REVIEW ARTICLE

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Indications for and Adverse Effects of Red-Cell Transfusion

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Approximately 11 million units of red cells are transfused annually in the United States, making red-cell transfusion one of the most common medical interventions. Red cells are typically administered as a concentrate, called packed red cells, with a preservative solution (hematocrit, 60%) that allows up to 42 days of refrigerated storage. On average, transfusion of 1 unit of red cells, which has a volume of 350 ml, results in a hemoglobin increment of 1 g per deciliter in an adult with stable blood volume.

In this review, we describe the evidence underlying current transfusion guidelines, trends in use, the infectious and noninfectious risks of transfusion, and ongoing research. We describe the effects of transfusion in adults who have cardiovascular disease or gastrointestinal bleeding, who are critically ill, or who are undergoing orthopedic surgery, as well as the effects in children. Discussions of the safety of transfusion in resource-poor countries and the efficacy of transfusion in premature infants, pregnant women, and patients with hemorrhagic shock or congenital anemias are beyond the scope of this review.

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INDICATIONS FOR RED-CELL TRANSFUSION

OVERALL INDICATIONS

Randomized clinical trials have shown that earlier results from observational studies overestimated the risks associated with blood transfusion. Most trials have randomly assigned patients to a higher hemoglobin concentration as the threshold for transfusion (referred to as liberal transfusion) or to a lower hemoglobin concentration as the threshold (referred to as restrictive transfusion). If implemented and designed correctly, such a trial design should provide guidance about transfusion efficacy and safety associated with clinically meaningful differences in the mean hemoglobin concentration and the number of units of blood transfused.

A total of 31 trials were included in a recent systematic review and meta-analysis evaluating the efficacy of red-cell transfusion.[1] The trials enrolled a total of more than 12,000 patients, and the most common indications for transfusion were orthopedic surgery (in 10 trials), critical care (6), cardiac surgery (5), gastrointestinal bleeding (5), and acute coronary syndromes (2).[2-7] Patients in the restrictive-transfusion group were 43% less likely to receive a red-cell transfusion than those in the liberal-transfusion group, and the mean hemoglobin concentration was 1.3 g per deciliter lower. Overall, 30-day mortality was similar in the two transfusion groups (risk ratio with restrictive transfusion, 0.97; 95% confidence interval [CI], 0.81 to 1.16) (Fig. 1). Other outcomes also did not differ significantly between transfusion groups, including pneumonia (risk ratio with restrictive transfusion,

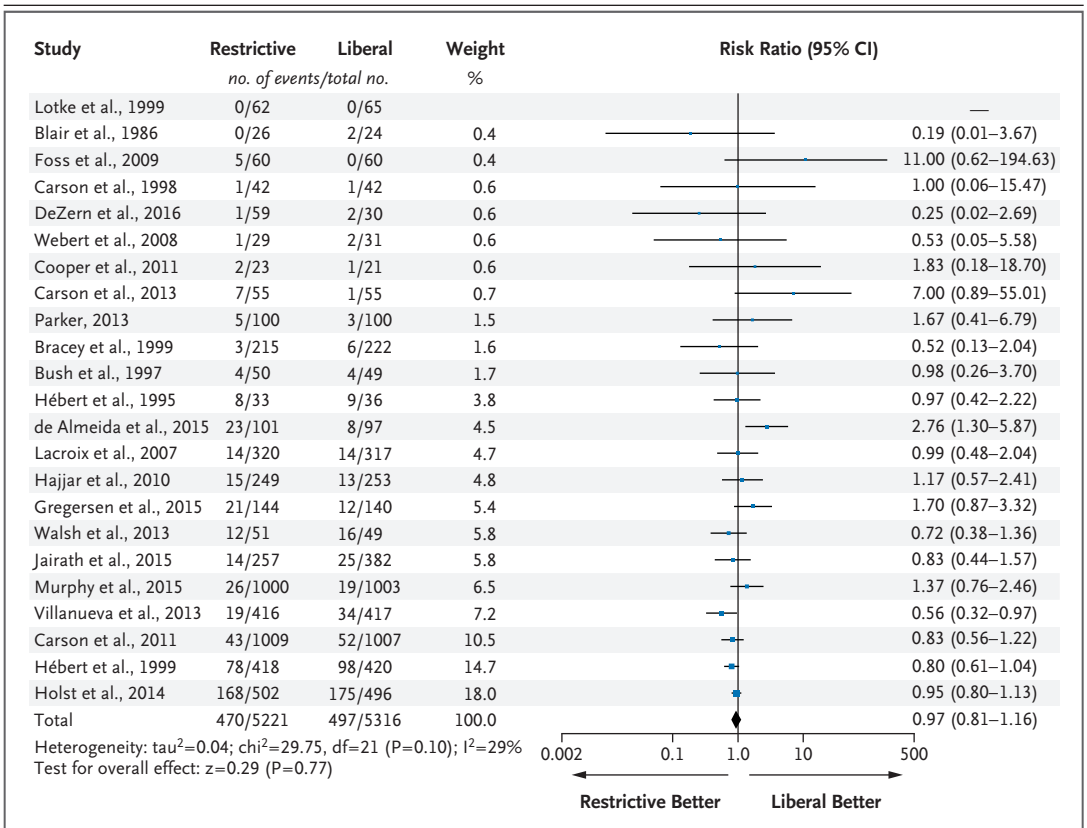

Figure 1. Clinical Trials Comparing the Effect of Restrictive versus Liberal Transfusion on 30-Day Mortality.

Data are from a meta-analysis of 31 studies, of which 23 reported 30-day mortality.[1] Risk ratios were calculated with the use of the Mantel–Haenszel test. The blue boxes indicate risk ratios, and the size of each box is proportional to the sample size of the corresponding study. CI denotes confidence interval, and df degrees of freedom; I^2 is the percentage of total variation that is due to heterogeneity rather than chance.

0.94; 95% CI, 0.80 to 1.11), myocardial infarction (risk ratio, 1.08; 95% CI, 0.74 to 1.60), and congestive heart failure (risk ratio, 0.78; 95% CI, 0.45 to 1.35). In addition, long-term mortality, with a mean of 3.1 years of follow-up, was similar in the two groups (hazard ratio for liberal transfusion as compared with restrictive transfusion, 1.09; 95% CI, 0.95 to 1.25) in one trial.[8]

Many trials have used a restrictive transfusion threshold of 7 g per deciliter or 8 g per deciliter.[9] Among the trials assessing 30-day mortality, the results with a threshold of 7 g per deciliter were similar to those with a threshold of 8 g per deciliter (test for differences, P=0.56; I^2=0%). However, most of the trials using 7 g per deciliter as the threshold for restrictive transfusion involved patients in intensive care units (ICUs), whereas the trials using 8 g per deciliter as the threshold involved patients with various diagnoses. Therefore, it may not be appropriate to generalize the results of trials that used the lower threshold to clinical settings in the trials using the higher threshold. It is possible that mortality is not influenced by a lower transfusion threshold, but the rate of myocardial infarction (in patients with preexisting cardiovascular disease or in those undergoing cardiac surgery) or recovery of functional capacity (in patients undergoing orthopedic surgery) could be adversely affected by a transfusion threshold of 7 g per deciliter rather than 8 g per deciliter.

INDICATIONS FOR SUBGROUPS OF PATIENTS

Adults with Cardiovascular Disease

The risk of death is strongly associated with the level of anemia and is increased among patients

with cardiovascular disease.[10,11] Thus, it follows that patients with cardiovascular disease might benefit from a higher transfusion threshold.

Overall, restrictive transfusion is not associated with an increased risk of myocardial infarction; however, there is some evidence supporting a benefit of liberal transfusion in patients with underlying cardiovascular disease. In a trial involving 2007 patients undergoing cardiac surgery, 90-day mortality was higher in the restrictive-transfusion group than in the liberal-transfusion group (4.2% vs. 2.6%; hazard ratio, 1.64; 95% CI, 1.00 to 2.67; P=0.045), although short-term outcomes (30-day mortality, myocardial infarction, and others) were similar in the two groups.[7] In a pilot trial involving 110 patients with acute ischemic heart disease, 7 deaths occurred in the restrictive-transfusion group, as compared with 1 death in the liberal-transfusion group (absolute risk difference, 11.2 percentage points; 95% CI, 1.5 to 20.8; P=0.08 with adjustment for age).[12] In a cluster-randomized trial involving 936 patients with gastrointestinal bleeding, there was a trend toward increased mortality among patients with underlying ischemic heart disease; mortality was 3% with liberal transfusion but 12% with restrictive transfusion (absolute difference, 10.7 percentage points; 95% CI, −9.8 to 31.2; P=0.11 for interaction).[13] In contrast, in a trial involving 2016 patients with cardiovascular disease or risk factors for it who were undergoing hip-fracture repair, mortality was similar with liberal transfusion and restrictive transfusion (5.2% and 4.3%, respectively; odds ratio, 1.23; 95% CI, 0.71 to 2.12).[4] Several trials are under way to address this question of restrictive versus liberal transfusion in patients with cardiovascular disease: Transfusion Requirements in Cardiac Surgery III (TRICS III; ClinicalTrials.gov number, NCT02042898), with a projected sample of 5000 patients; Cost-Effectiveness and Cost-Utility of Liberal vs. Restrictive Red Blood Cell Transfusion Strategies in Patients with Acute Myocardial Infarction and Anaemia (REALITY; NCT02648113), with a projected sample of 630 patients; and Myocardial Ischemia and Transfusion (MINT; NCT02981407), with a projected sample of 3500 patients.

A meta-analysis of selected trials that provided data on patients with cardiovascular disease showed no difference in mortality between the liberal and restrictive transfusion thresholds, but an increase in the risk of myocardial infarction, acute coronary syndrome, or cardiac arrest was associated with restrictive transfusion (4.5% vs. 2.5%; risk ratio, 1.78; 95% CI, 1.18 to 2.70).[14] These results should be interpreted with caution because not all trials that enrolled patients with cardiovascular disease were included in this analysis. Furthermore, it may not be appropriate to combine data from patients who had preexisting coronary artery disease with data from those with acute coronary syndromes, since the risks associated with anemia and efficacy of transfusion may be different; patients with active ischemia often undergo cardiac interventions and intensive pharmacologic treatment, whereas those with preexisting cardiovascular disease are heterogeneous with respect to disease severity and may have undefined cardiovascular disease. This analysis also did not include patients undergoing cardiac surgery.

Adults with Gastrointestinal Bleeding

Three trials involving a total of 1522 patients with gastrointestinal bleeding showed that mortality was lower with a restrictive transfusion threshold than with a liberal transfusion threshold (risk ratio, 0.65; 95% CI, 0.43 to 0.97; difference in rate of transfusion, 24.5 percentage points).[1,5,13,15] Rebleeding also was lower with a restrictive transfusion threshold (risk ratio, 0.54; 95% CI, 0.51 to 0.93). The rebleeding rate in the liberal-transfusion group may have been higher because of increased intravascular pressure from a higher volume of fluid (blood), leading to rupture of thrombus at the site of the bleeding vessel.

Other Subgroups of Adults

Five trials involving a total of 2840 patients in ICUs, including 998 patients with septic shock,[6] showed no significant difference in mortality between the two transfusion thresholds (risk ratio with restrictive transfusion, 0.97; 95% CI, 0.75 to 1.25; absolute difference in rate of transfusion, 36.3 percentage points).[1] Similarly, the mortality rates in five trials involving a total of 2831 patients undergoing orthopedic surgery were similar with the two transfusion thresholds, although they were slightly higher with restrictive transfusion (risk ratio, 1.27; 95% CI, 0.72 to 2.25; absolute difference in rate of transfusion, 54.7 percentage points).[1]

Children

Only one trial has evaluated a hemoglobin concentration of less than 9.5 g per deciliter as a threshold for transfusion in children. That trial, involving 637 children in ICUs, compared a restrictive transfusion threshold of 7 g per deciliter with a liberal threshold of 9.5 g per deciliter.[3] There was no difference in either the primary outcome of new or progressive multiple-organ dysfunction syndrome (12% in both groups; absolute risk reduction with the restrictive strategy, 0.4 percentage points; 95% CI, −4.6 to 5.4) or mortality. Another trial involving children (Transfusion of Prematures Trial [TOP; NCT01702805]) is under way.

GUIDELINES AND RECOMMENDATIONS

Multiple guidelines for red-cell transfusion have been published in the past 5 years (Table 1), and their quality has been assessed.[25] Most guidelines advise a restrictive transfusion threshold of 7 to 8 g per deciliter in asymptomatic patients. Several of the guidelines recommend that transfusion not be based on the hemoglobin concentration alone but also on consideration of overall clinical status, the patient's preference, and alternative therapies.[9,17,23,24] The guidelines differ widely for patients with acute coronary syndromes, recommending a transfusion threshold of 7 g of hemoglobin per deciliter,[20] 8 g per deciliter,[16,20,23,26] 9 g per deciliter,[22] or 10 g per deciliter.[19] We do not have high-quality evidence to guide decisions about transfusion in patients with acute coronary syndromes,[9] since only two small pilot trials, involving a total of 154 patients,[12,27] have been published.

Overall, the clinical-trial data clearly show the safety of a restrictive threshold of 7 to 8 g of hemoglobin per deciliter in most patients. We advise following AABB (formerly the American Association of Blood Banks) guidelines (one of us is a coauthor of these guidelines), which recommend using the restrictive transfusion threshold that was tested in clinical trials: 8 g of hemoglobin per deciliter in patients with preexisting cardiovascular disease and those undergoing cardiac or orthopedic surgery and 7 g per deciliter in most other patients, including those in ICUs. It is important to recognize that adequate evidence from clinical trials is lacking for transfusion strategies in many subgroups of patients, including patients with acute coronary syndromes, those with long-term dependence on transfusion, and patients with hematologic disorders, cancer, thrombocytopenia, or acute neurologic disorders.[9] We also advise that in making decisions about transfusion, other clinical factors, including hemodynamic status, rate of bleeding, symptoms, and overall status of the patient, be considered in addition to the hemoglobin concentration. Physiological or laboratory biomarkers for guiding decisions about transfusion have not been established. Except in cases of acute bleeding, the physician should prescribe only 1 unit of red cells at a time and should measure the hemoglobin concentration and perform a clinical assessment before administering additional blood transfusions.

TRENDS IN THE USE OF RED-CELL TRANSFUSIONS

Red cells are the most commonly transfused blood component in developed countries. Despite predictions that red-cell use could increase as the U.S. population ages, with greater use of transfusions in patients who have cancer or cardiac disease, the number of red-cell transfusions has fallen from a high of almost 15 million units in 2008 to approximately 12 million units in 2015 (Fig. 2). Red-cell transfusions over time have fallen from 50 units per 1000 population in 2008 to approximately 40 units per 1000 population in 2013.[28,30] The increasing adoption of patient-focused blood-management programs in hospitals worldwide accounts for most of these decreases.[31]

Patient-focused blood-management programs have taken advantage of the evidence, cited above, that restrictive red-cell transfusion practices are safe. In an effort to reduce red-cell transfusions, these programs have promoted the adoption of surgical techniques that reduce blood loss and the administration of hemostatic agents such as tranexamic acid, with better hemostatic monitoring through the use of thromboelastography.[32] Rates of red-cell transfusion in the United States are still among the highest in developed countries, suggesting that patient-focused blood-management programs have ad-

ditional capacity to reduce unnecessary blood transfusions (Fig. 3). However, U.S. medical practice, with major programs for trauma resuscitation and aggressive programs of solid-organ and stem-cell transplantation, may explain the persistently high rates of red-cell transfusion in the United States.

IMPROVING SAFETY

TRANSFUSION-TRANSMITTED DISEASES

In developed countries, the risk of a disease transmitted by transfused red-cell concentrates has become very small (Fig. 4), with a risk of less than 1 in 1 million for the pathogens of greatest concern, including the human immunodeficiency virus (HIV) and hepatitis C virus (HCV).[38] Although it is always possible that a new infectious agent will be introduced into the blood supply, current blood-collection programs use a combination of a medical history from volunteer donors, limited physical examinations, geographic and travel exclusions for areas where disease is known to be endemic and testing is not practical or of proven efficacy, and a battery of serologic and nucleic acid tests to reduce the risk of infectious complications. Volunteer blood donations in the United States are tested for syphilis (despite the absence of recent documented cases),[39] hepatitis B virus (HBV),[40] HIV,[41] human T-cell lymphotropic virus,[42] HCV,[41] West Nile virus,[43] and Chagas' disease,[44] with the recent addition of testing for Zika virus.[45] Although the tests are performed to eliminate infectious units from the blood supply, some of the tests are more likely to identify previous infections (in particular, syphilis or hepatitis B, with the latter indicated by the presence of hepatitis B core antibody). Initial testing for these agents is performed with the use of serologic methods that have been enhanced over time with new generations of assays that have improved sensitivity and specificity. For additional recipient safety, nucleic acid testing is performed for HBV, HCV, HIV, West Nile virus, and Zika virus. Donor red cells can also be tested for antibody to cytomegalovirus for patients at high risk, but leukoreduced red cells are considered equally safe with respect to the risk of cytomegalovirus.[46] Bacterial infections, a major problem in platelets that are stored at room temperature, are not a major concern in red cells stored in refrigerators.[47] U.S. donors are not tested for malaria, but infectious donors are eliminated on the basis of travel exclusions.[48] Babesia infection is becoming recognized as a growing problem (associated with 15 to 20% mortality) in some areas of the United States, such as New England, and testing programs are currently being evaluated for possible implementation.[49-51] Other agents also under study include dengue virus,[52] chikungunya virus,[53] and hepatitis E virus.[54]

PATHOGEN REDUCTION

Pathogen-reduction technology represents a proactive approach to improving blood safety by broadly inactivating potential infectious agents in the blood component. This technology is now available in the United States for platelets and plasma.[55] Several systems are under study for the treatment of red cells, using chemical processing with an alkylating agent (S-303) and glutathione (Intercept, Cerus) or a combination of riboflavin and ultraviolet light (Mirasol, Terumo BCT). Neither system is licensed in the United States. The advantages of pathogen-reduction technology would include reduction of residual infections with viruses, bacteria, or parasites that are not detected by current testing systems and prevention of some infections that have not yet been recognized as transmitting disease through transfusion. Pathogen-reduction technology will also inactivate white cells in blood that are not removed by leukoreduction filters, eliminating the need to irradiate red cells in order to prevent transfusion-associated graft-versus-host disease and potentially reducing the risk of febrile nonhemolytic transfusion reactions.[56] It is also anticipated that pathogen-reduction technology could eliminate some of the current donor travel exclusions and testing for some agents for which the risk of breakthrough infections is very low. In vitro studies have shown that pathogen-reduction technology kills high levels of viruses and bacteria in red cells, and a clinical study showed that whole blood treated with riboflavin and ultraviolet light reduced malaria transmission.[57] These safety advantages of treating red cells with pathogen-reduction technology will need to be weighed against some degree of cell damage and the likelihood of increased costs of such treatment.

Table 1. Red-Cell Transfusion Guidelines Published between 2012 and 2017.*

Sponsor and Year	Recommended Hemoglobin Concentration as Threshold for Transfusion			Comments
	Overall	Subgroups	Cardiovascular Disease	
AABB, 2016[9]	Restrictive transfusion threshold of 7 g/dl for hospitalized adults who are hemodynamically stable, including critically ill patients, and 8 g/dl for patients undergoing orthopedic or cardiac surgery and those with preexisting cardiovascular disease	No recommendation for patients with acute coronary syndromes or thrombocytopenias or for those requiring long-term transfusion	8 g/dl in patients with preexisting cardiovascular disease	Good practice includes consideration of overall clinical situation, patient's preference, and alternative therapies, in addition to hemoglobin concentration
National Guideline Centre, 2016[16]	Restrictive transfusion threshold of 7 g/dl, with target of 7–9 g/dl for patients without major hemorrhage	Patients with major hemorrhage, acute coronary syndromes, or chronic anemia are excluded	Consider a transfusion threshold of 8 g/dl, with target of 8–10 g/dl after transfusion for patients with acute coronary syndromes; further research required for patients with chronic cardiovascular disease	Transfuse single unit in patients without active bleeding; reassess after each single-unit transfusion
American Society of Anesthesiologists, 2015[17]	Restrictive transfusion threshold of 6–10 g/dl, with consideration of potential or ongoing bleeding, intravascular volume status, signs of organ ischemia, and adequacy of cardiopulmonary reserve			Transfuse single unit; multimodal protocols or algorithms may help reduce use of blood products; however, no single algorithm or protocol can be recommended at this time
British Committee for Standards in Haematology, 2014[18]	For adults with myelodysplastic syndromes, the transfusion threshold should be individualized			
National Comprehensive Cancer Network, 2013[19]	In patients with cancer and asymptomatic anemia, restrictive transfusion threshold of 7–9 g/dl; in patients with symptomatic anemia, transfuse to correct hemodynamic instability and maintain adequate oxygen delivery, with transfusion goal of 8–10 g/dl		Use threshold of 10 g/dl for patients with acute coronary syndromes or acute MI	
American College of Physicians, 2013[20]	Guidelines focused on patients with heart disease; current evidence does not support benefit of liberal transfusion in patients with asymptomatic anemia and heart disease		Use threshold of 7–8 g/dl in hospitalized patients with coronary heart disease, including patients with acute coronary syndromes	

Surviving Sepsis Campaign Guidelines Committee, including the Pediatric Subgroup, 2013[21]	In adults with sepsis, in the absence of hypoperfusion, myocardial ischemia, severe hypoxemia, acute hemorrhage, and ischemic coronary artery disease, provide transfusion when the hemoglobin concentration is <7.0 g/dl		Recommendations exclude patients with acute or chronic ischemic heart disease
British Committee for Standards in Haematology, 2013[22]	In critically ill adults, use transfusion threshold of 7 g/dl or lower, with a target hemoglobin range of 7–9 g/dl, unless specific coexisting conditions or acute illness–related factors modify clinical decision making; transfusion trigger should not exceed 9 g/dl in most critically ill patients	In early resuscitation of patients with severe sepsis, if there is clear evidence of inadequate oxygen delivery, use target threshold of 9–10 g/dl; during later stages of severe sepsis, use 7 g/dl threshold with target of 7–9 g/dl; for patients with traumatic brain injury, use target threshold of 7–9 g/dl; for patients with traumatic brain injury and evidence of cerebral ischemia or stroke, use target threshold >9 g/dl	In critically ill patients with stable angina, use threshold of 7 g/dl; in patients with acute coronary syndromes, use threshold of 8–9 g/dl Do not use transfusion to assist in weaning patient from mechanical ventilation when hemoglobin >7 g/dl
Patient Blood Management Guidelines: Modules 1–4, National Blood Authority, Australia, 2012[23]	Restrictive transfusion level should not be dictated by hemoglobin concentration alone but should also be based on assessment of clinical status; threshold of <7 g/dl likely to be appropriate; threshold of 7–9 g/dl should be based on need to relieve clinical symptoms and signs of anemia; threshold of >9 g/dl generally not needed		Threshold of <8 g/dl may be associated with reduced mortality; effect of threshold of 8–10 g/dl is uncertain and may be associated with increased risk of recurrent MI; threshold >10 g/dl is not advisable
KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease, 2012[24]	For patients with chronic kidney disease: transfusion in those with nonacute anemia should be based not on an arbitrary hemoglobin concentration but on symptoms of anemia; transfuse when rapid correction of anemia is required to stabilize the patient's condition (e.g., acute hemorrhage, unstable coronary artery disease)		Data from randomized, controlled trials are lacking for patients with chronic kidney disease; therefore, transfusion guidelines are based on observational data

* KDIGO denotes Kidney Disease: Improving Global Outcomes, and MI myocardial infarction.

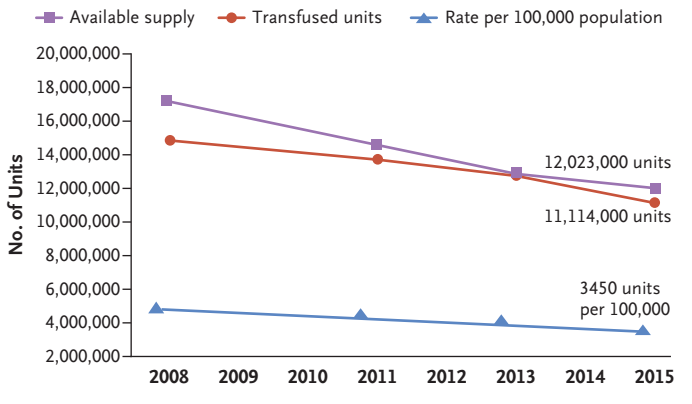

Figure 2. Trends in U.S. Blood Supplies and Use, 2008–2015.

Shown are data on the total available supply of whole blood or red cells (total units collected minus units lost because of reactive test results and other production factors), the total number of units transfused, and the rate of transfusion per 100,000 U.S. population. Data for 2013 are from the Blood Collection, Utilization, and Patient Blood Management Survey, conducted by the AABB[28]; 2015 data are from the Centers for Disease Control and Prevention National Blood Collection and Utilization Survey (NBCUS).[29]

NONINFECTIOUS HAZARDS OF TRANSFUSION

Because the infectious risks of red-cell transfusion in Western countries are at an all-time low, the noninfectious hazards have become the primary transfusion complications observed in clinical practice. The most important of these risks are shown in Figure 4. Historically, mild fever, chills, and allergic reactions were the most common reactions, reported in approximately 0.5 to 1% of transfusion episodes. With improvements in recognition and reporting of complications, transfusion-associated circulatory overload is now among the most common hazards of transfusion, reported in 1 to 5% of transfusion episodes.[58,59] Transfusion-associated circulatory overload is characterized by a cardiogenic pulmonary edema resulting in acute respiratory distress. This reaction occurs most commonly in patients who already have fluid overload as a result of congestive or coronary artery heart disease or acute renal failure.[58] Diagnostic criteria for transfusion-associated circulatory overload include the develop-

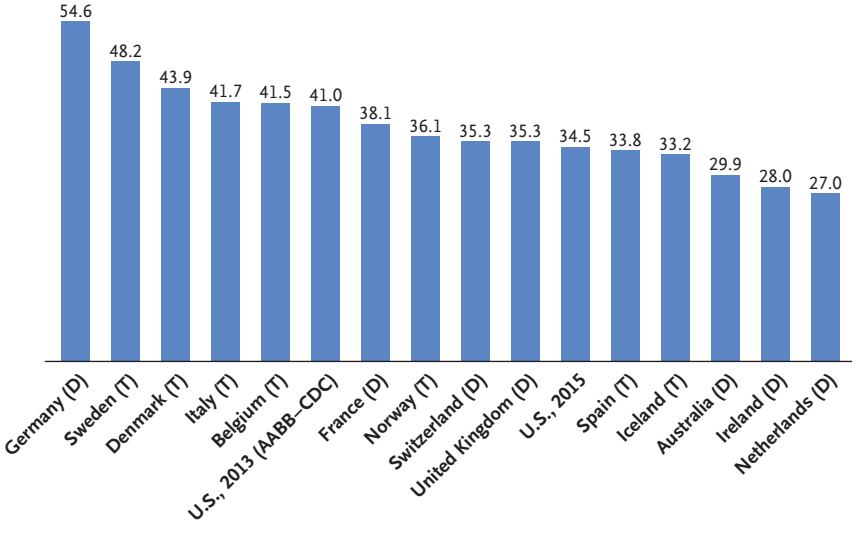

Figure 3. Transfusion Rates in the United States in 2013 and 2015, as Compared with Rates in Other Developed Countries.

The number above each bar is the number of transfused red-cell units per 1000 population. Transfusion rates in the United States in 2013 and 2015 are compared with the most recent data on transfusion rates in Europe (2013).[33] The U.S. rate of transfusion in 2013, 41.0 units per 1000 population, is the midpoint of the rates estimated separately on the basis of the 2013 AABB Blood Collection, Utilization, and Patient Blood Management Survey[28] (40.3 units per 1000) and the 2013 Centers for Disease Control and Prevention (CDC) NBCUS (41.7 units per 1000).[29] The U.S. rate of transfusion in 2015, 34.5 units per 1000, is based on the 2015 NBCUS.[30] The data shown are for distributed (D) or transfused (T) units of blood, which are typically nearly equivalent.

ment or exacerbation of respiratory distress within 6 to 12 hours after transfusion, with evidence of fluid overload, pulmonary edema, an enlarged cardiac silhouette, elevated brain natriuretic peptide levels, a positive fluid balance, and a response to diuretics.[60,61] Prevention and treatment of transfusion-associated circulatory overload include transfusing the minimum number of components, slowing the rate of transfusion (maximum rate, 4 hours per component), and administering diuretics before or between transfusions.[62]

A less common cause of respiratory distress is transfusion-related acute lung injury, a noncardiogenic pulmonary edema occurring within 6 hours after transfusion and characterized by hypoxemia and bilateral pulmonary infiltrates on chest films.[63] The diagnosis is made in the absence of other risk factors for the acute respiratory distress syndrome and can be quite difficult to establish, particularly in critically ill patients. On the basis of the most current data, the risk of transfusion-related acute lung injury across all blood components is estimated at 1 case per 12,000 units.[64] Transfusion-related acute lung injury is reversible in most cases within 24 to 96 hours after cessation of the transfusion and is successfully managed with supportive care. The pathogenesis is primarily mediated by leukoagglutinating antibodies in donor plasma, although causes not mediated by antibodies are postulated in up to 20% of cases.[63,65] With the adoption of mitigation strategies, the risk of transfusion-related acute lung injury associated with transfusion of plasma-rich components (plasma and platelets) has decreased dramatically over the past 10 years.[66] The risk with red cells and lesser amounts of plasma is much lower, and the numbers of deaths reported to the Food and Drug Administration (FDA) that were attributed to acute lung injury associated with transfusion of red cells have not changed during this period.[67]

Hemolytic transfusion reactions may be acute (i.e., immediate) or delayed. Immediate reactions are mainly due to administration of ABO-incompatible red cells as a result of human error in blood sampling or patient identification. Preformed complement-binding antibodies mediate intravascular hemolysis, with frequent acute renal failure and mortality ranging from 8 to 44%, depending on how much incompatible blood is transfused.[68] These transfusion reactions account for approximately six to nine deaths reported annually to the FDA.[69] Delayed hemolytic transfusion reactions are mediated by non-ABO antibody levels that fall below the limit detectable in pretransfusion testing when the patient is transfused with red cells expressing the cognate antigen. An anamnestic response can ensue 3 to 21 days after transfusion, with a spike in the antibody titer and extravascular destruction of the transfused red cells. As a result of the slower rate of extravascular red-cell removal in the spleen, delayed hemolytic transfusion reactions generally are less severe than immediate reactions and are not associated with permanent renal failure or death.

A rare but often fatal complication is transfusion-associated graft-versus-host disease, which is due to engraftment of viable donor T cells from the blood component in a susceptible recipient. The T cells mediate a graft-versus-host reaction like that seen in allogeneic hematopoietic stem-cell transplantation, with the added feature of pancytopenia and a resistance to therapy resulting in high mortality (>90%). This severe complication can be prevented by irradiation of blood components, which inactivates T cells in the

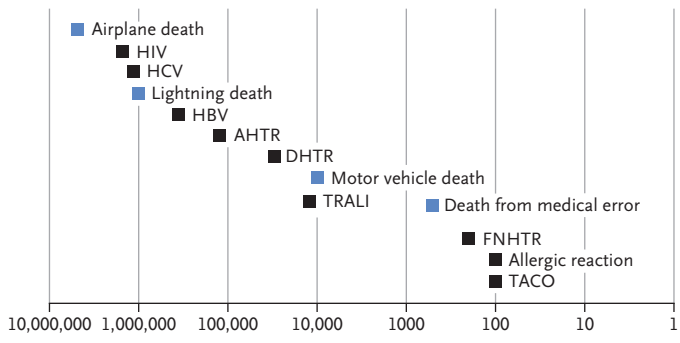

Figure 4. Infectious and Noninfectious Adverse Effects of Red-Cell Transfusions as Compared with Other, Unrelated Risks.

Adverse effects of transfusions (black boxes) are shown per transfused unit of red cells, except for transfusion-associated circulatory overload (TACO), which is per transfusion episode. For unrelated risks (blue boxes), the risk of an airplane death is per flight,[34] the risk of death from lightning is per year,[35] the risk of death from a motor vehicle accident is per 10,000 persons,[36] and the risk of death from medical error is per hospital admission.[37] AHTR denotes acute hemolytic transfusion reaction, DHTR delayed hemolytic transfusion reaction, FNHTR febrile nonhemolytic transfusion reaction, HBV hepatitis B virus, HCV hepatitis C virus, and TRALI transfusion-related acute lung injury.

blood components. Other hazards of transfusion include iron overload, anaphylaxis, and immunomodulation.

Transfusion-associated iron overload occurs in patients with congenital or acquired anemia requiring long-term red-cell support. Each unit of packed red cells contains about 250 mg of iron. Accumulated iron can result in damage to the heart, liver, and endocrine organs. Transfusion-associated iron overload can be diagnosed by means of liver biopsy or noninvasively by means of magnetic resonance imaging or serum ferritin testing. Chelation therapy is the main treatment approach.[70]

Immunomodulation encompasses a wide variety of immunologic sequelae of allogeneic blood transfusion. Many of the effects are attenuated by using leukoreduced blood components, which account for more than 90% of red-cell and platelet transfusions in the United States. The extent to which the immunomodulatory effects of transfusion alter clinical outcomes remains a matter of controversy.[71]

Finally, massive transfusion can be associated with a number of complications, including hypothermia, hyperkalemia, dilutional coagulopathy, and citrate toxicity.[72] Citrate anticoagulant is quickly metabolized in the liver, but when sufficient citrate is transfused rapidly or there is liver failure, it can bind to divalent cations, resulting in hypocalcemia and hypomagnesemia. Hepatic metabolism of citrate to bicarbonate can result in metabolic alkalosis. Massively transfused patients require close laboratory and clinical monitoring to identify these complications.

FUTURE RESEARCH

New technologies are being developed to aid in making decisions about transfusion of red cells. The hemoglobin concentration reflects the oxygen-carrying capacity of blood but does not indicate the level of tissue oxygenation. Noninvasive methods of directly assessing tissue oxygenation are being studied[73-76] and may be combined with plasma measurements, such as lactate[75] or base deficit,[73] to better identify the need for red-cell transfusion. Effective and safe alternatives to red cells in the form of hemoglobin-based oxygen carriers remain elusive. Decades of laboratory and clinical research have yet to yield an FDA-approved product[77]; however, clinical trials are proceeding with first-generation and next-generation hemoglobin-based oxygen carriers (NCT02684474 and NCT01881503).[78] Finally, advances in cellular engineering have made the production of red cells in vitro from hematopoietic stem cells a tantalizing concept. Small volumes have been produced in bioreactors, but the feasibility of scaling up to a clinical dose of 200 ml per unit has yet to be demonstrated.[79,80]

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