascular and metabolic response to acute normovolemic anemia. Effects of anesthesia. Anesthesiology 2000; 93(4):1011–6.
16. Spahn DR, Seifert B, Pasch T, et al. Haemodilution tolerance in patients with mitral regurgitation. Anaesthesia 1998;53(1):20–4.
17. Roseberg B, Wulff K. Hemodynamics following normovolemic hemodilution in elderly patients. Acta Anaesthesiol Scand 1981;25(5):402–6.
18. Murphy GJ, Reeves BC, Rogers CA, et al. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 2007;116(22):2544–52.
19. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 2004; 292(13):1555–62.
20. Gerber DR. Transfusion of packed red blood cells in patients with ischemic heart disease. Crit Care Med 2008;36(4):1068–74.
21. Jani SM, Smith DE, Share D, et al. Blood transfusion and in-hospital outcomes in anemic patients with myocardial infarction undergoing percutaneous coronary intervention. Clin Cardiol 2007;30(10 Suppl 2):II49–56.
22. Madjdpour C, Heindl V, Spahn DR. Risks, benefits, alternatives and indications of allogenic blood transfusions. Minerva Anestesiol 2006;72(5):283–98.
23. Hébert PC, McDonald BJ, Tinmouth A. Clinical consequences of anemia and red cell transfusion in the critically ill. Crit Care Clin 2004;20(2):225–35.
24. Goodnough LT. Transfusion triggers. Surgery 2007;142(Suppl 4):S67–70.
25. Shander A, Goodnough LT. Update on transfusion medicine. Pharmacotherapy 2007;27(9 Pt 2):57S–68S.
26. Dodd RY. Current risk for transfusion transmitted infections. Curr Opin Hematol 2007;14(6):671–6.

27. Becker JL. Vector-borne illnesses and the safety of the blood supply. Curr Hematol Rep 2003;2(6):511–7.
28. Arguin PM, Singleton J, Rotz LD, et al. An investigation into the possibility of transmission of tick-borne pathogens via blood transfusion. Transfusion-Associated Tick-Borne Illness Task Force. Transfusion 1999;39(8):828–33.
29. Shander A. Emerging risks and outcomes of blood transfusion in surgery. Semin Hematol 2004;41(1 Suppl 1):117–24.
30. Klein HG. Pathogen inactivation technology: cleansing the blood supply. J Intern Med 2005;257(3):224–37.
31. Webert KE, Cserti CM, Hannon J, et al. Proceedings of a Consensus Conference: pathogen inactivation-making decisions about new technologies. Transfus Med Rev 2008;22(1):1–34.
32. Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. JAMA 2003;289(8):959–62.
33. Klein HG, Spahn DR, Carson JL. Red blood cell transfusion in clinical practice. Lancet 20074;370(9585):415–426.
34. Brown P. Creutzfeldt-Jakob disease: reflections on the risk from blood product therapy. Haemophilia 2007;13(Suppl 5):33–40.
35. Goodnough LT, Brecher ME, Kanter MH, et al. Transfusion medicine. First of two parts–blood transfusion. N Engl J Med 1999;340(6):438–47.
36. Editorial team. Fourth case of transfusion-associated vCJD infection in the United Kingdom. Euro Surveill 200718;12(1):E070118.4
37. Wagner SJ. Transfusion-transmitted bacterial infection: risks, sources and interventions. Vox Sang 2004;86(3):157–63.
38. Kleinman S, Chan P, Robillard P. Risks associated with transfusion of cellular blood components in Canada. Transfus Med Rev 2003;17(2):120–62.
39. Canadian Paediatric Society. Transfusion and risk of infection in Canada: Update 2006. Can J Infect Dis Med Microbiol 2006;17(2):103–7.
40. Cervia JS, Wenz B, Ortolano GA. Leukocyte reduction's role in the attenuation of infection risks among transfusion recipients. Clin Infect Dis 2007;45(8):1008–13.
41. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. N Engl J Med 1996;334(26):1685–90.
42. Shander A, Popovsky MA. Understanding the consequences of transfusion-related acute lung injury. Chest 2005;128(5 Suppl 2):598S–604S.
43. Waanders MM, Roelen DL, Brand A, et al. The putative mechanism of the immunomodulating effect of HLA-DR shared allogeneic blood transfusions on the alloimmune response. Transfus Med Rev 2005;19(4):281–7.
44. Goodnough LT. Risks of blood transfusion. Anesthesiol Clin North America 2005; 23(2):241–52, v.
45. Goodnough LT. Risks of blood transfusion. Crit Care Med 2003;31(12 Suppl): S678–86.
46. Bauer MP, Wiersum-Osselton J, Schipperus M, et al. Clinical predictors of alloimmunization after red blood cell transfusion. Transfusion 2007;47(11):2066–71.
47. Klein HG, Spahn DR, Carson JL. Red blood cell transfusion in clinical practice. Lancet 2007;370(9585):415–26.
48. Anderson K. Broadening the spectrum of patient groups at risk for transfusion-associated GVHD: implications for universal irradiation of cellular blood components. Transfusion 2003;43(12):1652–4.
49. Linden JV, Paul B, Dressler KP. A report of 104 transfusion errors in New York State. Transfusion 1992;32(7):601–6.

50. Skeate RC, Eastlund T. Distinguishing between transfusion related acute lung injury and transfusion associated circulatory overload. Curr Opin Hematol 2007;14(6):682–7.
51. King KE, Shirey RS, Thoman SK, et al. Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs. Transfusion 2004;44(1):25–9.
52. Tinmouth A, Fergusson D, Yee IC, et al. ABLE Investigators; Canadian Critical Care Trials Group. Clinical consequences of red cell storage in the critically ill. Transfusion 2006;46(11):2014–27.
53. Kriebardis AG, Antonelou MH, Stamoulis KE, et al. Storage-dependent remodeling of the red blood cell membrane is associated with increased immunoglobulin G binding, lipid raft rearrangement, and caspase activation. Transfusion 2007; 47(7):1212–20.
54. Ho J, Sibbald WJ, Chin-Yee IH. Effects of storage on efficacy of red cell transfusion: when is it not safe? Crit Care Med 2003;31(12 Suppl):S687–97.
55. Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 2008;358(12):1229–39.
56. Eder AF, Hillyer CD, Dy BA, et al. Adverse reactions to allogeneic whole blood donation by 16- and 17-year-olds. JAMA 2008;299(19):2279–86.
57. Leal-Noval SR, Rincón-Ferrari MD, García-Curiel A, et al. Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. Chest 2001;119(5):1461–8.
58. Chelemer SB, Prato BS, Cox PM Jr, et al. Association of bacterial infection and red blood cell transfusion after coronary artery bypass surgery. Ann Thorac Surg 2002;73(1):138–42.
59. Engoren MC, Habib RH, Zacharias A, et al. Effect of blood transfusion on long-term survival after cardiac operation. Ann Thorac Surg 2002;74(4):1180–6.
60. Koch CG, Li L, Van Wagoner DR, et al. Red cell transfusion is associated with an increased risk for postoperative atrial fibrillation. Ann Thorac Surg 2006;82(5): 1747–56.
61. Koch CG, Li L, Duncan AI, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 2006;34(6):1608–16.
62. Koch CG, Li L, Duncan AI, et al. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. Ann Thorac Surg 2006;81(5):1650–7.
63. Chang H, Hall GA, Geerts WH, et al. Allogeneic red blood cell transfusion is an independent risk factor for the development of postoperative bacterial infection. Vox Sang 2000;78(1):13–8.
64. Vincent JL, Baron JF, Reinhart K, et al. ABC (Anemia and Blood Transfusion in Critical Care) Investigators. Anemia and blood transfusion in critically ill patients. JAMA 2002;288(12):1499–507.
65. Corwin HL, Gettinger A, Pearl RG, et al. The CRIT Study: Anemia and blood transfusion in the critically ill–current clinical practice in the United States. Crit Care Med 2004;32(1):39–52.
66. Gong MN, Thompson BT, Williams P, et al. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. Crit Care Med 2005;33(6):1191–8.
67. Shorr AF, Jackson WL, Kelly KM, et al. Transfusion practice and blood stream infections in critically ill patients. Chest 2005;127(5):1722–8.
68. Taylor RW, O'Brien J, Trottier SJ, et al. Red blood cell transfusions and nosocomial infections in critically ill patients. Crit Care Med 2006;34(9):2302–8.

69. Zilberberg MD, Carter C, Lefebvre P, et al. Red blood cell transfusions and the risk of acute respiratory distress syndrome among the critically ill: a cohort study. Crit Care 2007;11(3):R63.
70. Zilberberg MD, Stern LS, Wiederkehr DP, et al. Anemia, transfusions and hospital outcomes among critically ill patients on prolonged acute mechanical ventilation: a retrospective cohort study. Crit Care 2008;12(2):R60.
71. Wu WC, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med 2001;345(17):1230–6.
72. Carson JL, Altman DG, Duff A, et al. Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture repair. Transfusion 1999;39(7):694–700.
73. nnerhofer P, Klingler A, Klimmer C, et al. Risk for postoperative infection after transfusion of white blood cell-filtered allogeneic or autologous blood components in orthopedic patients undergoing primary arthroplasty. Transfusion 2005;45(1):103–10.
74. Weber EW, Slappendel R, Prins MH, et al. Perioperative blood transfusions and delayed wound healing after hip replacement surgery: effects on duration of hospitalization. Anesth Analg 2005;100(5):1416–21.
75. Smith MJ, Le Roux PD, Elliott JP, et al. Blood transfusion and increased risk for vasospasm and poor outcome after subarachnoid hemorrhage. J Neurosurg 2004;101(1):1–7.
76. Claridge JA, Sawyer RG, Schulman AM, et al. Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. Am Surg 2002;68(7): 566–72.
77. Malone DL, Dunne J, Tracy JK, et al. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. J Trauma 2003;54(5): 898–905, discussion 905–7.
78. Dunne JR, Malone DL, Tracy JK, et al. Allogenic blood transfusion in the first 24 hours after trauma is associated with increased systemic inflammatory response syndrome (SIRS) and death. Surg Infect (Larchmt) 2004;5(4):395–404.
79. Silverboard H, Aisiku I, Martin GS, et al. The role of acute blood transfusion in the development of acute respiratory distress syndrome in patients with severe trauma. J Trauma 2005;59(3):717–23.
80. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340(6):409–17.
81. Lacroix J, Hébert PC, Hutchison JS, et al. TRIPICU Investigators; Canadian Critical Care Trials Group; Pediatric Acute Lung Injury and Sepsis Investigators Network. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med 2007;356(16):1609–19.
82. Goodnough LT, Bach RG. Anemia, transfusion, and mortality. N Engl J Med 2001;345(17):1272–4.
83. Participant of the Cost of Blood Consensus Conference, Charleston, SC, May 4–5, 2003. The cost of blood: multidisciplinary consensus conference for a standard methodology. Transfus Med Rev 2005;19(1):66–78.
84. Shander A, Hofmann A, Gombotz H, et al. Estimating the cost of blood: past, present, and future directions. Best Pract Res Clin Anaesthesiol 2007;21(2): 271–89.
85. Etchason J, Petz L, Keeler E, et al. The cost effectiveness of preoperative autologous blood donations. N Engl J Med 1995;332(11):719–24.

86. Crémieux PY, Barrett B, Anderson K, et al. Cost of outpatient blood transfusion in cancer patients. J Clin Oncol 2000;18(14):2755–61.
87. Marshall DA, Kleinman SH, Wong JB, et al. Cost-effectiveness of nucleic acid test screening of volunteer blood donations for hepatitis B, hepatitis C and human immunodeficiency virus in the United States. Vox Sang 2004;86(1): 28–40.
88. Shander A. Financial and clinical outcomes associated with surgical bleeding complications. Surgery 2007;142(4 Suppl):S20–5.
89. Whitaker BI, Sullivan M, Henry R, United States Department of Health and Human Services. The 2005 Nationwide Blood Collection and Utilization Survey Report. 2005 [cited 05-29-2008]. Available at: http://www.hhs.gov/bloodsafety/2005NBCUS.pdf.
90. World Health Organization, Twenty-Eighth World Health Assembly, Geneva, 13–30 May 1975:WHA28.72 Utilization and Supply of Human Blood and Blood Products, World Health Organization, Geneva, 1975 [cited 05-29-2008]. Available at: http://www.who.int/bloodsafety/en/WHA28.72.pdf.
91. Riley W, Schwei M, McCullough J. The United States' potential blood donor pool: estimating the prevalence of donor-exclusion factors on the pool of potential donors. Transfusion 2007;47(7):1180–8.
92. Sullivan MT, Cotten R, Read EJ, et al. Blood collection and transfusion in the United States in 2001. Transfusion 2007;47(3):385–94.
93. Zou S, Musavi F, Notari EP 4th, et al. ARCNET Research Group. Changing age distribution of the blood donor population in the United States. Transfusion 2008; 48(2):251–7.
94. Dann EJ, Bonstein L, Arbov L, et al. Blood bank protocols for large-scale civilian casualty events: experience from terrorist bombing in Israel. Transfus Med 2007; 17(2):135–9.
95. Sandler SG, Ouellette GJ. Transportation and other blood system issues related to disasters: Washington, DC experience of September 11, 2002. Vox Sang 2002;83(Suppl 1):367–70.
96. Spinella PC, Perkins JG, Grathwohl KW, et al. 31st Combat Support Hospital Research Working Group. Risks associated with fresh whole blood and red blood cell transfusions in a combat support hospital. Crit Care Med 2007; 35(11):2576–81.
97. World Health Organization. Global Consultation on Universal Access to Safe Blood Transfusion. 9–11 June 2007, Ottawa, Canada [cited 05-29-2008]. Available at: http://www.who.int/bloodsafety/publications/Report_Global_Consultation_Ottawa_2007.pdf.
98. Goodnough LT, Shander A, Brecher ME. Transfusion medicine: looking to the future. Lancet 2003;361(9352):161–9.
99. Bates I, Manyasi G, Medina Lara A. Reducing replacement donors in Sub-Saharan Africa: challenges and affordability. Transfus Med 2007;17(6):434–42.
100. World Health Organization. Global Database on Blood Safety Summary Report 2001–2. Geneva 2004 [cited 05-29-2008]. Available at. http://www.who.int/bloodsafety/GDBS_Report_2001-2002.pdf.
101. Gohel MS, Bulbulia RA, Slim FJ, et al. How to approach major surgery where patients refuse blood transfusion (including Jehovah's Witnesses). Ann R Coll Surg Engl 2005;87(1):3–14.
102. Goodnough LT, Shander A, Spivak JL, et al. Detection, evaluation, and management of anemia in the elective surgical patient. Anesth Analg 2005;101(6): 1858–61.