Blood Transfusion Therapy

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KEYWORDS

- Anemia • Red blood cell transfusion • Clinical decision support
- Restrictive transfusion practices

KEY POINTS

- Transfusion of red blood cells (RBCs) is a balance between providing benefit for patients while avoiding risks of transfusion.
- Randomized, controlled trials of restrictive RBC transfusion practices have shown equivalent patient outcomes compared with liberal transfusion practices, and meta-analyses have shown improved in-hospital mortality, reduced cardiac events, and reduced bacterial infections.
- This body of level 1 evidence has led to substantial, improved blood utilization and reduction of inappropriate blood transfusions with implementation of clinical decision support via electronic medical records, along with accompanying educational initiatives.

INTRODUCTION

Blood transfusion therapy is frequently used in the supportive care for treatment of anemia. The transfusion of red blood cells (RBC) is a balance between the benefits of maintaining oxygen delivery and the inherent risks from blood transfusion. The signs and symptoms of anemia vary based on the acuity of the anemia, compensatory change in blood volume, and the compensatory change in cardiac output from the patient's cardiovascular system. Chronic anemia is generally well tolerated due to compensatory expansion of intravascular plasma volume, increased cardiac output, vasodilatation, increased blood flow due to decreased viscosity, and not least, increased RBC 2,3 diphosphoglycerate, with a right shift of the oxygen dissociation curve, so that oxygen is unloaded to the peripheral tissues more readily. Symptoms of anemia are often nonspecific and can include fatigue, pallor, dizziness, headaches, vertigo, tinnitus, dyspnea, and inactivity. Fatigue particularly has been associated with poor quality of life.[1]

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The traditional therapy for chronic, medically related anemia has been RBC transfusions. However, transfusion therapy has been identified as one of the most overused (and inappropriate) therapeutic interventions by national accreditation (Joint Commission) and medical societies, such as the American Board of Internal Medicine,[2] the American Medical Association, the American Society of Hematology (ASH), and the American Association of Blood Banks (AABB; http://www.choosingwisely.org/doctor-patient-lists/american-society-of-hematology/). Recommendations have been published by several medical societies for RBC transfusion therapy in adult[3] and pediatric[4] patients.

The authors have previously reviewed blood transfusion practices,[3,5,6] and herein they provide an updated review of RBC therapy in adult and pediatric patients. The article summarizes current blood risks and indications for RBC transfusion. Important, alternative therapies for management of anemia, such as iron therapy and erythropoietic stimulating agents (ESAs), are outside the scope of this review, but have been published elsewhere.[7,8] Where possible, the article provides evidence-based guidelines for best transfusion practices.

RISKS OF BLOOD TRANSFUSION

Transfusion-transmitted infections prompted concern by patients and health care providers since the 1980s, with the recognition of transfusion transmission of human immunodeficiency virus (HIV) and hepatitis C virus (HCV).[9] These risks have decreased substantially, and responses to emerging pathogens transmitted by blood transfusion have been rapid (Fig. 1).[10] Nevertheless, emerging threats of blood-transmissible pathogens is always a concern, the most recent example of which is the Zika virus, in which potential blood donors who are acutely ill and viremic may be asymptomatic and not be deferred during donor screening.[11] For this reason, an experimental nucleic acid test (NAT) was implemented for universal donor testing by end of November 2016. Between 2007 and 2011, transfusion-related acute lung injury (TRALI) caused the highest percentage (43%) of fatalities reported to the US Food and Drug Administration (FDA), followed by hemolytic transfusion reactions (23%) caused by non-ABO- (13%) or ABO- (10%) incompatible blood transfusions.[12]

Increasing evidence suggests that a far greater number of patients now have adverse clinical outcomes (increased morbidity and mortality) associated with unnecessary blood transfusions.[13–15] Table 1 lists risks that include not only known transmissible pathogens for infectious disease, transfusion reactions, TRALI, errors in blood administration, and circulatory overload but also potential, as yet undefined risks such as immunomodulation (eg, perioperative infection or tumor progression), unknown or emerging risks (such as the new variant Creutzfeldt-Jakob disease and Zika virus),[10,16] and potential risks associated with storage lesions from blood transfusions.[17,18]

Awareness of blood risks and costs[19] has led providers to develop institution-based initiatives in Patient Blood Management, including the adoption of recommendations that limit the use of blood transfusion.[3] Patient Blood Management encompasses an evidence-based approach that is multidisciplinary (transfusion medicine specialists, surgeons, anesthesiologists, and critical care specialists) and multiprofessional (physicians, nurses, pump technologists, and pharmacists).[20] Preventative strategies are emphasized to identify, evaluate, and manage anemia in medical[6] and surgical[21] patients, use of pharmacologic interventions,[7,8] and the avoidance of unnecessary diagnostic testing to minimize iatrogenic blood loss[22]; and to establish clinical practice recommendations for blood transfusions.[3] For anemic patients being evaluated for
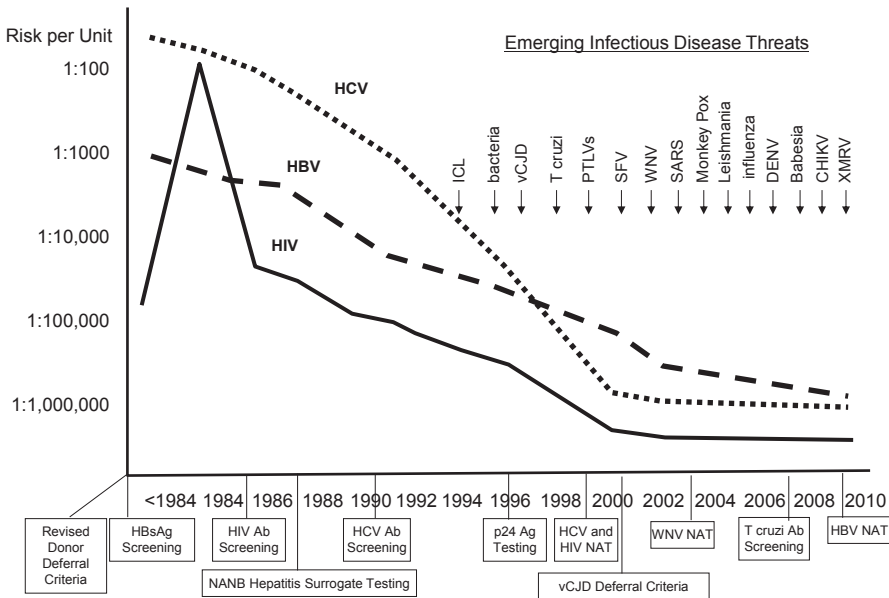
Fig. 1. Risks of major transfusion-transmissible viruses linked to interventions, and accelerating rate of EIDs of concern to blood safety. Evolution of the risks of transmission by blood transfusion for HIV, HBV, and HCV. Major interventions to reduce risks are indicated below the time line on the x-axis. Emerging infectious disease threats over the past 20 years are indicated above in the top right quadrant of the figure. Ab, antibody; Ag, antigen; CHIKV, Chikungunya virus; DENV, dengue virus; HBsAg, hepatitis B surface antigen; ICL, idiopathic CD4^{+} T lymphocytopenia; PTLV, posttransplant lymphoproliferative disease; SARS, severe acute respiratory syndrome; SFV, simian foamy virus; vCJD, variant Creutzfeldt-Jakob disease; WNV, West Nile virus; XMRV, xenotropic murine leukemia virus-related virus. (*From* Perkins HA, Busch MP. Transfusion-associated infections: 50 years of relentless challenges and remarkable progress. Transfusion 2010;50:2092; with permission.)

elective procedures with the potential for blood loss, counseling on the risks of blood transfusion should be provided and steps taken to further characterize and treat anemia before surgery,[21,23] because preoperative anemia is associated with increased morbidity,[24] mortality,[25,26] and hospital length of stay.[27]

INDICATIONS FOR RED BLOOD CELL TRANSFUSION THERAPY
Pediatric Patients

A single randomized, prospective multicenter trial to evaluate a hemoglobin (Hb) "trigger" in children was published in 2007.[28] In this study, more than 600 children admitted to the pediatric intensive care units (ICU) were randomized to either a restrictive-strategy group where Hb threshold was set at 7 g/dL or a liberal-strategy transfusion group where Hb threshold was set at 9 g/dL. The investigators found that the restrictive strategy resulted in a 44% decrease in the number of packed RBC transfusions without increasing rates of new or progressive multiorgan dysfunction, the primary outcome of the study. Several secondary outcomes, including sepsis, transfusion reactions, nosocomial respiratory infections, catheter-related infections, adverse events, length of stay in the ICU and hospital,

Table 1 Transfusion-associated adverse events	
I. Infectious Agents	
Transfusion-transmitted disease routinely tested	
Hepatitis B virus (HBV; 1970 [surface antigen]; 1986–1987 [core antibody]; 2009 [nucleic acid])	1:1,000,000
HIV (1985 [antibody]; 2000 [nucleic acid])	1:2,000,000
HCV (1986–1987 [alanine aminotransferase]; 1990 [antibody]; 1999 [nucleic acid])	1:2,000,000
Human T-cell lymphotropic virus (1988 [antibody])	Very rare
West Nile virus (2003 [nucleic acid])	Very rare
Bacteria (in platelets only; 2004)	1:20,000
Trypanosoma cruzi (2007 [antibody])	Very rare
Syphilis	Very rare
Cytomegalovirus (for patients at risk)	Rare
Zika virus	Rare
Transfusion-transmitted disease not currently routinely tested	Very rare or unknown
Hepatitis A virus	
Parvovirus B19	
Dengue fever virus	
Malaria	
Hepatitis E	
Babesia sp	
Plasmodium sp	
Leishmania sp	
Brucella sp	
New variant Creutzfeldt-Jakob disease prions	
Unknown pathogens	
II. Transfusion-associated adverse reactions events	
Estimated risk per unit infused	
ABO incompatible blood transfusions	1 in 60,000
Symptoms	40%
Fatalities	1 in 600,000
Delayed serologic reactions	1 in 1600
Delayed hemolytic reactions	1 in 6700
TRALI	1 in 20,000
Graft-versus-host disease	Very rare
Posttransfusion purpura	Very rare
Febrile, nonhemolytic transfusion reactions	
RBCs	1 in 200
Platelets	1 in 5–20
Allergic reactions	1 in 30–100
Transfusion-associated circulatory overload	1 in 12
Anaphylactic reactions (Immunoglobulin A deficiency)	1 in 150,000
Iron overload	Estimated 80–100 U for adults
Transfusion-related immunosuppression	Unestablished
Storage lesions	Unestablished

Adapted from Goodnough LT. Blood management: transfusion medicine comes of age. Lancet 2013;381:1792; with permission.

and mortality were no different between the groups. The investigators recommended a restrictive RBC transfusion strategy in pediatric patients who are stable in the ICU.[28]

In addition, the TOTAL trial involving children aged 6 to 60 months presenting with severe anemia due to malaria or sickle cell disease revealed significant improvements in signs and symptoms of anemia after RBC transfusion to increase Hb concentrations from 3.7 to 7.1 g/dL.[29] Serum lactate levels decreased from 9.1 mmol/L to less than or equal to 3 mmol/L 6 hours after transfusion in 59% of children. Similarly, cerebral tissue oxygen saturation, as measured by near-infrared spectrometry, increased by more than 5% at the completion of transfusion. Furthermore, rates of stupor or coma were reduced by half, whereas respiratory distress decreased by 60%. These findings suggest that tissue perfusion with Hb concentrations of 7 g/dL may be sufficient in this population.

Other randomized trials investigating Hb thresholds have been completed or are underway in neonates.[30–32] The Prematures in Need of Transfusion study[30] suggested that liberal RBC transfusions were beneficial to neurocognitive outcomes of premature infants at 18 to 22 months, in contrast to a randomized clinical trial that showed poorer neurologic outcomes at 7- to 10-year follow-up for those premature infants who were transfused liberally.[31] The Transfusion of Prematures trial is underway to address these conflicting results.[32] In a survey of pediatric centers from Children's Oncology Group, 60% of centers used a transfusion trigger of Hb 8 g/dL, whereas 25% of centers used 7 g/dL.[33]

The notable exception in which liberal RBC transfusions have been found to be superior for improved clinical outcomes is in children with sickle cell anemia, who have overt stroke or abnormal transcranial Doppler ultrasonography and who are managed with chronic blood transfusions to keep the percentage of sickle cell hemoglobin less than 30% and the total Hb level at approximately 10 g/dL.[34,35] Interruption of such aggressive transfusion therapy when children reach the age of 18 to 20 years during transition of care to adult medical services has been described as associated with increased mortality and overt stroke events.[36]

Adult Patients

Symptomatic manifestations in medical anemias generally occur when the Hb is less than two-thirds of normal (ie, <9–10 g/dL), because basal cardiac output increases with anemia and is manifested by symptoms of increased cardiac work.[37] The historical practice was to correct mild to moderate anemia with RBC transfusions in order to treat these signs and symptoms or to transfuse blood prophylactically. The view at that time was reflected in one publication that stated "when the concentration of hemoglobin is less than 8 to 10 g/dL, it is wise to give a blood transfusion before operation."[38]

This readjustment of the transfusion trigger from an Hb of 10 g/dL to a somewhat lower threshold was triggered by concern over blood risks, particularly HIV; accompanied by the realization in populations such as Jehovah's Witness patients, who decline blood transfusions because of religious beliefs, that morbidity and mortality do not increase until the Hb is very low.[39] Data from this population indicate that the critical level of hemodilution, as defined as the point at which oxygen consumption starts to decrease because of insufficient oxygen delivery, occurs at an Hb level of approximately 4 g/dL,[40] which was corroborated in a recent study of RBC transfusions in Ugandan children with SS anemia or malaria.[29]

For anemic patients known to have cardiovascular disease (CVD), perioperative mortality has been reported to be increased significantly, when compared with

patients not known to have CVD.[41] Management of anemia and the Hb threshold for RBC therapy should therefore be different for these patients. A post hoc analysis of one study[42] was accompanied by an editorial observing that "survival tended to decrease for patients with pre-existing heart disease in the restrictive transfusion strategy group, suggesting that critically ill patients with heart and vascular disease may benefit from higher Hb."[43] Previously published clinical practice guidelines concluded "the presence of coronary artery disease likely constitutes an important factor in determining a patient's tolerance to low Hb."[44] A retrospective analysis of 79,000 elderly patients (>65 years of age) hospitalized with acute myocardial infarction (MI) in the United States found that blood transfusion in patients whose admission hematocrit values were less than 33% was associated with significantly lower mortalities.[45] A more aggressive use of blood transfusion in the management of anemia in elderly patients with cardiac disease might well be warranted.[6,46]

There are an increasing number of randomized, controlled trials in adults providing level I evidence for blood transfusion practices. A previous systematic review of the literature to year 2000 identified 10 trials.[47] The investigators concluded at that time that the existing evidence supported the use of restrictive transfusion triggers in patients who were free of serious cardiac disease. A Cochrane systematic review of prospective randomized trials to 2012[48] compared "high" versus "low" Hb thresholds of 19 trials involving a total of 6264 patients. The investigators found that (1) "low" Hb thresholds were well tolerated; (2) RBC transfusions were reduced by 34% (confidence interval [CI] 24%–45%) in patients randomized to the "low" Hb cohorts; and (3) the number of RBC transfusions was reduced by 1.2 units (CI 0.5–1.8 units) in the "low" Hb cohorts. A more recent meta-analysis found that a restrictive RBC transfusion strategy aiming to allow an Hb concentration as low as 7 g/dL reduced cardiac events, rebleeding, bacterial infections, and mortality.[15]

There are 7 key randomized, clinical trials in adult patients that compare "restrictive" versus "liberal" RBC transfusion strategies in various clinical settings (**Table 2**). The Transfusion Requirements in Critical Care (TRICC) trial[49] found that intensive care patients could tolerate a restrictive transfusion strategy (Hb range 7–9 g/dL, 8.2 g/dL on average) as well as patients transfused more liberally (Hb range 10–12 g/dL, 10.5 g/dL on average), with no differences in 30-day mortalities. Similarly, in the Transfusion Requirements in Septic Shock trial[50] of lower (<7 g/dL) versus higher (<9 g/dL) Hb thresholds for transfusion in patients with septic shock, equivalent 90-day mortalities (43 vs 45%, respectively) were found for patients in the 2 cohorts. However, a retrospective study of 2393 patients[51] consecutively admitted to the ICU found that an admission hematocrit less than 25%, in the absence of transfusion, was associated with long-term mortality; so that there may be hematocrit levels below which the risk-to-benefit imbalance for transfusion reverses.

The Transfusion Requirements after Cardiac Surgery (TRACS) trial[52] was a large, single-center study of patients randomized to receive either restrictive (hematocrit >24%) or liberal (hematocrit >30%) RBC transfusions postoperatively. Thirty-day all-cause mortality was not different (10% vs 11%, respectively) between the 2 cohorts. The FOCUS trial found that elderly (mean >80 years of age) patients who underwent repair of hip fracture surgery tolerated an Hb trigger without RBC transfusions postoperatively to as low as 8 g/dL (or higher with transfusions, if symptomatic).[53] Subsequently, a single-center prospective study[54] of patients with upper gastrointestinal bleeding demonstrated that patients randomized to a restrictive (Hb <7 g/dL) versus a liberal (Hb <9 g/dL) Hb threshold for blood transfusions had significantly improved outcomes, including mortality at 45 days and rates of rebleeding.

Table 2
Seven key clinical trials in adults of red blood cell transfusion in adults

Clinical Setting (Ref)	Hemoglobin Threshold (g/dL)	Mean Age (y)	Patients Transfused (%)	Deviation from Transfusion Protocol (%)	Mean Hemoglobin (g/dL)[a]	Participation of Eligible Patients (%)
Intensive care[49]	7	57.1	67	1.4	8.5	41
	10	58.1	99	4.3	10.7	
CT surgery[52]	8	58.6	47	1.6	9.1	75
	10	60.7	78	0.0	10.5	
Hip fracture repair[53]	8	81.5	41	9.0	7.9	56
	10	81.8	97	5.6	9.2	
Acute upper GI bleeding[54]	7	NA	49	9.0	7.3	93
	9	NA	86	3.0	8.0	
Symptomatic coronary artery disease[55]	8	74.3	28.3	1.8	7.9	12.2
	10	67.3	NA[b]	9.1	9.3	
Sepsis trial[50]	7	67.0	64	5.9	7.7	82
	9	67.0	99	2.2	9.3	
TITR[56]	7.5	69.9	53.4	30	8–9	98
	9	70.8	92.2	45	9.2–9.8	

Abbreviations: CAD, coronary artery disease; CT, cardiothoracic; TITR, Transfusion Indication Threshold Reduction.
[a] Mean daily hemoglobin.
[b] NA: Not available.
From Goodnough LT, Shah N. Is there a "magic" hemoglobin number? Clinical decision support promoting restrictive blood transfusion practices. Am J Hematol 2015;90:929; with permission.

The MINT trial[55] was a pilot, feasibility study of liberal (Hb $\geq$10 g/dL) versus restrictive (Hb <8 g/dL) transfusion thresholds initiated for a planned enrollment of 200 patients with symptomatic coronary artery disease (acute coronary syndrome or stable angina undergoing cardiac catheterization), but was terminated at the end of 18 months after enrollment of only 110 patients; of eligible screened patients, only 12% were enrolled (see **Table 2**). The primary, composite outcome (death, MI, or revascularization) occurred in 10.9% of the liberal transfusion cohort, compared with 25.9% of the restrictive cohort (P = .054); mortality occurred in 1.8% and 13.0%, respectively (P = .032). In addition, the TITRe2 trial, which focused on postoperative coronary artery bypass graft and valve surgery patients, found no difference in primary outcomes of ischemic events (MI, stroke, bowel infarction, acute kidney injury) or infection (sepsis or wound infection) between restrictive (Hb <7.5 g/dL) and liberal (Hb <9 g/dL) transfusion triggers (35.1% vs 33.0%, P = .30). However, they observed more deaths in the restrictive group as compared with the liberal group (4.2% vs 2.6%, P = .045).[56] Furthermore, a recent meta-analysis stratifying study patients into "context-specific" risk groups based on patient characteristics and clinical setting found increased risk of inadequate oxygen delivery and mortality among patients with CVD undergoing cardiac or vascular surgery as well as elderly patients undergoing orthopedic surgery.[57] These trials[50,55,57] provide evidence that a more liberal transfusion practice to maintain higher Hb thresholds may represent prudent management of high-risk patients who have symptomatic coronary artery disease or are undergoing cardiac surgery.

One of the important limitations of prospectively, randomized clinical trials is that patients who are eligible and who agree to participate in the study may not be particularly reflective of all patients in these clinical settings. Only 41% of the patients who were determined to be eligible for the TRICC trial[49] and 56% of patients eligible for the FOCUS trial[53] were actually enrolled in the studies, leading to concerns over selection bias; did the treating physicians accurately predict which patients would survive the study, and not enroll the others, thereby ensuring that no differences in survival outcomes would be found between treatment groups?

Another limitation is the interpretation of the "transfusion trigger" in these studies. The mean pretransfusion Hb for patients in the "restrictive" red cell transfusion arm of the TRACS trial was 9.1 g/dL (see **Table 2**). Similarly, the mean Hb for patients in the "restrictive" arm of the TRICC trial was 8.5 g/dL; yet many have interpreted this study to advocate that an Hb of 7 g/dL is appropriate for use as the transfusion trigger in critical care patients.

Clinical Practice Guidelines

The number of published clinical practice guidelines for RBC[44,58–75] transfusions attests to the increasing interest and importance of appropriate blood utilization by professional societies and health care institutions (**Table 3**). The selection of a discrete Hb as a "trigger" for RBC transfusion has been controversial.[76] The guidelines generally acknowledge the necessity of considering patient covariables or other patient-specific criteria for making transfusion decisions. Among published guidelines, it is generally agreed that transfusion is not of benefit when the Hb is greater than 10 g/dL, but may be beneficial when the Hb is less than 6 to 7 g/dL.[61–63,66–72]

An editorial[77] summarized the implications of these trials and meta-analyses with a call for a target Hb level for transfusion, stating "it is no longer acceptable to

Table 3
Clinical practice guidelines for red blood cell transfusion

	RBC Transfusion		
Year	**Society**	**Recommendations**	**Reference**
1988	National Institutes of Health Consensus Conference	<7 g/dL (acute)	JAMA 1988;260:2700.[58]
1992	American College of Physicians (ACP)	No number	Ann Int Med 1992;116:393–402.[59]
1996/2006	American Society of Anesthesiologists (ASA)	<6 g/dL (acute) No number	Anesth 1996;84:732–747.[60] Anesth 2006;105:198–208.[61]
1997/1998	Canadian Medical Association (CMA)	No number	Can Med Assoc J 1997;156: S1–24.[44] J Emerg Med 1998;16:129–31.[62]
1998	College of American Pathologists (CAP)	6 g/dL (acute)	Arch Path Lab Med 1998;122:130–8.[63]
2001/2012	British Committee for Standards in Haematology	No number 7–8 g/dL[a]	Br J Haematol 2001;113:24–31.[64] http://www.bcshguidelines. com/documents/BCSH_ Blood_Admin_-_ addendum_August_ 2012.pdf.[65]
2001	Australasian Society of Blood Transfusion	7 g/dL	http://www.nhmrc.health. gov.au.[66]
2007/2011	Society of Thoracic Surgeons (STS) Society of Cardiovascular Anesthesiologists (CVA)	7 g/dL or 8 g/dL[a]	Ann Thorac Surg 2007;83:S27–86.[67] Ann Thorac Surg 2011;91:944–82.[68]
2009	American College of Critical Care Medicine Society of Critical Care Medicine	7 g/dL 7 g/dL	Crit Care Med 2009;37:3124–57.[69] J Trauma 2009;67:1439– 42.[70]
2011	Society for the Advancement of Blood Management	8 g/dL	Trans Med Rev 2011;232– 246.[71]
2012	National Blood Authority, Australia	No number	http://www.nba.gov.au/ guidelines/review.html.[75]
2012	AABB	7–8 g/dL or 8 g/dL[b]	Ann Int Med 2012;157:49–58.[72]
2012	Kidney Disease: Improving Global Outcomes[c]	No number	Kid Int 2012;2:311–316.[73]
2012	National Cancer Center Network (NCCN)	7–9 g/dL	JNCCN 2012;10:628–53.[74]

[a] For patients with acute blood loss.
[b] For patients with symptoms of end-organ ischaemia.
[c] Acute coronary syndrome or cardiac bypass patients.

From Goodnough LT, Levy JH, Murphy MF. Concepts of blood transfusion in adults. Lancet 2013;381:1848; with permission.

recommend that we transfuse using vague approaches such as clinical judgment or in the hope of alleviating symptoms." However, this approach would use transfusion to treat laboratory numbers, rather than patients, and would risk overinterpreting available evidence for a "transfusion trigger" and risk underestimating both the heterogeneity of anemias (eg, acute vs chronic) and the heterogeneity of patients (ie, comorbidities). Given the increasing evidence that shows blood transfusions are poorly effective and possibly harmful, the guiding principle for transfusion therapy should be that "Less is More.". The AABB[78] and the ASH[79] have published recommendations from the American Board of Internal Medicine's *Choosing Wisely* campaign advocating single-unit RBC transfusions for nonbleeding hospitalized patients, which nearly 25 years ago had previously been recommended by the American College of Physicians (ACP).[80] Additional RBC units should be prescribed only after reassessment of the patient between transfusion decisions.

Improving Blood Utilization

Both the pediatric[81] and the adult hospital[82,83] at Stanford Health Care (SHC) have reduced blood use by using computerized physician order entry (POE) process for blood transfusions. The Hb concentration threshold for blood transfusions decreased after clinical effectiveness teams instituted physician education and clinical decision support (CDS) in July 2010, via best practices alerts (BPA) at the time of electronic POE.[82–85] **Fig. 2** shows a subsequent analysis of trends in blood use at SHC. Overall blood component transfusions increased yearly until 2009; after the BPA was implemented in July 2010, however, RBC transfusions have decreased nearly 50% through 2015, over this same interval.[84] Clinical patient outcomes (length of stay, 30-day readmission rate, mortality) showed improvement associated with implementation of CDS for restrictive transfusion practice.
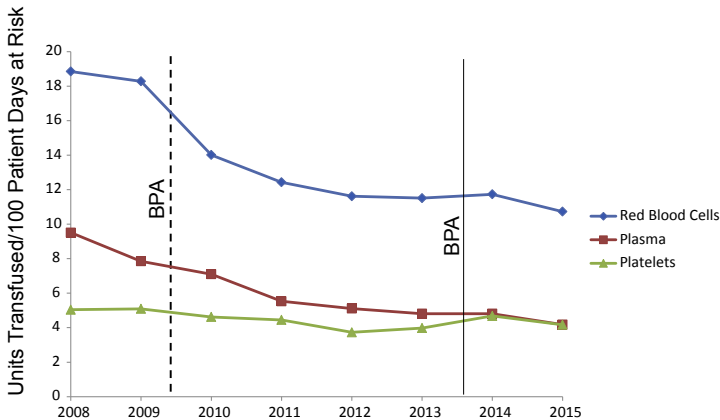
Blood components issued, 2008–2015
---- BPA (best practice alert) for RBC: July 2010
—— BPA for plasma: September 2014
Abscissa shows data for end of each year

Fig. 2. Blood components issued to patients at SHC. Transfusion of RBCs per 100 days at risk, decreased by 42% from 2009 through 2015. (*Adapted from* Goodnough LT, Shah N. The next chapter in patient blood management: real-time clinical decision support. Am J Clin Pathol 2014;142:743; with permission.)

Several other institutions have been able to use electronic health records to improve blood utilization, as most recently described by McKinney and colleagues.[86] In another analysis of 21 medical facilities in Kaiser Permanente Northern California and nearly 400,000 inpatients from 2009 to 2013, the incidence of RBC transfusion decreased from 14% to 10.8%, with a decline in pretransfusion Hb levels from 8.1 to 7.6 g/dL; yet 30-day mortality did not change significantly over this same time interval.[87]

Although the improvement in patient outcomes concurrent with reduction in RBC transfusions cannot be proven to be causal, it is reassuring that there was no deleterious effect on patient outcomes after hospital-wide adoption of restrictive transfusion practices.[13] A study monitoring for inappropriate undertransfusion found no evidence that cases of nonadministration of blood were unjustified.[88]

Additional benefits of the restrictive transfusion strategy included a significant improvement in the laboratory budget, with direct cost reductions of $1.6 million annually.[82] Purchase acquisition costs represents a fraction of total costs of blood transfusion that additionally include laboratory testing, reagent costs, nursing time dedicated to transfusion, and monitoring. An activity-based cost summary of blood transfusions estimates that total costs related to transfusion are 3.2 to 4.8 times the purchase costs.[19] Hence, the total transfusion-related savings potentially surpasses $30 million, over a 4-year period. In September 2014, the authors implemented a smart BPA for plasma, triggered when the last recorded international normalized ratio (INR) is less than 1.7 to guide more appropriate plasma transfusion.

This model of concurrent real-time utilization review can be supplemented by peer performance review committees, in which analysis of providers is undertaken for transfusions outside institutional-recommended guidelines. Because up to 30% of RBC transfusions continue to occur in patients whose Hb was greater than 8 g/dL at the authors' institution, peer-performance executive committees can help reduce variability by providers within clinical services that was unchanged by the CDS, and/or help modify the CDS for known clinical exceptions. This process serves as continuous education and feedback, which is seen as vital in the success of utilization programs[89] by augmenting improvements through CDS.

Other programs have been able to use electronic health records to improve blood utilization in a different manner. One center reconfigured their POE system for non-bleeding (excluding procedural units such as operating rooms, cardiac catheterization laboratories) patients to remove single-click ordering for 2-unit RBC transfusions; the provider must select from a drop-down menu if additional RBC units are desired. The proportion of 2-unit RBC transfusions decreased from 47% before to 15% after this intervention.[90] A second center similarly reported a reduction in 2-unit RBC orders (48% to 33%) and an increase in 1-unit RBC transfusions (22% to 48%), before and after, respectively, implementation of a comprehensive education and audit program promoting restrictive transfusion practices.[91] One review concluded that although CDS can improve RBC usage, further data are needed to assess whether CDS can improve plasma and platelet use utilization.[92] The authors have been able to show a 19% reduction in plasma utilization after implementing a smart BPA for plasma orders in the context of a most recent INR result in the patient's electronic medical record (EMR), at the authors' institution.[93]

Additional opportunities to improve blood utilization are in patients undergoing surgical procedures. Because the most important predictor of the need for blood transfusion during perioperative bleeding is the patient's preoperative RBC volume, preadmission testing to include identification and correction of anemia in patients undergoing elective surgical procedures is particularly important.[21] The authors' hospital

has initiated a checklist and boarding pass "timeout" before induction of anesthesia, designed to facilitate a conversation between the surgical and anesthesiology teams for individual patients on their anticipated blood loss, cross-matched blood availability, and strategies for managing blood loss anemia; this initiative was based on a strategy described by Atul Gawande using a surgical checklist at his own institution.[94]

SUMMARY

According to the Institute of Medicine, $2.5 trillion was spent on health care, consuming 17.6% of the gross domestic product. In 2009, almost one-third of this health care expenditure was estimated to be wasteful. Transfusion therapy has been identified as one of the most overused (and inappropriate) therapeutic interventions. Reducing this waste helps improve patient outcomes by reducing unnecessary blood donor exposures. The increased adoption of EMRs and features such as CDS allows the practice of prospective, real-time monitoring of transfusion therapy in an automated fashion at the critical time of POE.

Future measures include providing the prescriber with evidence-based and practical RBC ordering options,[95] and distributing the CDS burden to personnel with the highest knowledge base to make decisions. Long term, these users will be engaged for further education or refinement of CDS for continuous quality improvement.[96]

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