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Health Care–Associated Infection After Red Blood Cell Transfusion:

A Systematic Review and Meta-analysis

Jeffrey M. Rohde, MD, **Derek E. Dimcheff, MD, PhD**, **Neil Blumberg, MD**, **Sanjay Saint, MD, MPH**, **Kenneth M. Langa, MD, PhD**, **Latoya Kuhn, MPH**, **Andrew Hickner, MSI**, and **Mary A. M. Rogers, PhD**

University of Michigan, Division of General Medicine, Department of Internal Medicine, Ann Arbor (Rohde, Dimcheff, Saint, Langa, Hickner, Rogers); Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, New York (Blumberg); VA Ann Arbor Medical Center/University of Michigan Patient Safety Enhancement Program, Ann Arbor (Saint, Langa, Kuhn, Hickner, Rogers); VA Ann Arbor Health Services Research and Development Center of Excellence, Ann Arbor, Michigan (Saint, Langa, Kuhn); Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor (Saint, Langa, Rogers).

Abstract

IMPORTANCE—The association between red blood cell (RBC) transfusion strategies and health care–associated infection is not fully understood.

OBJECTIVE—To evaluate whether RBC transfusion thresholds are associated with the risk of infection and whether risk is independent of leukocyte reduction.

DATA SOURCES—MEDLINE, EMBASE, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, Cochrane Database of Sytematic Reviews, ClinicalTrials.gov, International Clinical Trials Registry, and the International Standard Randomized Controlled Trial Number register were searched through January 22, 2014.

Corresponding Author: Mary A. M. Rogers, PhD, Patient Safety Enhancement Program, Department of Internal Medicine, University of Michigan, 016-422W NCRC, Ann, Arbor, MI 48109-2800, (maryroge@umich.edu)..

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Study concept and design: Rohde, Dimcheff, Saint, Rogers.
Acquisition, analysis, or interpretation of data: Rohde, Dimcheff, Blumberg, Saint, Langa, Kuhn, Hickner, Rogers.
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Correction: This article was corrected on October 15, 2014, to fix errors in the data.

STUDY SELECTION—Randomized clinical trials with restrictive vs liberal RBC transfusion strategies.

DATA EXTRACTION AND SYNTHESIS—Twenty randomized trials with 8598 patients met eligibility criteria, of which 17 trials (n = 7456 patients) contained sufficient information for meta-analyses. DerSimonian and Laird random-effects models were used to report pooled risk ratios. Absolute risks of infection were calculated using the profile likelihood random-effects method.

MAIN OUTCOMES AND MEASURES—Incidence of health care–associated infection such as pneumonia, mediastinitis, wound infection, and sepsis.

RESULTS—The pooled risk of all serious infections was 10.6% (95% CI, 5.6%-15.9%) in the restrictive group and 12.7% (95% CI, 7.0%-18.7%) in the liberal group. The risk ratio (RR) for the association between transfusion strategies and infection (serious infections and selected infections, combined) was 0.92 (95% CI, 0.82-1.04) with little heterogeneity (I^2 = 6.3%; τ^2 = .0041). The RR for the association between transfusion strategies and serious infection was 0.84 (95% CI, 0.73-0.96; I^2 = 0%, τ^2 <.0001). The number needed to treat (NNT) with restrictive strategies to prevent serious infection was 48 (95% CI, 36-71). The risk of infection remained reduced with a restrictive strategy, even with leukocyte reduction (RR, 0.83 [95% CI, 0.69-0.99]). For trials with a restrictive hemoglobin threshold of <7.0 g/dL, the RR was 0.86 (95% CI, 0.72-1.02). With stratification by patient type, the RR for serious infection was 0.72 (95% CI, 0.53-0.97) in patients undergoing orthopedic surgery and 0.51 (95% CI, 0.28-0.95) in patients presenting with sepsis. There were no significant differences in the incidence of infection by RBC threshold for patients with cardiac disease, the critically ill, those with acute upper gastrointestinal bleeding, or for infants with low birth weight.

CONCLUSIONS AND RELEVANCE—Among hospitalized patients, a restrictive RBC transfusion strategy compared with a liberal transfusion strategy was not associated with a reduced risk of health care–associated infection overall, although it was associated with a reduced risk of serious infection. Implementing restrictive strategies may have the potential to lower the incidence of serious health care–associated infection.

Efforts to prevent health care–associated infection are among the priorities for the US Department of Health and Human Services[1] with the focus on common activities in the hospital setting, such as using bundles (defined as groups of effective practices) and checklists to prevent central line–associated bloodstream infection,[2] encouraging hand hygiene,[3] and avoiding the use of urinary catheters.[4] The estimated annual direct medical costs of health care– associated infections to US hospitals ranges from $28 billion to $45 billion, with about 1 in every 20 inpatients developing an infection related to their hospital care.[5]

Transfusion of red blood cells (RBCs) is a common inpatient therapy, with approximately 14 million units transfused in 2011 in the United States, 84.8% of which were leukocyte reduced.[6] Although direct transmission of infectious agents via allogeneic RBC transfusion is quite low in developed countries, transfusion is associated with immunomodulation, which may affect infection risk.[7-9] Although elevation of inflammatory markers seen in transfusion-related immunomodulation may be ameliorated through leukocyte reduction, other approaches to blood management include lowering the hemoglobin thresholds at

which RBC transfusions are indicated, so-called restrictive threshold strategies. Patient blood management (PBM) has been described as an evidence-based, multidisciplinary approach to optimizing the care of patients who might need a transfusion.[6] Such PBM interventions have been tested in randomized trials, including several recent trials.[10,11] We conducted a systematic review and meta-analysis of the randomized trials that incorporated 2 comparator groups—restrictive vs liberal RBC transfusion strategies—to evaluate their association with the incidence of health care–associated infection. In addition, we studied whether this association persisted when restricted to patients who received leukocyte-reduced RBC units.

Methods

Data Sources and Searches

We followed methods defined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines statement.[12] Eligibility criteria included the following requirements: (1) randomized trial, (2) use of 2 comparator groups in which 1 group received a restrictive RBC trans-fusion strategy and the other group received a liberal RBC transfusion strategy, and (3) infectious outcomes after randomization were reported. There were no restrictions regarding patient age or conditions.

The search sources included MEDLINE, EMBASE, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, ClinicalTrials.gov, International Clinical Trials Registry, and the International Standard Randomized Controlled Trial Number register. The search strategy began with specifications as outlined in the Cochrane review of transfusion thresholds for guiding allogeneic RBC transfusions[13]; specific search terms are listed (eTable 1 in the Supplement). No restrictions were placed on language or type of publication. Boolean search terms were used to capture the comparators relevant to transfusion thresholds, strategies, triggers, protocols, practices, policies, criteria, or standards. The date of the last search was January 22, 2014. A medical librarian with experience in searching for systematic reviews assisted.

Study Selection

Study selection was conducted through independent review. Two teams of independent reviewers (J. R. and D. D.; L. K. and M. A. M. R.) examined abstracts for eligibility based on study design (randomized trial) and comparators (RBC transfusion strategies). To divide the work effort, the first team reviewed entries prior to February 6, 2013, and the second team reviewed entries from February 6, 2013, to January 22, 2014. For publications with team member disagreement, the full-text articles were obtained and eligibility was determined through consensus. Trials that did not contain infectious outcomes were excluded, as well as studies with duplicate samples, ineligible comparators, and studies that described the methods of the trials but did not report results.

Data Extraction and Quality Assessment

A data extraction form was developed prior to manuscript review. It contained descriptive information regarding the study, as well as data regarding enrollment, randomization, hemoglobin thresholds, RBC transfusion use, quality (concealment of randomization, blinding, loss to follow-up, and protocol violations), funding, and infectious outcomes. Concealment of randomization was defined as (1) a direct statement of concealment, (2) use of centralized randomization at a coordinating center in trials with multiple sites, or (3) randomization by an independent statistician. Extraction of data was conducted independently by 2 investigators, with subsequent discussion and resolution of discrepancies by consensus.

Data Synthesis and Analysis

For each study, risk ratios were calculated comparing the cumulative risk of infection in the restrictive RBC transfusion group (numerator) to the cumulative risk of infection in the liberal RBC transfusion group (denominator). The DerSimonian and Laird random-effects model was used for pooling the risk ratios across studies. For 1 study,[14] a hazard ratio was reported and it was used to approximate the risk ratio of infection; a sensitivity analysis was completed with and without the inclusion of this study. Absolute risks of infection for the restrictive group and for the liberal group were pooled using the profile likelihood random-effects method with variance stabilized using the enhanced Freeman-Tukey arcsine transformation.[15,16] The profile likelihood method has demonstrated better performance than the DerSimonian and Laird method when there is heterogeneity.[16] Heterogeneity was assessed using 3 measures—between-study variance (τ^2), Cochran Q test, and the inconsistency index (I^2). Number needed to treat (NNT) was calculated using the pooled effects and the median risk of infection in the liberal RBC transfusion group. The NNT reflected the number of patients required to undergo the restrictive transfusion strategy in order to prevent an additional patient from developing an infection compared with the baseline risk (liberal RBC transfusion strategy). Publication bias was evaluated through visual inspection of the funnel plot and through the Harbord test of small-study effects and the Peters test of funnel asymmetry. Sensitivity analyses were performed relevant to study quality assessments (concealed randomization, blinding, withdrawals, and protocol violations). Stata/MP (StataCorp), version 13.0, was used for the analyses. The 2-tailed α level was .05.

The pooled risk ratio for all studies was calculated. In addition, results were stratified by (1) trials that reported all serious infections combined and (2) trials that reported specific types of infections. This was done because the underlying hypothesis was that allogeneic RBC transfusion exerts systemwide effects on immunity.[17-19] When only 1 type of infection is reported (eg, wound infections), individuals with infections at other sites, such as pneumonia or bloodstream infection, contaminate the comparison group representing those patients with-out (wound) infection. If there is a true systemwide effect, this reporting bias tends to drive the risk ratio toward the null.

Meta-analyses were stratified by clinical setting (eg, cardiac surgery and critical care) because variation based on underlying conditions was a possibility.[13] In addition, we

evaluated whether leukocyte reduction of the RBC units could account for risk differences; results were stratified by the use of leukocyte-reduced RBC units vs unknown or partial use of leukocyte-reduced RBC units.

We evaluated whether the risk of infection varied by the degree of hemoglobin threshold restriction (ie, <7 g/dL in the restrictive transfusion group). Random-effects meta-regression was conducted to investigate the association between the difference in hemoglobin thresholds (threshold in liberal group − threshold in restrictive group) and the risk ratios (dependent variable), with the hypothesis that a wider difference in hemoglobin thresholds between the 2 groups would be expected to yield risk ratios farther from the null. Residual maximum likelihood was used to estimate the between-study component of variance.

Results

Search Results

There were 2267 publications retrieved from the search and 2189 were excluded because they were not randomized trials, had inappropriate comparators, or both (**Figure 1**). Of the 78 potential studies, 58 were excluded because they did not report infectious outcomes, were duplicate samples, contained ineligible comparators, were papers describing methods only, or were not trials. There were 20 trials with 8598 patients that met eligibility criteria and were included in this systematic review (**Table 1**).[10,11,14,20-37] Sufficient information was available to pool data from 17 randomized trials for meta-analyses.[10,11,14,20-33,35] **Table 2** lists the infection outcomes that were reported in each study.

Five trials were conducted within the United States, 3 in the Netherlands, 2 in Canada, 2 in Denmark, 1 in the United Kingdom, 1 in Brazil, 1 in Spain, and 5 were conducted in facilities within multiple countries (Canada, United States, Belgium, United Kingdom, Australia, and Ireland). Patient enrollment spanned from 1994 in the Transfusion Requirements in Critical Care (TRICC) trial to 2012 in the Carson and coauthors[10] trial of symptomatic coronary artery disease and the de Gast-Bakker and coauthors[25] trial of pediatric cardiac patients. In trials with adult participants, the hemoglobin threshold ranged from 6.4 g/dL to 9.7 g/dL in the restrictive group, and the hemoglobin threshold in the liberal group ranged from 9.0 g/dL to 11.3 g/dL. Baseline hemoglobin levels were quite comparable (eTable 2 in the Supplement). There were considerable percentages of patients receiving transfusions after randomization, even in the restrictive groups (cardiac, 27%-60%; critically ill, 46%-67%; gastrointestinal, 49%; low birth weight, 89%; orthopedics, 34%-45%; sepsis, 56%). Patients in the restrictive group received fewer RBC units than in the liberal group with the exception of 2 trials.[14,32] In 1 trial, the study was reported in abstract form and this information was not stated.[14] In the other trial, RBC transfusion use was greater in the restrictive than liberal group in 1 of the 3 participating hospitals.[32] The authors published a subsequent paper in which they analyzed the data by RBC transfusion use rather than by random assignment.[38] For purposes of our analyses, we used the trial data as randomly assigned, which is conservative in that 2 fewer infections were reported in the restrictive group in the subsequent report.[38]

Concealed randomization occurred in 14 of the 20 trials (eTable 3 in the Supplement). Some of the trials included blinding of treatment assignments to patients,[21,30,31] surgical staff,[22] investigators who performed the outcome assessments,[10,21,29-33] statisticians,[27,35] or independent data and safety monitors.[22,27,35] The percentage of patients who withdrew or were excluded after randomization was low in most trials and ranged from 0% to 17%. The frequency of protocol violations or nonadherence to assigned treatment varied across studies. In a trial of patients undergoing cardiac surgery, nonadherence to protocol occurred in most of the patients in the liberal group (59%) and in 16% of patients in the restrictive group.[24] In a randomized trial of patients presenting with acute myocardial infarction, the protocol allowed suspension by the treating physician but, once resolved,transfusion was then given according to the aprior is trategies; the number of suspensions was not listed.[23]

Of the 20 randomized trials, results from 1 study could not be pooled in the meta-analysis because the unit of observation was operations, not individuals.[36] In this study, the rate of fever or infection was 1.7% (95% CI, 0.5%-3.8%) in the restrictive group and it was 2.3% (95% CI, 0.9%-4.7%) in the liberal group. In 2 other trials, the comparators did not include specific hemoglobin thresholds in the protocol but, rather, restriction of transfusion during a certain period (before surgery in 1 trial and after child birth in another trial).[34,37] In both studies, there was no significant difference in the risk of infection between the randomized groups.

There was one pediatric trial[27] in which there was a separate analysis for patients with sepsis.[35] In patients with sepsis, there was a significant reduction in the risk of nosocomial infection in those randomized to the restrictive transfusion strategy compared with the liberal strategy, with a risk ratio of 0.51 (95% CI, 0.28-0.95; $P = .033$).

Meta-analyses

In the 17 trials with 7456 patients, the overall pooled risk ratio for the association between transfusion thresholds (restrictive vs liberal) was 0.92 (95% CI, 0.82-1.04; $P = .206$) as shown in the forest plot in Figure 2. Heterogeneity was not significant (Cochran Q test, $P = .380$; $I^2 = 6.3\%$; $\tau^2 = .0041$). Publication bias was not evident through inspection of the funnel plot or by the Harbord test ($P = .465$) or Peters test ($P = .822$).

For trials in which all serious infections were combined as the outcome, the pooled risk ratio was 0.84 (95% CI, 0.73-0.96; $P = .012$) with no significant heterogeneity (Cochran Q test, $P = .577$; $I^2 = 0\%$; $\tau^2 < .0001$). Absolute risks of infection were also pooled. For those patients receiving the restrictive transfusion strategies, the summary risk of infection (all serious infections) was 10.6% (95% CI, 5.6%-15.9%) and, for patients receiving the liberal transfusion strategies, the summary risk of infection was 12.7% (95% CI, 7.0%-18.7%). The NNT with a restrictive strategy in order to prevent all serious infections was 48 (95% CI, 36-71) and the number of avoided infections per 1000 patients was 21 (95% CI, 14-28).

Trials restricted to those with concealed randomization yielded a pooled risk ratio (RR) for all serious infections of 0.83 (95% CI, 0.72-0.95; $P = .009$; Cochran Q test, $P = .581$; $I^2 = 0.0\%$; $\tau^2 < .0001$). When the studies were limited to those in which there were <5% withdrawals, the pooled RR was 0.84 (95% CI, 0.73-0.97; $P = .019$; Cochran Q test, $P =$.

563; I^2 = 0%; τ^2<.0001). Restriction to studies with <5% protocol violations yielded a pooled RR of 0.84 (95% CI, 0.68-1.03; *P* = .095; Cochran *Q* test, *P* = .348; I^2 = 9.0%; τ^2=.0044).

Of the 17 trials shown in Figure 2, 7 trials exclusively used RBC units that were leukocyte-reduced. Restriction of the meta-analysis to these 7 trials yielded a pooled RR of 0.83 (95% CI, 0.69-0.99; *P* = .044; I^2 = 0%; τ^2<.0001). Thus, the risk of infection remained reduced with a restrictive strategy, even with leukocyte reduction.

We also conducted the meta-analysis with stratification by clinical setting, which is shown in **Figure 3**. There was no statistically significant difference in the risk of infection for cardiac patients (RR, 1.30 [95% CI, 0.85-1.97]; *P* = .229), individuals who were critically ill (RR, 0.83 [95% CI, 0.65-1.04]; *P* = .104), patients with acute upper gastrointestinal bleeding (RR, 0.90 [95% CI, 0.69-1.17]; *P* = .412) and low birth weight infants (RR, 1.06 [95% CI, 0.85-1.31]; *P* = .627). However, there was a significant difference in the risk of serious infection in patients undergoing hip replacement or knee replacement surgery who were randomized to the restrictive strategy (RR, 0.72 [95% CI, 0.53-0.97]; *P* = .034) compared with those in the liberal strategy groups; this excludes those trials in which urinary tract infections were reported.

Three of the randomized trials used a low hemoglobin threshold of <7.0 g/dL in the restrictive group whereas the remaining trials used higher thresholds. The pooled RR for these 3 trials was 0.86 (95% CI, 0.72-1.02; *P* = .078) with no significant heterogeneity (Cochran *Q* test, *P* = .892, I^2 = 0%, τ^2<.0001). The forest plot of these trials is shown in eFigure 1 in the Supplement.

There were 15 trials with data necessary for calculating differences in hemoglobin thresholds between liberal and restrictive groups. The remaining trials had thresholds that varied by patient age, time since surgery, blood sampling methods, or respiratory support. The relationship between the difference in thresholds and risk ratios of infection is shown in eFigure 2 in the Supplement, generated from meta-regression. The RR was 0.91 (95% CI, 0.61-1.36) when 15 trials were included and 0.90 (95% CI, 0.55-1.48) when restricted to the 7 trials in which all serious infections were included.

Discussion

Among hospitalized patients, a restrictive RBC transfusion strategy compared with a liberal transfusion strategy was not associated with a reduced risk of health care–associated infection overall, although it was associated with a reduced risk of serious infection. The best evidence is provided by those trials that minimized reporting bias by including all infections and that were not confounded by leukoreduction (ie, all patients received leukocyte-reduced RBC units).

Leukocyte reduction of RBCs has been shown to decrease the risk of health care–associated infection[7] and because only 85% of RBC units are leukocyte-reduced in the United States, adoption of universal leukocyte reduction may be an important first step to infection prevention. However, even with leukocyte-reduced RBC units, adherence to a restrictive

transfusion strategy is an important second step in preventing health care–associated infections. The elevated risk for health care–associated infection with the liberal use of leukocyte-reduced RBC units may stem from the persistence of trans-fusion-related immunomodulation despite reduction of leukocytes. The exact components in allogeneic transfusions that mediate immunomodulation are not fully known and may not all be derived from leukocytes. Additionally, it was not clear if leukocyte reduction occurred before or after storage of the RBC units in all of the studies.

The results showed little statistical heterogeneity overall, although stratification by patient type did suggest clinical heterogeneity. For individuals undergoing hip or knee arthroplasty and for patients with sepsis, a restrictive RBC transfusion strategy yielded significantly reduced risks of serious infection than more liberal strategies, a finding that could lead to decreased morbidity as well as considerable potential cost savings if the restrictive strategy was uniformly applied nationwide. There was, however, 1 orthopedic trial[14] in older, frail individuals that suggested similar infection rates and this may be a population that deserves further study. This study used a slightly different outcome—time to first treatment-requiring infection as indicated by a positive urine culture or suspected infection.

We found that transfusion strategies yielded similar infection risks in patients with cardiac disease. The pooled point estimate was elevated at 1.30 (95% CI, 0.85-1.97) with little statistical heterogeneity. In some of the cardiac trials, the differences between RBC transfusion use in the study groups were not particularly great. For example, in the Bracey and coauthors[20] trial, 60% of patients in the restrictive group and 64% of patients in the liberal group received a transfusion. In 1 cardiac trial,[24] nonadherence to assignment occurred in a large proportion of the participants, making it difficult to evaluate the comparisons presented. Further investigation into the effectiveness of RBC transfusion strategies in cardiac patients may benefit from complete ascertainment of infectious outcomes. In a recent study at 10 centers in the United States and Canada, 5158 cardiac patients were followed-up with uniform collection of infection data and 5.8% were found to have major infections after cardiac surgery.[39] The most prevalent types of infection in this cohort were pneumonia, *Clostridium difficile* infection, and bloodstream infection. There was a 29% increase in the risk of major infection with each RBC unit transfused.[39] In the Transfusion Requirements After Cardiac Surgery (TRACS) randomized trial[21] included in our systematic review (the largest randomized trial of transfusion strategies in cardiac patients to date), the risk of infection after cardiac surgery increased 20% with every RBC unit received ($P = .007$). The infectious complications measured in this trial were septic shock, mediastinitis, and pneumonia.

We found only 2 trials in critically ill patients, 1 in adults and another in children.[26,27]Each of these trials encompassed heterogeneous groups of patients, presenting with cardiac disease, pulmonary disease, sepsis, and multiple coexisting conditions. Both risk ratios were slightly below the null but, when pooled, the results were not statistically significant. Although no overall effects were seen, it may be valuable to assess whether there are benefits of a restrictive strategy within particular subgroups of critically ill patients because 1 trial reported lower health care– associated infections in patients with sepsis and restrictive

thresholds.[35] Hébert and coauthors,[26] in particular, noted heterogeneous results in patients who were critically ill.

The results of this review give further support to a recent systematic review and clinical practice guideline put forth by the AABB (formerly the American Association of Blood Banks).[40] This guideline recommends adherence to a restrictive transfusion strategy for the majority of hospitalized patients and lists specific hemoglobin-based recommendations for varied patient populations; yet only 27% of hospitals that responded to the 2011 National Blood Collection and Utilization Survey reported implementing restrictive use of transfusions postoperatively.[6] Additionally, only 31% of responding hospitals reported having a blood management program.[6]

There are limitations to this systematic review. First, reporting of infectious outcomes varied across studies. In some trials, all infections were listed whereas in others only specific types of infections were reported. Second, strategies were employed with varying transfusion triggers, although half of the trials used a threshold of <8.0 g/dL in the restrictive group. Third, the decision to transfuse is a judgment that depends on clinical signs and symptoms and not solely on a laboratory value. This was explicitly incorporated into the protocol for several of the trials in this review.[10,22,29,33,34] Therefore, the proportions of patients actually transfused varied across the trials. Finally, the data were sparse for certain patient groups, such as the trial in pediatric cardiac intensive care with 60 patients.[22] Additional trials may provide greater insight into the risks and benefits of the 2 strategies.

We recommend that future trials of blood management techniques uniformly measure health care–associated infection as patient outcomes and that summary numbers of patients with infection be reported so that hypotheses relevant to transfusion-related immunomodulation can be evaluated. These should include definitions as outlined by the US Centers for Disease Control and Prevention.[41] Recent evidence regarding the use of procalcitonin for the identification of bacterial infections may prove to be valuable in this regard.[42]

Conclusions

Among hospitalized patients, a restrictive RBC transfusion strategy compared with a liberal transfusion strategy was not associated with a reduced risk of health care–associated infection overall, although it was associated with a reduced risk of serious infection. Implementing restrictive strategies may have the potential to lower the incidence of serious health care– associated infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. US Department of Health and Human Services. [February 4, 2014] National action plan to prevent healthcare-associated infections: roadmap to elimination. http://www.health.gov/hai/prevent_hai.asp.
2. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med. 2006; 355(26):2725–2732. [PubMed: 17192537]
3. Boyce JM, Pittet D. Healthcare Infection Control Practices Advisory Committee; HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force; Society for Healthcare Epidemiology of America/Association for Professionals in Infection Control/Infectious Diseases Society of America. Guideline for Hand Hygiene in Health-Care Settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/ APIC/IDSA Hand Hygiene Task Force. MMWR Recomm Rep. 2002; 51(RR-16):1–45. [PubMed: 12418624]
4. Saint S, Greene MT, Kowalski CP, Watson SR, Hofer TP, Krein SL. Preventing catheter-associated urinary tract infection in the United States: a national comparative study. JAMA Intern Med. 2013; 173(10):874–879. [PubMed: 23529579]
5. Scott, RD. [February 4, 2014] The direct medical costs of health care–associated infections in US hospitals and the benefits of prevention. http://www.cdc.gov/HAI/pdfs/hai/Scott_CostPaper.pdf.
6. Whitaker, BI.; Hinkins, S. [2/5/2014] The 2011 national blood collection and utilization survey. http://www .bloodsurvey.org.
7. Lannan KL, Sahler J, Spinelli SL, Phipps RP, Blumberg N. Transfusion immunomodulation—the case for leukoreduced and (perhaps) washed transfusions. Blood Cells Mol Dis. 2013; 50(1):61–68. [PubMed: 22981700]
8. Buddeberg F, Schimmer BB, Spahn DR. Transfusion-transmissible infections and transfusion-related immunomodulation. Best Pract Res Clin Anaesthesiol. 2008; 22(3):503–517. [PubMed: 18831300]
9. Fergusson D, Khanna MP, Tinmouth A, Hébert PC. Transfusion of leukoreduced red blood cells may decrease postoperative infections: 2 meta-analyses of randomized controlled trials. Can J Anaesth. 2004; 51(5):417–424. [PubMed: 15128625]
10. Carson JL, Brooks MM, Abbott JD, et al. Liberal vs restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J. 2013; 165(6):964–971, e1. [PubMed: 23708168]
11. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013; 368(1):11–21. [PubMed: 23281973]
12. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009; 151(4):264–269, W64. [PubMed: 19622511]
13. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2012; 4:CD002042. [PubMed: 22513904]
14. Gregersen M, Borris LC, Damsgaard EM. A liberal blood transfusion strategy after hip fracture surgery does not increase the risk of infection in frail elderly. Eur Geriatr Med. 2012; 3(suppf 1):S74. doi:10.1016/j.eurger.2012.07.139.
15. Freeman MF, Tukey JW. Transformations related to the angular and the square root. Ann Math Stat. 1950; 21:607–611.
16. Kuhnert R, Böhning D. A comparison of 3 different models for estimating relative risk in meta-analysis of clinical trials under unobserved heterogeneity. Stat Med. 2007; 26(11):2277–2296. [PubMed: 16991109]
17. Hill GE, Frawley WH, Griffith KE, Forestner JE, Minei JP. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a meta-analysis. J Trauma. 2003; 54(5):908–914. [PubMed: 12777903]

18. Rogers MA, Blumberg N, Saint S, Langa KM, Nallamothu BK. Hospital variation in transfusion and infection after cardiac surgery: a cohort study. BMC Med. 2009; 7:37. [PubMed: 19646221]
19. Rogers MA, Blumberg N, Saint SK, Kim C, Nallamothu BK, Langa KM. Allogeneic blood transfusions explain increased mortality in women after coronary artery bypass graft surgery. Am Heart J. 2006; 152(6):1028–1034. [PubMed: 17161047]
20. Bracey AW, Radovancevic R, Riggs SA, et al. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. Transfusion. 1999; 39(10):1070–1077. [PubMed: 10532600]
21. Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA. 2010; 304(14):1559–1567. [PubMed: 20940381]
22. Cholette JM, Rubenstein JS, Alfieris GM, Powers KS, Eaton M, Lerner NB. Children with single-ventricle physiology do not benefit from higher hemoglobin levels post cavopulmonary connection: results of a prospective, randomized, controlled trial of a restrictive versus liberal red-cell transfusion strategy. Pediatr Crit Care Med. 2011; 12(1):39–45. [PubMed: 20495502]
23. Cooper HA, Rao SV, Greenberg MD, et al. Conservative vs liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). Am J Cardiol. 2011; 108(8):1108–1111. [PubMed: 21791325]
24. Shehata N, Burns LA, Nathan H, et al. A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery. Transfusion. 2012; 52(1):91–99. [PubMed: 21790621]
25. de Gast-Bakker DH, de Wilde RB, Hazekamp MG, et al. Safety and effects of 2 red blood cell transfusion strategies in pediatric cardiac surgery patients: a randomized controlled trial. Intensive Care Med. 2013; 39(11):2011–2019. [PubMed: 23995984]
26. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care: Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999; 340(6):409–417. [PubMed: 9971864]
27. LaCroix J, Hébert PC, Hutchison JS, et al. TRIPICU Investigators; Canadian Critical Care Trials Group; Pediatric Acute Lung Injury and Sepsis Investigators Network. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med. 2007; 356(16):1609–1619. [PubMed: 17442904]
28. Kirpalani H, Whyte RK, Andersen C, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) vs liberal (high) transfusion threshold for extremely low birth weight infants. J Pediatr. 2006; 149(3):301–307. [PubMed: 16939737]
29. Carson JL, Terrin ML, Barton FB, et al. A pilot randomized trial comparing symptomatic vs hemoglobin level–driven red blood cell transfusions following hip fracture. Transfusion. 1998; 38(6):522–529. [PubMed: 9661685]
30. Grover M, Talwalkar S, Casbard A, et al. Silent myocardial ischaemia and haemoglobin concentration: a randomized controlled trial of transfusion strategy in lower limb arthroplasty. Vox Sang. 2006; 90(2):105–112. [PubMed: 16430668]
31. Foss NB, Kristensen MT, Jensen PS, Palm H, Krasheninnikoff M, Kehlet H. The effects of liberal vs restrictive transfusion thresholds on ambulation after hip fracture surgery. Transfusion. 2009; 49(2):227–234. [PubMed: 19389209]
32. So-Osman C, Nelissen R, Te Slaa R, Coene L, Brand R, Brand A. A randomized comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells. Vox Sang. 2010; 98(1):56–64. [PubMed: 19656349]
33. Carson JL, Terrin ML, Noveck H, et al. FOCUS Investigators. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med. 2011; 365(26):2453–2462. [PubMed: 22168590]
34. Prick BW, Jansen AJG, Steegers EAP, et al. Transfusion policy after severe postpartum haemorrhage: a randomised non-inferiority trial. BJOG. [published online January 10, 2014]. doi: 10 .1111/1471-0528.12531.
35. Karam O, Tucci M, Ducruet T, Hume HA, Lacroix J, Gauvin F. Canadian Critical Care Trials Group; PALISI Network. Red blood cell transfusion thresholds in pediatric patients with sepsis. Pediatr Crit Care Med. 2011; 12(5):512–518. [PubMed: 21057356]

36. Vichinsky EP, Haberkern CM, Neumayr L, et al. The Preoperative Transfusion in Sickle Cell Disease Study Group. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. N Engl J Med. 1995; 333(4):206–213. [PubMed: 7791837]
37. Howard J, Malfroy M, Llewelyn C, et al. The Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study: a randomised, controlled, multicentre clinical trial. Lancet. 2013; 381(9870):930–938. [PubMed: 23352054]
38. So-Osman C, Nelissen R, Brand R, et al. The impact of a restrictive transfusion trigger on post-operative complication rate and well-being following elective orthopaedic surgery: a post-hoc analysis of a randomised study. Blood Transfus. 2013; 11(2):289–295. [PubMed: 23399367]
39. Horvath KA, Acker MA, Chang H, et al. Blood transfusion and infection after cardiac surgery. Ann Thorac Surg. 2013; 95(6):2194–2201. [PubMed: 23647857]
40. Carson JL, Grossman BJ, Kleinman S, et al. Clinical Transfusion Medicine Committee of the AABB. Red blood cell transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2012; 157(1):49–58. [PubMed: 22751760]
41. Centers for Disease Control and Prevention. [February 5, 2014] CDC/NHSN surveillance definitions for specific types of infections. http://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf.
42. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis. 2013; 13(5):426–435. [PubMed: 23375419]

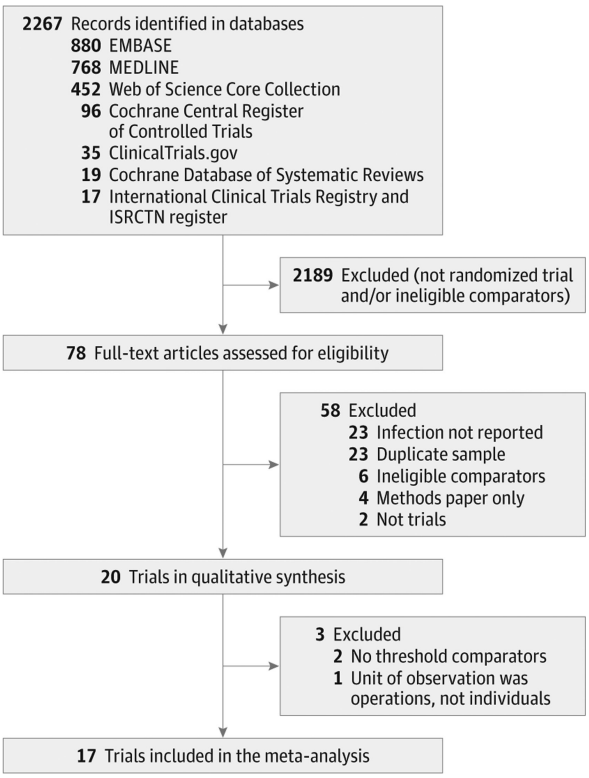

Figure 1.
Flow Diagram of Search Strategy

Source	Restrictive Transfusion Threshold: No. of Events	Restrictive Transfusion Threshold: Total No. of Patients	Liberal Transfusion Threshold: No. of Events	Liberal Transfusion Threshold: Total No. of Patients	Risk Ratio (95% CI)
All serious infections, combined					
Bracey et al,[20] 1999	5	212	3	216	1.70 (0.41-7.02)
Hébert et al,[26] 1999	42	418	50	420	0.84 (0.57-1.24)
LaCroix et al,[27] 2007	65	320	79	317	0.82 (0.61-1.09)
Foss et al,[31] 2009	6	60	11	60	0.55 (0.22-1.38)
Hajjar et al,[21] 2010	29	249	25	253	1.18 (0.71-1.95)
So-Osman et al,[32] 2010	18	299	31	304	0.59 (0.34-1.03)
Carson et al,[33] 2011	56	1009	74	1007	0.76 (0.54-1.06)
Villanueva et al,[11] 2013	84	444	94	445	0.90 (0.69-1.17)
Subtotal $I^2 = 0.0\%$, $P = .58$					0.84 (0.73-0.96)
Specific infections					
Carson et al,[29] 1998	0	42	2	42	0.20 (0.01-4.04)
Grover et al,[30] 2006	2	109	3	109	0.67 (0.11-3.91)
Kirpalani et al,[28] 2006	96	223	93	228	1.06 (0.85-1.31)
Gregersen et al,[14] 2012					1.25 (0.87-1.78)
Cholette et al,[22] 2011	0	31	1	31	0.33 (0.01-7.88)
Cooper et al,[23] 2011	1	23	0	19	2.50 (0.11-58.06)
Shehata et al,[24] 2012	3	25	0	25	7.00 (0.38-128.87)
Carson et al,[10] 2013	2	54	0	55	5.09 (0.25-103.64)
de Gast-Bakker et al,[25] 2013	6	53	5	54	1.22 (0.40-3.76)
Subtotal $I^2 = 0.0\%$, $P = .70$					1.11 (0.92-1.33)
Overall $I^2 = 6.3\%$, $P = .38$					0.92 (0.82-1.04), $P = .21$

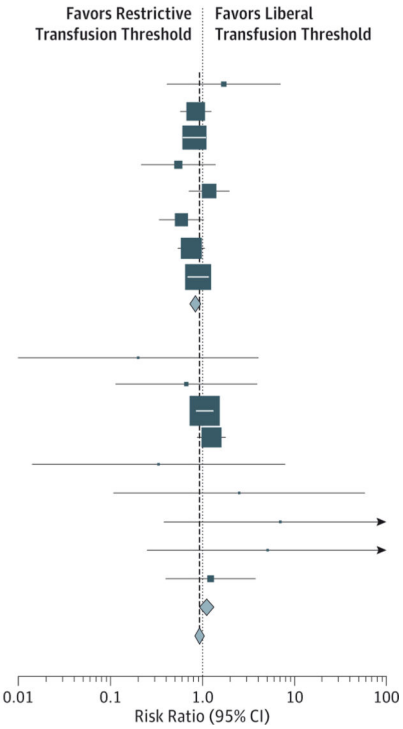

Figure 2.

Forest Plot of Risk Ratios for Infection Comparing Restrictive vs Liberal Transfusion Strategies

Source	Restrictive Transfusion Threshold: No. of Events	Restrictive Transfusion Threshold: Total No. of Patients	Liberal Transfusion Threshold: No. of Events	Liberal Transfusion Threshold: Total No. of Patients	Risk Ratio (95% CI)
Cardiac					
Bracey et al,[20] 1999	5	212	3	216	1.70 (0.41-7.02)
Hajjar et al,[21] 2010	29	249	25	253	1.18 (0.71-1.95)
Cholette et al,[22] 2011	0	31	1	31	0.33 (0.01-7.88)
Cooper et al,[23] 2011	1	23	0	19	2.50 (0.11-58.06)
Shehata et al,[24] 2012	3	25	0	25	7.00 (0.38-128.87)
Carson et al,[10] 2013	2	54	0	55	5.09 (0.25-103.64)
de Gast-Bakker et al,[25] 2013	6	53	5	54	1.22 (0.40-3.76)
Subtotal $I^2 = 0.0\%$, ($P = .78$)					1.30 (0.85-1.97)
Critical care					
Hébert et al,[26] 1999	42	418	50	420	0.84 (0.57-1.24)
LaCroix et al,[27] 2007	65	320	79	317	0.82 (0.61-1.09)
Subtotal $I^2 = 0.0\%$, ($P = .89$)					0.83 (0.65-1.04)
Gastrointestinal					
Villanueva et al,[11] 2013	84	444	94	445	0.90 (0.69-1.17)
Low birthweight					
Kirpalani et al,[28] 2006	96	223	93	228	1.06 (0.85-1.31)
Orthopedic					
Carson et al,[29] 1998	0	42	2	42	0.20 (0.01-4.04)
Grover et al,[30] 2006	2	109	3	109	0.67 (0.11-3.91)
Foss et al,[31] 2009	6	60	11	60	0.55 (0.22-1.38)
Carson et al,[33] 2011	56	1009	74	1007	0.76 (0.54-1.06)
Subtotal $I^2 = 0.0\%$, ($P = .77$)					0.72 (0.53-0.97)
Overall $I^2 = 0.0\%$, ($P = .62$)					0.92 (0.81-1.03), $P = .16$

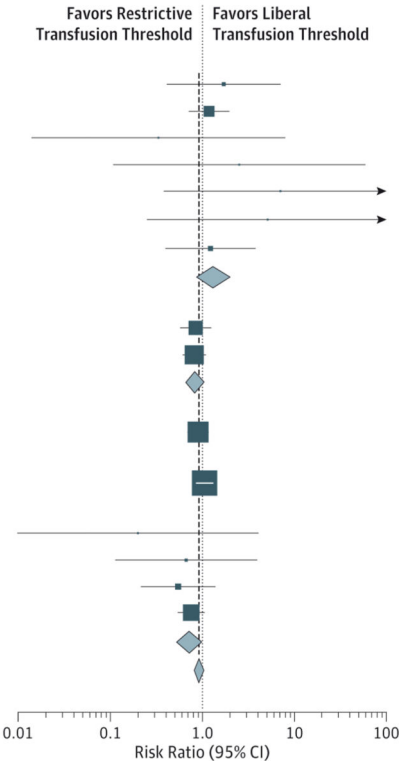

Figure 3.

Forest Plot of Risk Ratios for Infection Comparing Restrictive vs Liberal Transfusion Strategies by Patient Type

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Table 1

Characteristics of the Randomized Trials Comparing Restrictive vs Liberal RBC Transfusion Strategies

				Age, Mean (SD),y		No. Randomized		Transfusion Threshold	
Source	**Patients**	**Site**	**Period of Enrollment**	**Restrictive Group**	**Liberal Group**	**Restrictive Group**	**Liberal Group**	**Restrictive Group**	**Liberal Group**
Cardiac patients									
Bracey et al,[20] 1999	Underwent first elective coronary artery bypass graft surgery	1 US hospital	2/4/1997 to 11/15/1997	61 (11)	62 (11)	212	216	Hb <8.0 g/dL	Hb <9.0 g/dL
Hajjar et al,[21] 2010	Scheduled for elective cardiac surgery with cardiopulmonary bypass	ICU at 1 hospital in Brazil	2/9/2009 to 2/1/2010	58.6 (12.5)	60.7 (12.5)	255	257	Hct <24% (Hb 8.0 g/dL)	Hct <30% (Hb 10.0 g/dL)
Cholette et al,[22] 2011	Infants and children with elective partial or total cavopulmonary connection	1 US hospital	8/2006 to 9/2009	Mo (range) 27(23)	Mo (range) 32.5 (27)	31	31	Hb <9.0 g/dL with symptomatic anemia	Hb <13.0 g/dL
Cooper et al,[23] 2011	Acute myocardial infarction and Hct ≤30% within 72 h of symptom onset	3 US hospitals	3/2003 through 10/2009	70.3 (14.3)	76.4 (13.5)	24	21	Hct <24% (Hb 8.0 g/dL); maintenance goal range, 24%-27% (Hb 8-9 g/dL)	Hct <30% (Hb 10.0 g/dL); maintenance goal range, 30%-33% (Hb 10-11 g/dL)
Shehata et al,[24] 2012	Adults having elective cardiac surgery	1 hospital in Canada	2007 to 2010	67.2 (11.2)	68.8 (9.2)	25	25	Hb ≤7.0 g/dL during surgery or Hb ≤ 7.5 g/dL postoperatively	Hb ≤9.5 g/dL during surgery or Hb ≤10.0 g/dL postoperatively
Carson et al,[10] 2013	Adults with acute coronary syndrome or stable angina undergoing cardiac catheterization	8 US hospitals	3/15/2010 to 5/8/2012	74.3 (11.1)	67.3 (13.6)	55	55	Symptomatic anemia; also in the absence of symptoms, if Hb <8.0 g/dL	Hb <10.0 g/dL
de Gast-Bakker et al,[25] 2013	Noncyanotic congenital heart defects between 6 wk and 6 y of age	Pediatric ICU at 1 hospital in the Netherlands	4/2009 to 1/2012	Median (IQR), mo 9.5 (3.6-30.4)	Median (IQR), mo 7.3 (3.0-29.7)	53	54	Hb ≤8.0 g/dL	Hb <10.8 g/dL

				Age, Mean (SD),y		No. Randomized		Transfusion Threshold	
Source	**Patients**	**Site**	**Period of Enrollment**	**Restrictive Group**	**Liberal Group**	**Restrictive Group**	**Liberal Group**	**Restrictive Group**	**Liberal Group**
Critical care patients									
Hébert et al,[26] 1999	Critically ill with euvolemia admitted to the ICU	22 tertiary-level and 3 community ICUs in Canada	11/1994 to 11/1997	57.1 (18.1)	58.1 (18.3)	418	420	Hb <7.0 g/dL; maintenance range, 7.0-9.0 g/dL	Hb ≤10.0 g/dL; maintenance range, 10.0-12.0 g/dL
LaCroix et al,[27] 2007	Stable, critically ill children in ICU	19 tertiary-care pediatric ICUs in Belgium, Canada, UK, and US	11/26/2001 to 8/28/2005	Mean (SD), mo 35.8 (46.2)	Mean (SD), mo 39.6 (51.9)	327	321	Hb ≤7 g/dL; target range after transfusion, 8.5-9.5 g/dL	Hb ≤9.5 g/dL; target range after transfusion, 11-12 g/dL
Gastrointestinal bleeding									
Villanueva et al,[11] 2013	Severe acute upper gastrointestinal bleeding	1 hospital in Spain	6/2003 to 12/2009	64 (16)	66 (15)	461	460	Hb ≤7 g/dL; target range, 7-9 g/dL	Hb ≤9 g/dL; target range, 9-11 g/dL
Low birth weight									
Kirpalani et al,[28] 2006	Infants weighing <1000 g at birth	10 neonatal ICUs in Canada, US, and Australia	1/2000 to 2/2003	Gestational age, mean (SD), wk 26.1 (1.9)	Gestational age, mean (SD), wk 26.1 (1.8)	223	228	Varied by age, capillary vs central blood sampling and respiratory support; range, ≤6.8-≤11.5 g/dL.	Varied by age, capillary vs central blood sampling and respiratory support; range, ≤7.7-≤13.5 g/dL.
Orthopedics									
Carson et al,[29] 1998	Undergoing hip fracture repair surgery	4 hospitals (3 in the US, 1 in Scotland)	3/1996 to 3/1997	83.3 (10.8); range, 32-95	81.3 (8.1); range, 50-94	42	42	Symptomatic anemia or Hb <8.0 g/dL in absence of symptoms	Hb <10.0 g/dL
Grover et al,[30] 2006	Undergoing elective hip and knee replacement surgery	3 hospitals in England	2 y (exact dates not stated)	70.7 (7.1)	71.5 (7.6)	109[a]	109[a]	Hb <8.0 g/dL; maintenance range, 8.0-9.5 g/dL	Hb <10.0 g/dL; maintenance range, 10.0-12.0 g/dL
Foss et al,[31] 2009	Cognitively intact patients with hip fracture admitted from home	1 hospital in Denmark	2/2004 to 7/2006	81 (7.3)	81 (6.8)	60	60	Hb <8.0 g/dL	Hb <10.0 g/dL

				Age, Mean (SD),y		No. Randomized		Transfusion Threshold	
Source	**Patients**	**Site**	**Period of Enrollment**	**Restrictive Group**	**Liberal Group**	**Restrictive Group**	**Liberal Group**	**Restrictive Group**	**Liberal Group**
So-Osman et al,[32] 2010	Elective orthopedic hip and knee replacement surgery	3 hospitals in the Netherlands	2001 to 2003	70.7 (10.2)	70.3 (9.7)	309	310	Gradated scale based on age and hours after surgery; lowest Hb threshold range, 6.4-9.7 g/dL	Varied by hospital, age and condition of patients, symptoms of anemia, and time
Carson et al,[33] 2011	≥50 y of age with history of, or risk factors for, cardiovascular disease, and Hb <10.0 g/dL after hip fracture surgery	47 clinical sites in the US and Canada	7/19/2004 to 2/28/2009	81.5 (9.0)	81.8 (8.8)	1009	1007	Symptomatic anemia or if Hb <8.0 g/dL	Hb <10.0 g/dL
Gregersen et al,[14] 2012	Hip fracture patients with postoperative anemia admitted from nursing home or senior housing for surgery	1 hospital in Denmark	Not stated in abstract	Aged ≥65 y	Aged ≥65 y	Not stated in abstract	Not stated in abstract	Hb <9.7 g/dL	Hb <11.3 g/dL
Postpartum									
Prick et al,[34] 2014	Postpartum women with acute anemia without severe anemic symptoms or severe comorbidities	37 facilities in the Netherlands	5/2004 to 2/2011	30.9 (5.3)	30.7 (5.0)	262	259	RBC transfusion was allowed if severe symptoms of anemia developed or at their physicians' discretion	Received at least 1 RBC unit; aimed to reach an Hb of at least 8.9 g/dL
Sepsis									
Karam et al,[35] 2011	Stabilized, critically ill children in pediatric CCU	19 pediatric CCUs in Belgium, Canada, UK, US	Not stated	Mean (SD), mo 29.4(39.6)	Mean (SD), mo 32.9 (43.2)	69	68	Hb <7.0 g/dL; target range after transfusion, 8.5-9.5 g/dL	Hb <9.5 g/dL; target range after transfusion, 11.0 -12.0 g/dL
Sickle cell									
Vichinsky et al,[36] 1995	With sickle cell anemia undergoing elective surgery, and without	36 surgical centers in the US	1988 to 1993	Age, (%), y 0-9 (40) 10-19(36) ≤20 (24)	Age, (%), y 0-9 (40) 10-19(35) ≥20 (25)	273	278	Hb maintenance range, 9.0-11.0 g/dL, regardless of Hb S level	Hb maintenance range, 9.0-11.0 g/dL; Hb S level of ≤30%

				Age, Mean (SD),y		No. Randomized		Transfusion Threshold	
Source	**Patients**	**Site**	**Period of Enrollment**	**Restrictive Group**	**Liberal Group**	**Restrictive Group**	**Liberal Group**	**Restrictive Group**	**Liberal Group**
	transfusion within 3 mo before surgery								
Howard et al,[37] 2013	With sickle cell disease scheduled for low-risk or medium-risk operations	22 sites in Canada, Ireland, the Netherlands, and UK	11/2007 to 3/2011	Median (IQR), y 13.3 (6.4-21.4)	Median (IQR), y 15.1 (7.6-37.4)	34	36	No preoperative RBC transfusion	Preoperative RBC transfusion within 10 d before surgery, with transfusion aimed at increasing Hb to 10.0 g/dL.

Abbreviations: CCU, critical care unit; Hb, hemoglobin; Hct, hematocrit; ICU, intensive care unit; RBC, red blood cell.

[a] Not directly stated; n = 109 with electrocardiography recordings.

Table 2

Infection Outcomes in Randomized Trials of Restrictive vs Liberal Transfusion Strategies

Source	Infection Outcome Definition
Bracey et al,[20] 1999	Serious infections,[a] such as culture-proven pneumonia, mediastinitis, wound infection, or septicemia
Carson et al, 1998[29]	Modified CDC case definition of pneumonia[a]: chest radiograph with new or progressive infiltrate, consolidation, or cavitation and any of the following: new-onset purulent sputum or change in character of sputum, or the isolation of the organism from blood culture, transtracheal aspirate, bronchial brushings, or biopsy; did not consider a patient with rales and purulent sputum to have pneumonia; pleural effusion not used in chest radiograph definition
Carson et al,[33] 2011	Infections[a]: wound infection; CDC definition of pneumonia
Carson et al,[10] 2013	Composite 30 d and 6 mo infection outcome of blood stream infection and of pneumonia[a]; outcome adjudications and event classifications were performed by infectious disease specialist masked to the assignment group; unscheduled hospital admission at 30 d and 6 mo due to infection
Cholette et al,[22] 2011	Staphlyococcal sepsis[a]
Cooper et al,[23] 2011	Death due to sepsis[a]
deGast-Bakker et al,[25] 2013	Respiratory tract infection[a]
Foss et al,[31] 2009	Any infectious complication[a]; pneumonia; sepsis; wound infection
Gregersen et al,[14] 2012	Infections requiring treatment indicated by a positive urine culture or suspected infection[a]
Grover et al,[30] 2006	New infections requiring antibiotic therapy: chest infection[a]; wound infection
Hajar et al,[21] 2010	Infectious complications[a] included septic shock, defined by standard criteria; mediastinitis, defined as a superficial or deep infection of the sternotomy wound with positive findings on cultures obtained from the wound; and pneumonia described as having new, persistent, or progressive lung infiltrate on a chest radiograph and at least 2 of the following criteria present: temperature ≥38° C, leukocytosis >12 000 cells/μL or leukopenia <3000 cells/μL, or purulent endotracheal secretions with a Gram stain showing >25 neutrophils and <10 epithelial cells per field
Hébert et al,[26] 1999	Infectious complications[a] (bacteremia, catheter-related sepsis, and septic shock); pneumonia
Howard et al,[37] 2013	Infection-related complication
Karam et al,[35] 2011	Nosocomial infections[a]
Kirpalani et al,[28] 2006	Blood culture-proven sepsis[a]
LaCroix et al,[27] 2007	Nosocomial infections[a] (sepsis, nosocomial respiratory tract infections, and catheter-related infections)
Prick et al,[34] 2014	Endometritis; for subset followed-up for 6 wk: urinary tract infection, infected surgery wound, infected episiotomy/rupture, and endometritis
Shehata et al,[24] 2012	Sepsis[a]; pneumonia
So-Osman et al,[32] 2010	Postoperative infections[a] were predefined according to CDC criteria; all wounds were prospectively scored for possible infection at postoperative day 5
Vichinsky et al,[36] 1995	Fever or infection was defined as a temperature >38.5° C or a documented infection lasting at least 48 h[a]
Villanueva et al,[11] 2013	In-hospital bacterial infections[a]; pneumonia

Abbreviation: CDC, US Centers for Disease Control and Prevention.

[a]Included in the analyses shown in forest plots.