

## CURRENT CONCEPTS REVIEW

# Perioperative Blood Transfusions in Orthopaedic Surgery

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- ▶ Blood transfusion after orthopaedic surgery accounts for 10% of all packed red blood-cell transfusions, but use varies substantially across hospitals and surgeons.
- ▶ Transfusions can cause systemic complications, including allergic reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, graft-versus-host disease, and infections.
- ▶ Tranexamic acid is a new cost-effective blood management tool to reduce blood loss and decrease the risk of transfusion after total joint arthroplasty.
- ▶ Current clinical evidence does not justify transfusions for a hemoglobin level of >8 g/dL in the absence of symptoms.
- ▶ Studies have also supported the use of this trigger in patients with a history or risk of cardiovascular disease.

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In the United States, 24 million blood components are administered annually<sup>1</sup>. Orthopaedics accounts for 10% of all packed red blood-cell transfusions, 39% of which are used in arthroplasty<sup>2</sup>. There are ongoing efforts to conserve blood and decrease allogeneic transfusions for patient safety and to reduce cost. A variety of approaches, including preoperative, intraoperative, and postoperative techniques, have been used; the evidence for and cost-effectiveness of these techniques vary<sup>3-7</sup>.

Despite these factors, universal transfusion criteria are lacking. Because there is no clear understanding of what level of postoperative anemia can be tolerated, there is substantial variation in transfusion protocols, which makes comparing blood-preservation strategies even more difficult. Unnecessary transfusion of packed red blood cells increases risks and costs and wastes a scarce resource<sup>8</sup>. In this article, we discuss potential complications of transfusions to underscore the risks to

patients, address strategies to decrease the need for transfusion, and review the orthopaedic literature to determine an acceptable level of postoperative anemia.

### Transfusion Complications

Historically, blood transfusions have been associated with high complication rates. In the early 1900s, ABO blood grouping brought transfusions to common practice. Since then, other blood groups, including Rh and minor antigens, have been identified. Despite screening, however, transfusion-associated morbidity and mortality persist (Tables I<sup>9,10</sup> and II<sup>11-18</sup>), and incompatibilities are the second most frequent cause of transfusion-associated mortality in the U.S.<sup>16</sup>. These complications are reviewed to highlight the risks that are predominantly associated with allogeneic packed red blood-cell transfusions but that can also occur with other blood components.

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**TABLE I Transfusion-Associated Mortality and Morbidity Divided by Complication**

Complication	Mortality (no. [%])		Morbidity (no. [%])	
	U.S.* (N = 198)	SHOT† (N = 293)	Major (N = 1264)	Minor (N = 15,357)
Hemolytic reaction	53 (27)	24 (8.2)	110 (8.7)	897 (5.8)
Allergic reaction	12 (6)	42 (14.3)	267 (21.1)	3222 (21.0)
Transfusion-related acute lung injury	74 (37)	84 (28.7)	341 (27.0)	106 (0.7)
Transfusion-associated circulatory overload	35 (18)	20 (6.8)	92 (7.3)	151 (1.0)
Graft-versus-host disease	2 (1)	27 (9.2)	0 (0)	0 (0)
Infection	21 (11)	29 (9.9)	97 (7.7)	12 (0.1)

\*Data are from the U.S. Food and Drug Administration cumulative reporting of transfusion-related mortalities from 2008 to 2012<sup>10</sup>. †Data are from the cumulative reports of Serious Hazards of Transfusion (SHOT), the U.K. hemovigilance system, from 2008 to 2012, for mortality and major and minor morbidity<sup>9</sup>.

### Allergic Reaction

Allergic reactions can be caused by many factors in the transfused product, including blood components such as plasma proteins, processing chemicals, and cytokines. Reactions to transfused packed red blood cells (0.15% to 15%) are a common source of morbidity<sup>12</sup>.

Clinical manifestations range in severity from urticaria to anaphylaxis. Less severe reactions are often treated with diphenhydramine, whereas more severe cases usually require corticosteroids, and anaphylaxis requires epinephrine<sup>12</sup>. There is little evidence suggesting that pretransfusion administration of acetaminophen and diphenhydramine prevents such reactions. One randomized controlled trial of pretransfusion use of these medications found no difference in transfusion reactions but a nonsignificant decreased rate of febrile reactions with pretreatment<sup>19</sup>.

### Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury is a clinical diagnosis of acute lung injury characteristically occurring within six hours of a transfusion; a subset, delayed transfusion-related acute lung injury, occurs within seventy-two hours. If other potential etiologies coexist, the response is considered a possible transfusion-related acute lung injury. Blood from donors who have been pregnant multiple times<sup>20</sup> or have had previous transfusions presents the highest risk because of increased antibodies<sup>21</sup>. Using only male plasma donors has decreased transfusion-related acute lung injury rates by >60%<sup>22,23</sup>. The National Institutes of Health Blood Bank allows AB plasma donation only from men<sup>24</sup>.

The prevalence of transfusion-related acute lung injury has been reported to range from 0.08% to 15%, and its associated mortality is from 5% to 10%<sup>15,17,18</sup>. Of all transfusion complications, it is associated with the highest mortality and major morbidity<sup>1</sup>. A randomized clinical trial showed that restrictive transfusion strategies decreased this complication from 11.4% (forty-eight of 420 patients) to 7.7% (thirty-two of 418 patients)<sup>25</sup>.

Patients can present with respiratory distress, tachycardia, fever, hypothermia, and hypotension. Anaphylactic reactions can be similar, but transfusion-related acute lung injury has no urti-

caria, and chest radiographs show pulmonary edema. Transfusion-related acute lung injury is treated with supportive measures, with 70% to 90% of patients requiring mechanical ventilation<sup>18</sup>.

### Transfusion-Associated Circulatory Overload

Transfusion-associated circulatory overload results in pulmonary edema from fluid overload<sup>11</sup>. According to the definition of the Public Health Agency of Canada, transfusion-associated circulatory overload occurs within six hours after a transfusion, but cases can occur up to twenty-four hours<sup>26</sup>. In the last decade, the prevalence has increased, with rates reported to range from 1% to 8% for patients undergoing hip and knee arthroplasty and from 6% to 11% for patients in the intensive care unit<sup>11,14</sup>. The overall mortality rate has been reported to be as high as 2% to 15%<sup>11,14-16</sup>.

Risk factors include increasing age, positive fluid balance, left ventricular dysfunction, renal dysfunction, acute myocardial infarction, chronic pulmonary disease, acute and chronic anemia, plasma transfusion, and multiple blood product transfusions<sup>11,15</sup>. Patients at age extremes are at greatest risk: 64% of patients who have transfusion-associated circulatory overload

**TABLE II Prevalence and Mortality Rates of Transfusion Complications**

Complication	Prevalence (%)	Mortality (%)
Allergic reaction	0.15 to 15*	<1*
Transfusion-related acute lung injury <sup>15,17,18</sup>	0.08 to 15	5 to 10
Transfusion-associated circulatory overload	1 to 11†	2 to 15‡
Graft-versus-host disease <sup>13</sup>	<1	84 to 100§

\*Data are from Hirayama<sup>12</sup>. †Data are from Alam et al.<sup>11</sup> and Lieberman et al.<sup>14</sup>. ‡Data are from Alam et al.<sup>11</sup>, Lieberman et al.<sup>14</sup>, Menis et al.<sup>15</sup>, and a U.S. Food and Drug Administration report<sup>16</sup>. §Mortality rates for severe reactions. Milder presentations are not diagnosed, and consequently overall mortality rates are unknown.

TABLE III Orthopaedic Studies with Data on the Odds Ratio for the Risk of Surgical Site Infection with Transfusion

Study	Level of Evidence	Patient Group	SSI Criteria*	Transfusion a Risk Factor for SSI*	
				Y/N	Odds Ratio
Garcia-Alvarez et al. <sup>34</sup> (2010)	II	Subcapital femoral neck fractures	CDC	Y	1.96
Morris et al. <sup>36</sup> (2003)	II	Lower extremity oncologic	Erythema or purulent drainage in 30 days	Y	
Thanni and Aigoro <sup>37</sup> (2004)	III	Internal fixation of long bone fractures	Purulent discharge or culture positive nonpurulent discharge	N	
Ho et al. <sup>35</sup> (2007)	III	Adolescent idiopathic scoliosis posterior spinal arthrodesis	Delayed infection of >6 m	Y	
Schwarzkopf et al. <sup>33</sup> (2010)	III	Thoracic and lumbar spinal surgery	CDC criteria within 30 days	Y	8.02
Woods et al. <sup>38</sup> (2013)	III	Lumbar spinal surgery	CDC criteria within 30 days	N†	
Newman et al. <sup>39</sup> (2014)	III	Primary total hip and knee arthroplasty	Reoperation for suspected infection within 3 mo of index surgery	Y	2.85

\*SSI = surgical site infection, and CDC = Centers for Disease Control and Prevention definition of infection<sup>40</sup>. †Transfusion was not found to be a risk factor for SSI, but a volume-dependent increased odds was noted.

are seventy years or older<sup>11</sup>. Frequently seen symptoms include dyspnea, hypoxemia, orthopnea, hypertension, tachycardia, and congestive heart failure<sup>11,15</sup>.

The risk of this complication is reduced with pretransfusion fluid overload evaluation<sup>14</sup>, slow transfusion speed (<120 mL/hr)<sup>11</sup>, and transfusion of a single unit<sup>11</sup>. For patients with congestive heart failure and renal dysfunction, transfusions should be given during dialysis. Trials support pretransfusion furosemide usage, but ideal dosing has not been determined<sup>11,14</sup>. As opposed to post-transfusion administration, pretransfusion use maximizes diuretic effectiveness<sup>11</sup>.

Intravenous furosemide is a first-line treatment, after which afterload reducers, including angiotensin-converting enzyme inhibitors, hydralazine, and nitroglycerin, are used<sup>11</sup>.

#### Venous Thromboembolism

Studies have suggested an increased risk of deep venous thrombosis (DVT) and pulmonary embolism with transfusion<sup>27,28</sup>. A database study of patients with colorectal resection showed a significant dose-dependent increased rate of venous thromboembolism (VTE) at thirty days, with VTE developing in 1.8% (353) of 19,588 patients who had no transfusion, 3.7% (sixty-five) of 1751 patients who had one to two units, 4.9% (twenty-three) of 466 patients who received three to five units, and 9.4% (thirteen) of 138 patients who had transfusion of six or more units<sup>27,28</sup>. There is evidence to suggest that autologous predonation of blood leads to fewer DVTs<sup>29,30</sup>. These studies suggest that a combination of decreased preoperative hematocrit and depletion of other unaccounted blood proteins may explain the decreased rate of DVTs.

#### Graft-Versus-Host Disease

Graft-versus-host disease presents along a spectrum of severity, with mild presentations being unrecognized and severe reactions having high mortality rates (84% to 100%)<sup>13</sup>. In graft-versus-host disease, donor T lymphocytes proliferate (sometimes for years), leading to immune reactions against antigens in the recipient. Major risk factors are immunosuppression, similar donor and recipient human leukocyte antigen haplotypes, cardiopulmonary bypass with cardiothoracic surgery, and newer blood products. Newer blood products (less than four days from donation) and products not irradiated or leukoreduced are higher risk because T-cell survival and function are greater.

Clinical manifestations occur two to thirty days after a transfusion and include fever, skin blistering, diarrhea, hepatitis, and marrow aplasia. The end stage is multiorgan failure, marrow failure, infection, and bleeding<sup>13</sup>. Management is supportive. Immunosuppressive medications are not effective, and the effectiveness of antibiotics is unknown. Blood irradiation and leukoreduction decrease the risk of graft-versus-host disease, with irradiation being more effective<sup>13</sup>. U.S. blood products are irradiated if a patient is at risk for graft-versus-host disease, a family member donates, or cross-matching requires a strong human leukocyte antigen similarity<sup>13</sup>.

#### Blood-Borne Infections

Before the recognition of human immunodeficiency virus and hepatitis, blood transfusions resulted in many new infections. Extensive screening has since been implemented to prevent transfusion of infected blood. Per U.S. Food and Drug Administration (FDA)

TABLE IV Orthopaedic Studies with Data on Surgical Site and Overall Infection Rates with and without Allogeneic Blood Transfusion\*

Study	Level of Evidence	Patient Group	SSI Criteria	No. of Patients	SSI Rate (No Transfusion vs. Transfusion) (%)	Overall Infection Rate (No Transfusion vs. Transfusion) (%)
Basora et al. <sup>42</sup> (2010)	II	Primary TKA	CDC criteria <sup>40</sup>	910	6.8 vs. 6.6	NR
Drosos et al. <sup>43</sup> (2012)	II	Primary TKA	Pyrexia and erythema, swelling, and/or drainage on POD 4	248	7.1 vs. 18.3; AT, 8.7	NR
Innerhofer et al. <sup>45</sup> (2005)	II	Primary THA and TKA	Purulent drainage and painful erythema	286	1.0 vs. 3.0†; AT, 0	6.9 vs. 13.3†; AT, 1.2†
Innerhofer et al. <sup>46</sup> (1999)	II	Primary or revision THA or TKA, spine surgery, and pelvic surgery	Purulent exudate	317	NR	4.7 vs. 14.8†; AT, 3.5†
Llewelyn et al. <sup>48</sup> (2004)	II	Primary or revision THA or TKA§ before and after LR	Purulent discharge	1477 before LR and 1436 after LR	3.6 vs. 7.1 before LR†; 2.8 vs. 5.0 after LR†	9.1 vs. 15 before LR†; 9.4 vs. 11.9 after LR†
Shander et al. <sup>49</sup> (2009)	II	Primary or revision THA or TKA, partial hip arthroplasty, and shoulder arthroplasty	CDC criteria <sup>40</sup>	900	NR	2.0 vs. 6.1†; AT, 1.2
Levi and Sandberg <sup>47</sup> (1998)	III	Femoral neck fractures	Culture positive or frank pus	695	3.7 vs. 7.1†	NR
Steinitz et al. <sup>41</sup> (2001)	III	Primary THA	NR	1206	NR	8.4 vs. 14.3†; AT, 0#
Friedman et al. <sup>44</sup> (2014)	III	Primary THA and TKA	Coded as wound inflammation or infection	12,177	1.7 vs. 2.4; AT, 1.3	8.0 vs. 9.9; AT, 7.3

\*SSI = surgical site infection, TKA = total knee arthroplasty, THA = total hip arthroplasty, CDC = Centers for Disease Control and Prevention, NR = not reported, AT = transfused with autologous blood, POD = postoperative day, and LR = leukoreduction. †Study did not evaluate the significance of this comparison. ‡Significant differences. §Study included cardiac patients, and the numbers for orthopaedic patients were separately extracted for this table. #Only eleven patients received autotransfusion.

regulations, all blood is screened for hepatitis B and C, human immunodeficiency virus, human T-lymphotrophic virus, syphilis, West Nile virus, and Chagas disease<sup>31</sup>. However, blood products may contain diseases not tested for such as chikungunya, malaria, other viruses, bacteria, parasites, and prions<sup>31-33</sup>.

### Immunomodulation

There is increased concern about the effects of blood transfusions on the immune system (immunomodulation). Transfusion recipients are more susceptible to pneumonia, urinary tract infection, and surgical site infections. Irradiation, leukoreduction timing, and blood storage time may minimize these risks.

Seven studies specific to orthopaedics have described the odds ratio of surgical site infections with transfusion (Table III)<sup>33-40</sup>. Five studies (two with Level-II evidence and three with Level-III) found transfusions were associated with surgical site infection (odds ratio, 1.96 to 8.02)<sup>33-36,39</sup>; two Level-III studies found no association<sup>37,38</sup>. Ho et al.<sup>35</sup> found that delayed infection (six months) after spinal arthrodesis for adolescent idiopathic scoliosis was associated with perioperative blood transfusions. Newman et al.<sup>39</sup> reported that allogeneic transfusion was associated with increased odds (odds ratio, 2.85) of reoperation for infection within three months of primary hip and knee arthroplasty. Multiple studies found a significant dose-dependent

increase in both surgical site and overall infections with transfusion<sup>34,35,38,41</sup>.

Another nine studies of orthopaedic patients described the rates of surgical site infection and/or overall postoperative infections (urinary tract infection, pneumonia, and surgical site infection) (Table IV)<sup>40-49</sup>. The studies generally found significantly greater surgical site<sup>43-45,47,48</sup> and overall infection rates with transfusion<sup>41,44-46,48,49</sup>. Some studies showed similar rates of infection between patients who had no transfusion and those who received autologous units<sup>41,44-46,49</sup>, suggesting that a mechanism independent of storage may be responsible for immunomodulation. The surgical site infection rate was 1.0% to 7.1% for patients who had no transfusion, 0% to 8.7% for autologous transfusion, and 2.4% to 18.3% for allogeneic transfusion<sup>42-45,47,48</sup>. The overall infection rate was 2.0% to 9.4% for patients who had no transfusion, 0% to 7.3% for those who had autologous transfusion, and 6.1% to 14.8% for those who had allogeneic transfusion<sup>41,44-46,48,49</sup>.

In summary, most studies in orthopaedics have suggested allogeneic transfusions are associated with greater infection rates. Those studies<sup>33-38,41-49</sup> are limited by being observational, and the need for a transfusion may be a marker for patients prone to infections. Although the studies adjusted for comorbidities, other factors may have been responsible. The lower rates with autologous transfusion warrant further investigation.

TABLE V Strategies to Reduce the Need for Transfusion

Timing	Intervention	Studies
Preoperative	Iron therapy, intravenous erythropoietin, autologous blood transfusion, and discontinuation of anticoagulation medicines (aspirin and nonsteroidal anti-inflammatory drugs)	Cherian et al. <sup>6</sup> and Slappendel et al. <sup>50</sup>
Intraoperative	Pharmacologic: fibrin sealants, desmopressin, thrombin, lavage with epinephrine or norepinephrine, epsilon-aminocaproic acid, and tranexamic acid; Nonpharmacologic: normovolemic hemodilution, hypotensive anesthesia, tourniquets, bipolar sealants, and cell saver	Aguilera et al. <sup>51</sup> , Banerjee et al. <sup>3</sup> , Cherian et al. <sup>4</sup> , Chimento et al. <sup>52</sup> , Gilbody et al. <sup>53</sup> , Martin et al. <sup>54</sup> , Thoms and Marwin <sup>55</sup> , and Yang et al. <sup>56</sup>
Postoperative	Autologous blood transfusion drains and not using drains	Jauregui et al. <sup>7</sup>

### Strategies to Reduce the Need for Transfusion

Multiple strategies have been developed to reduce blood loss and the need for transfusion by intervening preoperatively, intraoperatively, and postoperatively. Other articles have reviewed these techniques<sup>4-7</sup> (Table V)<sup>3,4,6,7,50-56</sup>. Not all have proven to be beneficial or cost-effective. Of those listed, the available literature favors the following: the preoperative use of erythropoietin in certain populations and for patients who have a preoperative hemoglobin of <10 g/dL<sup>57</sup>; the use of regional and hypotensive anesthesia<sup>5</sup>; and the intraoperative use of tranexamic acid, which is the most promising technique. Many recent studies have focused on its use in both local and systemic administrations and have found decreased blood loss and transfusion rates without evidence of significantly increased rates of complications<sup>51-54,56</sup>. However, those studies used various treatment dosages, timings, and formulations, and additional study is needed to determine the most efficacious approach.

Despite these various approaches to reduce the need for transfusion, no consensus on when to transfuse has been developed. Consequently, comparing the impact on transfusion rates across studies is difficult. Minimizing variation in transfusions thresholds will also lead to more effective use of blood.

### Transfusion Variation

On the basis of an international survey of blood utilization, orthopaedics uses 6% to 13.8% of allogeneic and autologous packed red blood cells: total hip arthroplasty uses 4.85%; total knee arthroplasty, 1.93%; and other orthopaedic surgery (not including trauma), 7.04%<sup>58</sup>. Transfusion practices vary among clinicians and hospitals. According to one 2009 study, only 47% (ninety-one) of 195 hospitals in the U.K. had transfusion protocols, and the rate of transfusions for total hip arthroplasty ranged from 0% to 100%<sup>59</sup>. A 2013 study of eighty-eight U.S. arthroplasty surgeons found differing transfusion rates: 4.8% to 63.8% for total knee and 4.3% to 86.8% for total hip procedures<sup>60</sup>. Surgeons' rationales ranged from minimizing blood use to limiting dizziness and facilitating recovery<sup>59</sup>. Even when protocols exist, they are inconsistently applied<sup>61,62</sup>. Another study examined information from the database of the University Health System Consortium (a large group of academic hospitals and their affiliates across the U.S.) from 2006 through 2010 and found that transfusion rates for primary total hip arthroplasty ranged from

1.5% to 77.8%<sup>63</sup>. The odds ratio of receiving a transfusion at a hospital with a high rate of transfusions compared with that at a hospital with an average rate of transfusions was 2.41<sup>63</sup>. A study of the U.S. Nationwide Inpatient Sample found that transfusion rates in patients undergoing total hip arthroplasty from 2005 through 2008 had increased from 18.12% to 21.21%<sup>64</sup>. Those investigators also found substantial variation in practice, with hospitals in the Northeast region having an odds ratio of 1.4 of providing a transfusion compared with all other regions<sup>64</sup>.

A systematic review of factors affecting orthopaedic transfusion decision making by Barr et al.<sup>65</sup> found that the most common factors were low hemoglobin levels and older age. However, the impact of other factors varied substantially, further indicating the wide variation in practice. Hemoglobin thresholds are often the main transfusion criteria, but the target is controversial<sup>159,65</sup>. A survey of provider practices showed wide ranges among orthopaedists, with the trigger hemoglobin levels ranging from 6 to 11 g/dL<sup>2</sup>. Barr et al.<sup>65</sup> found that a higher threshold was used for a patient with symptoms of anemia (8.5 to 12 g/dL) than for one without such symptoms (6 to 9 g/dL). Other factors predisposing to receiving a blood transfusion were lower body weight, comorbidities (rheumatoid arthritis, history of anemia, diabetes, cardiovascular disease, renal failure, or metastasis), and complexity of surgery.

### Clinical Studies on Restrictive Transfusion in Adults

Given this wide variety in practices, assessment of the rationale and evidence for transfusion is warranted to avoid unnecessary risk. Packed red blood cells are given for concerns of decreased oxygen delivery. However, the decreased viscosity of anemic blood can compensate with greater blood flow. Research indicates no clinically relevant difference in oxygen delivery for hemoglobin levels from 6 to 10 g/dL<sup>1</sup>. In studies of Jehovah's Witness patients<sup>66,67</sup>, the risk of morbidity and mortality increased only for a hemoglobin level of <7 g/dL. Goodnough et al.<sup>1</sup> suggested that cardiovascular disease or older age warrants a higher target.

Randomized controlled trials of patients in critical care, after cardiothoracic surgery, and with gastrointestinal bleeding found similar to better mortality and morbidity outcomes with restrictive (a hemoglobin level of 7 to 8 g/dL) compared with liberal (a hemoglobin level of 9 to 10 g/dL) transfusion

protocols<sup>25,68,69</sup>. A Cochrane review of medical and surgical populations noted that, compared with liberal transfusion protocols, restrictive protocols resulted in similar complication rates, significantly lower in-hospital mortality, similar thirty-day mortality, and comparable duration of stay and function assessed by ambulatory status and fatigue questionnaires<sup>70</sup>. Those authors concluded that restrictive thresholds can be used for most patients, even those with a history of cardiovascular disease<sup>70</sup>.

A systematic review of the literature identified seven studies involving orthopaedic patients that used restrictive protocols (see Appendix)<sup>71-77</sup>. The largest study, a randomized controlled trial of patients who were surgically treated for a hip fracture by Carson et al.<sup>72</sup>, had approximately 1000 patients per group. The authors conducted a pilot study of eighty-four patients with hemoglobin levels of <10 g/dL in the first three postoperative days<sup>71</sup>. The patients were randomized to a liberal (10 g/dL) or restrictive (8 g/dL or symptoms of anemia) transfusion group. There was no difference in ability to walk 10 ft (3 m) or in mortality rates at sixty days. No significant difference was found in outcome between these groups or in the subgroup of patients with cardiovascular disease<sup>71</sup>. Using these results, a larger study (2000 patients) was powered to 90% to detect an absolute 8% intergroup difference<sup>72</sup>. The inclusion criteria were refined to only patients with history of, or risk factors for, cardiovascular disease. Despite this sicker population, no significant difference was found in the primary outcome of mortality and inability to walk. No significant differences were found with respect to mortality rates at thirty and sixty days, complications, duration of stay, functional activity, surgical site infection, or DVT and pulmonary embolism. The restrictive transfusion protocol used only one-third the number of packed red blood-cell units used by the liberal protocol<sup>72</sup>.

Another randomized controlled trial of 120 patients with a hip fracture focused on the ability to walk, comparing liberal (10 g/dL) and restrictive (8 g/dL) transfusion thresholds<sup>73</sup>. Despite randomization, the two groups had different baseline characteristics: the restrictive group had higher American Society of Anesthesiologists scores and number of screw fixations, whereas the liberal group had more sliding hip screws and intramedullary devices. No difference was found in functional outcome (walking ability, duration of stay, and number of patients achieving independent walking) except for patient-reported fatigue scores on postoperative day 2. However, the restrictive group had significantly more cardiovascular complications (10% versus 2%) and thirty-day mortality (8% versus 0%).

Other studies have evaluated patients who had total hip and knee arthroplasties<sup>74-77</sup>. Three of the studies were limited by inconsistent baseline comparison protocol<sup>75-77</sup> and variations at different test sites for a multisite trial<sup>76,77</sup>. In fact, one of the studies<sup>77</sup> found a 39% increase in the transfusion rate with the new so-called restrictive protocol at one of the study sites. Consequently, these researchers performed a post hoc analysis of their data by switching the patient classification in that hospital such that the new protocol was considered liberal because it was less restrictive than the established protocol. Patient classification in the other hospitals remained the same. With this recategorization, they found that the restrictive group

**TABLE VI Grades of Recommendation for Summaries or Reviews of Orthopaedic Surgical Studies\***

Recommendation	Grade of Evidence*
Limit transfusion of allogeneic packed red blood cells to patients who have a hemoglobin level of <8 g/dL or symptomatic anemia.	A
Avoid transfusion of allogeneic packed red blood cells because it can increase the risk of infection.	B
Avoid transfusion of packed red blood cells because it can increase deep venous thrombosis and pulmonary embolism rates.	I
*Grade A indicates good evidence (Level-I studies with consistent findings) for or against recommending the intervention; Grade B, fair evidence (Level-II or III studies with consistent findings) for or against recommending the intervention; Grade C, conflicting or poor-quality evidence (Level-IV or V studies) not allowing a recommendation for or against the intervention; and Grade I, there is insufficient evidence to make a recommendation <sup>78</sup> .	

had significantly reduced blood usage (26.4% versus 39.1%) and significantly lower infection rates (5.4% versus 10.2%), specifically urinary tract infections (8% versus 12%) and surgical site infection (2% versus 9%). Similar to the study by Carson et al.<sup>72</sup>, no difference was detected in functional outcomes measured, that is, quality of life and fatigue<sup>76</sup>.

Grover et al.<sup>74</sup> focused on identifying silent myocardial ischemia in patients with total knee and hip arthroplasties with protocols similar to those in the study by Carson et al.<sup>72</sup>. Patients more than fifty-five years old were monitored from twelve hours before until three days after surgery to identify electrocardiographic changes. Patients with certain cardiovascular history were excluded because of the difficulty of identifying electrocardiographic changes. There was no difference in the number of silent ischemic events, but when ischemic, the liberal group had a significantly greater ischemic load (minutes of ischemia on a Holter monitor divided by total monitoring time). Sufficient power was lacking for conclusive evidence. No differences in duration of stay or complications were found<sup>74</sup>.

Many studies are severely limited compared with the study by Carson et al.<sup>72</sup> because they did not restrict patient enrollment to those who would definitely receive a transfusion in the liberal protocol. The other studies contained, in both groups, patients with a hemoglobin level of >10 g/dL who would not receive a transfusion under either protocol. Additionally, multiple studies are hindered by inconsistent preintervention protocols<sup>75-77</sup>.

Overall, Grade-A evidence<sup>78</sup> supports using a restrictive hemoglobin transfusion trigger of 8 g/dL or symptomatic anemia for patients with or without a history of cardiovascular disease because there is no impact on cardiovascular complications, rehabilitation, or duration of stay (Table VI). Grade-B evidence<sup>78</sup> suggests that transfusions increase infection rates. In

their review, Carson et al.<sup>70</sup> found a nonsignificant 19% decrease in infection rates with restrictive protocols. Grade-I evidence<sup>78</sup> supports the association between transfusions and VTEs.

Slappendel et al.<sup>50</sup> conducted an analysis of their database of information on orthopaedic patients and standardized their perioperative management to minimize blood transfusions. Their interventions included iron and/or erythropoietin pretreatment for certain patients, stopping aspirin and nonsteroidal anti-inflammatories, perioperative normothermia, postoperative blood salvage, use of aprotinin (aprotinin is no longer approved in the U.S., and this study was conducted before the introduction of tranexamic acid), and consistent use of a restrictive transfusion trigger. They found that the transfusion rate was reduced from 34% to 7% and the rate of deep wound infections from 2.6% to 1.5%<sup>50</sup>. Their report showed that implementation of a consistent transfusion protocol leads to improved results, and current data on various transfusion interventions should be used in constructing an institution's protocol.

Transfusion of packed red blood cells has multiple associated complications and may place patients at greater risk for infections, including surgical site infections. Although there are many techniques for minimizing the need for a transfusion, there is substantial variation in transfusion practices with no universally accepted protocol at the present time. Current evidence suggests that a restrictive protocol (a hemoglobin

level of <8 g/dL) is not detrimental to patient outcomes and can decrease the risk of infection and cost. More conservative transfusion protocols should be adopted and integrated with the use of blood preservation techniques in a standardized fashion, similar to the work of Slappendel et al.<sup>50</sup>. Such standardization and critical review of practices will more efficiently use blood products, protect patients, and decrease costs.

## Appendix

 A table showing data on restrictive transfusion threshold studies in orthopaedics is available with the online version of this article as a data supplement at [jbj.org](http://jbj.org). ■

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