CHEST

Red Blood Cell Transfusion in Critically Ill Adults

An American College of Chest Physicians Clinical Practice Guideline

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BACKGROUND: Blood products frequently are administered to critically ill patients. Considering recent trials and practice variability, a comprehensive review of current evidence was deemed essential to offer pertinent guidance to critical care practitioners. This American College of Chest Physicians (CHEST) guidelines panel examined the literature on RBC transfusions among critically ill patients overall and specific subgroups, including patients with gastrointestinal bleeding, acute coronary syndrome (ACS), cardiac surgery, isolated troponin elevation, and septic shock, to provide evidence-based recommendations.

STUDY DESIGN AND METHODS: A panel of experts developed six Population, Intervention, Comparator, and Outcome questions addressing RBC transfusions in critically ill patients and performed a comprehensive evidence review. The panel applied the Grading of Recommendations, Assessment, Development, and Evaluations approach to assess the certainty of evidence and to formulate and grade recommendations. A modified Delphi technique was used to reach consensus on the recommendations.

RESULTS: The initial search identified a total of 3,082 studies, and after the initial screening, 38 articles were reviewed. Among them, 23 studies met inclusion criteria, comprising 22 randomized controlled trials and one cohort study. Based on the analysis of these studies, the panel formulated two strong and four conditional recommendations. The overall quality of evidence for recommendations ranged from very low to moderate.

CONCLUSIONS: In most critically ill patients, a restrictive strategy was preferable to a permissive approach because it does not increase the risk of death or complications, but does decrease RBC use significantly. Data from critically ill subpopulations also supported a restrictive approach, except in patients with ACS, for whom favoring a restrictive approach could increase adverse outcomes. CHEST 2025; 167(2):477-489

KEY WORDS: acute coronary syndrome; cardiac surgery; critically ill; GI bleed; red blood cell; sepsis; septic shock; transfusion

ABBREVIATIONS: ACS = acute coronary syndrome; CHEST = American College of Chest Physicians; ESICM = European Society of Intensive Care Medicine; GIB = gastrointestinal bleeding; LOS = length of stay; MD = mean difference; MI = myocardial infarction; MINT = Myocardial Injury and Transfusion; RCT = randomized controlled trial; RR = risk ratio

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Summary of Recommendations and Suggestions

These recommendations do not apply to critically ill adults with hemodynamic instability resulting from acute hemorrhage or to those with neurologic injuries or trauma.

1. In critically ill patients, we recommend a restrictive RBC transfusion strategy over a permissive RBC transfusion strategy (Strong Recommendation, Moderate Certainty of Evidence).

2. In critically ill patients with acute gastrointestinal bleeding, we recommend a restrictive RBC transfusion strategy over a permissive RBC transfusion strategy (Strong Recommendation, Moderate Certainty of Evidence).

3. In critically ill patients with acute coronary syndrome, we suggest against a restrictive RBC transfusion strategy (Conditional Recommendation, Low Certainty of Evidence).

4. In critically ill patients undergoing cardiac surgery, we suggest a restrictive RBC transfusion strategy over a permissive RBC transfusion strategy during the perioperative period (Conditional Recommendation, Moderate Certainty of Evidence).

5. In critically ill patients with isolated elevation of serum troponin without other evidence of cardiac ischemia, we suggest a restrictive RBC transfusion strategy over a permissive RBC transfusion strategy (Conditional Recommendation, Very Low Certainty of Evidence).

6. In patients with septic shock and end-organ hypoperfusion, we suggest against adding permissive RBC transfusion thresholds to usual care (Conditional Recommendation, Low Certainty of Evidence).

Remarks: Studies evaluating protocol-driven approaches to goal-directed therapy in septic shock were not considered in the evidence review.

Background

In the United States, approximately 25% of critically ill patients receive RBC transfusions, totaling approximately 1.8 million units annually.[1-3] The primary indication is low hemoglobin (80%), whereas less frequently encountered indications include active bleeding (27%) and hemodynamic instability (23%).[3,4] Since the publication of the Transfusion Requirements in Critical Care (TRICC) trial,[5] > 30 trials have examined RBC transfusion strategies in a variety of clinical settings. Recently, new studies and updated meta-analyses and guidelines have been published. Despite this evidence, significant variability exists in clinical practice regarding the indications for RBC transfusions, with most occurring in patients with hemoglobin levels of > 7 g/dL.[3]

Although RBC transfusions can be life-saving, they carry significant risks of adverse effects, including transfusion-related acute lung injury, transfusion-associated circulatory overload, and immunomodulating effects that may increase the risk of nosocomial infections.[1,6] These side-effects may be severe and even life-threatening. The entire process, from distribution to administration of RBCs, incurs substantial costs, which vary globally.[7,8] Optimal health care delivery minimizes unnecessary RBC transfusions, preserving them for patient groups with proven benefit. By optimizing the management of limited resources like RBCs, both individual patients and the broader at-risk critically ill population stand to benefit.[9] Given new evidence and ongoing variability in practice, an expert panel identified, synthesized, and weighted the evidence to provide clinical recommendations for RBC transfusion in critically ill patients.

Methods

Standardized methodology for clinical practice guidelines as per American College of Chest Physicians (CHEST)

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policy was followed. At this juncture, with several studies underway in critically ill patients with neurologic injuries and the trauma population, we decided to forego recommendations in these critical care subgroups.

Expert Panel Composition

The cochairs nominated a diverse and multidisciplinary panel based on their expertise encompassing critical care medicine, cardiology, hematology, and gastroenterology and hepatology. The final panel consisted of the two guideline cochairs, nine panelists, two methodologists, one medical librarian, and one liaison to CHEST Guidelines Oversight Committee.

Conflicts of Interest

Financial relationships for each chair and the panelists were reviewed by the CHEST Professional Standards Committee for potential conflicts of interest according to the CHEST Conflict of Interest Policy.[10]

Question Development

The panel developed six clinical questions using the Population, Intervention, Comparator, and Outcome format regarding the transfusion of RBC in different clinical scenarios. The panel ranked outcomes for each question to determine critical and important outcomes a priori (e-Table 1).

Literature Search

A comprehensive search of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials using relevant key words was performed in May 2021 (e-Table 2), with an updated search performed in MEDLINE in January 2024. Searches were limited to English language randomized controlled trials (RCTs), cohort studies, and case-control studies with at least 30 participants. Systematic reviews and prior guidelines were reviewed for context and completeness.

Study Selection and Data Extraction

Relevant citations identified during the literature search were reviewed in duplicate using predefined criteria over two rounds of study selection: reviewing titles and abstracts in the first round and reviewing full texts in the second round (e-Figs 1-6). Data were extracted, analyzed, and summarized for each individual Population, Intervention, Comparator, and Outcome question.

Assessing the Quality of Evidence

Risk of bias was assessed using the Cochrane Risk of Bias Tool for RCTs and the Risk of Bias in Nonrandomized Studies of Intervention based on study design.[11,12] A meta-analysis was performed when possible using a random effects model. Results are reported as risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes with accompanying 95% CIs. The overall certainty of the evidence was assessed for each outcome of interest using the Grading of Recommendations, Assessment, Development, and Evaluations approach (e-Table 3).[13]

Development of Recommendations

The panel reviewed and discussed the evidence. Recommendations were drafted using the Grading of Recommendations, Assessment, Development, and Evaluations approach, with strong recommendations using the wording "we recommend" and conditional recommendations using the wording "we suggest."[14] Panel members voted individually via SurveyMonkey on the direction and strength of the recommendation.[15] Per CHEST policy, consensus was achieved with 80% agreement in directionality with at least 75% of the panel participating. The guidelines were reviewed and approved by the Guidelines Oversight Committee and CHEST presidential leadership.

Results

The hemoglobin thresholds prompting RBC transfusion varied across studies, with a restrictive threshold generally defined as a hemoglobin level of 7 to 8 g/dL and a permissive threshold typically ranging from a hemoglobin level of 8.5 to 10 g/dL (Table 1). Hemodynamic instability typically has been defined as hypotension (mean arterial pressure, < 65 mm Hg, or systolic BP, < 100 mm Hg), tissue hypoperfusion caused by acute bleeding, or both.

Question 1: Should critically ill patients be treated with a restrictive or permissive RBC transfusion strategy?

1. In critically ill patients, we recommend a restrictive RBC transfusion strategy over a permissive RBC transfusion strategy (Strong Recommendation, Moderate Certainty of Evidence).

Justification

This recommendation, applicable to most critically ill patients, is supported by evidence from several high-quality RCTs involving approximately 16,000 patients (evidence profile 1, supplementary material). Comparisons between a restrictive and a permissive RBC transfusion strategy yielded no significant differences in ICU mortality

TABLE 1] Hemoglobin Thresholds in Studies Included per Recommendation

Population	Hemoglobin Threshold, g/dL	
	Restrictive	Permissive
Overall critically ill	7.0-8.0	9.0-10.0
Gastrointestinal bleeding	7.0-8.0	8.0-10.0
Acute coronary syndrome	7.0-8.0	10.0
Underwent cardiac surgery	7.5-8.0	8.5-10.0
Isolated troponin elevation	N/A	N/A
Septic shock	7.0	9.0

Data are presented as ranges. N/A = no studies available.

(RR, 1.00; 95% CI, 0.8-1.25),[5,16-19] 30-day mortality (RR, 0.99; 95% CI, 0.87-1.13),[5,17-30] or 1-year mortality (RR, 0.99; 95% CI, 0.87-1.13).[31,32] Although the restrictive group exhibited a slightly longer ICU length of stay (LOS) than the permissive group (MD, +0.12 days; 95% CI, +0.01 to +0.23 days), this finding is not clinically significant. Additionally, no difference in hospital LOS was found (MD, –0.2 days; 95% CI, –0.51 to +0.12 days).[5,17-21,23-29,33-36]

The restrictive approach proved superior to the permissive strategy in reducing adverse event rates (RR, 0.45; 95% CI, 0.22-0.94), but not in reducing secondary infections (RR, 1.03; 95% CI, 0.94-1.12). Similarly, no differences were found in organ-specific or system-specific adverse events, including cardiac, renal, pulmonary, and thromboembolic complications (Table 2).[5,18-30,33-36]

Given the absence of a discernible impact on mortality and the potential reduction in overall adverse events, a restrictive approach was determined to be the preferred strategy. This approach minimized RBC use without any clinical consequences in most critically ill patients. Since the publication of the TRICC trial,[5] all studies have favored a more restrictive approach with the possible exception of the recently published Myocardial Injury and Transfusion (MINT) trial.[20] In the trials evaluating ICU mortality, the clinical teams were encouraged strongly to transfuse one RBC unit at a time and repeat hemoglobin measurements after each unit. Using this approach, the number of RBC units transfused was decreased by 50%.[5,16-19]

Given the complexity of ICU care, specific subpopulations were addressed in subsequent recommendations.

What Others Are Saying

This recommendation aligned with those of other professional societies, including the Critical Care Societies Collaborative, the European Society of Intensive Care Medicine (ESICM), and the Association for the Advancement of Blood & Biotherapies.[37-39]

Research Priorities

Although the use of restrictive RBC transfusion strategies alone may not need much further inquiry, using individual patient data meta-analysis may help to identify more specific subgroup effects, particularly in patients with various forms of cardiovascular diseases, ranging from acute ischemia to chronic heart diseases. Research on measures of oxygen use or biomarkers of oxygen delivery in tissue beds and overall may allow more targeted approaches to RBC transfusions.

Question 2: Should critically ill patients who have acute gastrointestinal bleeding be treated with a restrictive or permissive RBC transfusion strategy?

TABLE 2] Pooled Analysis Comparing Restrictive vs Permissive Strategies in Overall Critically Ill Patients

Outcome	Relative Risk (95% CI)	Absolute Risk (95% CI)
ICU mortality	1.00 (0.80-1.25)	0 fewer per 1,000 (46 fewer-57 more)
1-y mortality	0.99 (0.87-1.13)	4 fewer per 1,000 (54 fewer-54 more)
30-d mortality	0.99 (0.87-1.13)	1 fewer per 1,000 (14 fewer-14 more)
ICU length of stay	NA	0.12 d higher (0.01 higher-0.23 higher)
Hospital length of stay	NA	0.2 d lower (0.51 lower-0.12 higher)
Adverse events	0.45 (0.22-0.94)	8 fewer per 1,000 (11 fewer-1 fewer)
Secondary infections	1.03 (0.94-1.12)	3 more per 1,000 (6 fewer-13 more)
Cardiac adverse events	0.94 (0.77-1.16)	4 fewer per 1,000 (16 fewer-11 more)
Renal adverse events	0.99 (0.89-1.10)	1 fewer per 1,000 (9 fewer-8 more)
Pulmonary adverse events	0.98 (0.88-1.08)	2 fewer per 1,000 (15 fewer-10 more)
Thromboembolism	0.83 (0.60-1.15)	4 fewer per 1,000 (9 fewer-3 more)

NA = not applicable.

2. In critically ill patients with acute gastrointestinal bleeding, we recommend a restrictive RBC transfusion strategy over a permissive RBC transfusion strategy (Strong Recommendation, Moderate Certainty of Evidence).

Justification

Acute gastrointestinal bleeding (GIB) is a life-threatening condition that often necessitates ICU care, including the critical decision of when to transfuse RBCs. We identified three relevant RCTs that included patients with acute upper GIB and an observational study of patients with acute lower GIB (evidence profile 2, supplementary material).[24-26,40]

Villanueva et al[24] randomized 921 patients with acute upper GIB and early access to endoscopy to either a restrictive or permissive RBC transfusion strategy. The restrictive approach led to lower rates of rebleeding, fewer adverse events, and lower 6-week all-cause mortality. An open-label, cluster RCT with 936 patients reported no significant mortality difference between both RBC transfusion strategies, but noted lower transfusion rates and decreased health care costs with the restrictive approach.[26] A smaller single-center open-label RCT showed that a restrictive approach was noninferior to a permissive strategy.[25] In aggregate, the restrictive transfusion strategy reduced short-term mortality (RR, 0.68; 95% CI, 0.48-0.97) without affecting hospital LOS (MD, −0.69 days; 95% CI, −1.98 to +0.60 days).

The restrictive approach proved superior to the permissive strategy with lower risk of acute transfusion reactions and serious adverse transfusion effects. However, no significant differences were found in the risk of infections, need for surgery in upper GIB (Table 3), or organ-specific or system-specific adverse events, including cardiac, renal, pulmonary, and thromboembolic (evidence profile 2, supplementary material). The data on lower GIB was limited to a retrospective study, which did not show differences in mortality or need for surgery between a restrictive and a permissive approach.[40]

Given the lower risk of mortality and adverse reactions, the adoption of a restrictive transfusion strategy emerged as the preferred recommendation. The restrictive strategy was superior in patients with and without portal hypertension-related GIB. Notably, portal pressure gradients increased in patients treated with a permissive strategy within the first 5 days of bleeding onset.[24]

What Others Are Saying

This recommendation aligned with those of the American Association for the Study of Liver Diseases, the American College of Gastroenterology, and the American Gastroenterological Association.[41-44]

Research Priorities

Studying the feasibility, implementation, and adherence to a restrictive transfusion strategy in acute GIB is a priority. Additionally, examining interprofessional knowledge transmission through a systems-based approach that adheres to the principles of quality improvement is essential.

Question 3: Should critically ill patients with acute coronary syndrome be treated with a restrictive or permissive RBC transfusion strategy?

3. In critically ill patients with acute coronary syndrome, we suggest against a restrictive RBC transfusion strategy (Conditional Recommendation, Low Certainty of Evidence).

Justification

The optimal transfusion strategy for patients with acute coronary syndrome (ACS) has been controversial, balancing improved oxygen delivery to the myocardium against the potential expansion of vascular volume and increase in blood viscosity from

TABLE 3] Pooled Analysis Comparing Restrictive vs Permissive Strategies in Gastrointestinal Bleeding

Outcome	Relative Risk (95% CI)	Absolute Risk (95% CI)
30-d mortality	0.68 (0.48-0.97)	27 fewer per 1,000 (43 fewer-2 fewer)
Hospital length of stay	NA	0.69 d lower (1.98 lower-0.6 higher)
Need for surgery in upper gastrointestinal bleeding	0.67 (0.16-2.91)	13 fewer per 1,000 (33 fewer-74 more)
Acute transfusion reactions	0.35 (0.20-0.61)	37 fewer per 1,000 (45 fewer-22 fewer)
Adverse transfusion effects[a]	0.73 (0.58-0.91)	54 fewer per 1,000 (83 fewer-18 fewer)
Infections in upper gastrointestinal bleeding	0.96 (0.79-1.17)	11 fewer per 1,000 (58 fewer-47 more)

NA = not applicable.
[a]Serious adverse events defined as an event that endangers the health or safety of the patient.

overtransfusion.[45] This recommendation is supported by four RCTs involving a total of 4,324 patients (evidence profile 3, supplementary material).[20-23]

The pooled analysis showed a trend toward higher mortality with the restrictive approach (RR, 1.13; 95% CI, 0.67-1.91), but this difference was not statistically significant. The MINT trial substantially influenced this analysis because of its large sample size because it recruited three times more patients than the other studies combined. The 30-day mortality in the restrictive group was 9.9%, compared with 8.3% in the permissive group, a difference not reaching statistical significance (RR, 1.19; 95% CI, 0.96-1.47). However, cardiac death rates were 5.5% in the restrictive group and 3.2% in the permissive group (RR, 1.74; 95% CI, 1.26-2.40). Moreover, the point estimates for myocardial infarction (MI) or death and for recurrent MI consistently favored the permissive strategy.[20] Although a statistically significant increase in adverse outcomes such as death and recurrent MI might not have been found, concern exists that a restrictive approach allowing hemoglobin levels of 7 or 8 g/dL might increase the risk of adverse outcomes in patients with acute MI. From these data, it was unclear whether a gradient effect was present in which risk progressively increased to < 10 g/dL or a threshold effect at 10 g/dL. That is, these data do not indicate whether 9 g/dL is as safe as 10 g/dL. Patient symptoms and physiologic variables should be considered when choosing a transfusion threshold for patients with ACS.

Long-term follow-up of patients described a 1-year mortality of 23.1% in the restrictive and 20.4% in the permissive group (RR, 1.87; 95% CI, 0.74-4.69).[31] Moreover, no significant differences were identified in hospital LOS, ICU LOS, or the risk of adverse events (Table 4). Overall, the increased point estimates in the risk of 30-day mortality, need for revascularization, and cardiac and renal adverse effects associated with a restrictive transfusion strategy outweighed the potential benefits on lower rates of infection and thromboembolism.

What Others Are Saying

The ESICM guidelines, released before the publication of the MINT trial, suggested an RBC transfusion threshold of 9 to 10 g/dL in patients with ACS.[20,37] However, given that it is unclear if a difference in outcomes occurs at higher hemoglobin levels, even in the range of a permissive approach, the panel opted to suggest against a restrictive approach.

Research Priorities

Studies exploring the impact on patient outcomes of a restrictive hemoglobin threshold of 8 g/dL or 9 g/dL are necessary. Further exploration of effect modifiers within the MINT trial may help to guide clinicians. Subgroup analysis, especially focused on type 1 MI vs 2 MI, as well as patients with heart failure and chronic kidney disease, are welcomed.

Question 4: Should critically ill patients undergoing cardiac surgery be treated with a restrictive or permissive RBC transfusion strategy?

4. In critically ill patients undergoing cardiac surgery, we suggest a restrictive RBC transfusion strategy over a permissive transfusion strategy during the perioperative period (Conditional Recommendation, Moderate Certainty of Evidence).

TABLE 4] Pooled Analysis Comparing Restrictive vs Permissive Strategies in Patients With Acute Coronary Syndrome

Outcome	Relative Risk (95% CI)	Absolute Risk (95% CI)
30-d mortality	1.13 (0.67-1.91)	10 more per 1,000 (26 fewer-73 more)
Need for revascularization	1.09 (0.73-1.63)	2 more per 1,000 (6 fewer-13 more)
Hospital length of stay	NA	MD 0.02 d more (0.37 fewer-0.41 more)
Adverse transfusion effects	1.87 (0.31-11.06)	1 more per 1,000 (1 fewer-10 more)
Infections	0.87 (0.17-4.40)	10 fewer per 1,000 (61 fewer-252 more)
Cardiac adverse events	1.16 (0.94-1.45)	10 more per 1,000 (4 fewer-29 more)
Renal adverse events	1.06 (0.84-1.32)	7 more per 1,000 (20 fewer-39 more)
Thromboembolism	0.75 (0.46-1.24)	5 fewer per 1,000 (10 fewer-5 more)
Pulmonary adverse events	0.96 (0.77-1.19)	3 fewer per 1,000 (17 fewer-14 more)

MD = mean difference; NA = not applicable.

Justification

This recommendation is substantiated by seven high-quality clinical trials mostly of patients undergoing coronary artery bypass graft, valvular surgery, or both.[27-29,33-36] Despite the moderate certainty of evidence, a conditional recommendation was issued because the studies showed serious imprecision in the point estimates for several outcomes (evidence profile 4, supplementary material).

Three studies examined 30-day mortality comparing both transfusion strategies in patients undergoing cardiac surgery.[27-29] Mazer et al[27] enrolled 5,243 patients, showing that a restrictive strategy was noninferior to a permissive approach and led to 20% less patients receiving RBC transfusions. Two smaller studies, although using slightly different transfusion thresholds, yielded similar outcomes.[28,29] In aggregate, no significant difference was found between the restrictive and permissive RBC transfusion threshold for 30-day mortality (RR, 1.12; 95% CI, 0.95-1.32). The hospital LOS did not differ between strategies (MD, –0.02 days; 95% CI, –0.19 to +0.15 days), whereas the ICU LOS favored the permissive strategy (MD, 0.12 days; 95% CI, 0.03-0.21 days), a finding without clinical significance.[27-29,33-36]

One small study evaluated adverse transfusion reactions, but reported no events in either group.[36] No differences were found between the restrictive and permissive strategies in terms of infections; thromboembolism; or cardiac, renal, or pulmonary complications (Table 5).[27-29,33-36]

Overall, no important differences in outcomes or adverse events were noted between strategies among the 8,208 patients enrolled in the seven trials. However, considering the 40% lower number of RBC units transfused to patients in the restrictive group, a restrictive strategy is the preferred approach.[28]

What Others Are Saying

This recommendation aligned with those of other professional societies, including the ESICM and the Society of Thoracic Surgeons, which recommend a restrictive approach in this patient population.[37,46]

Research Priorities

Further research may clarify the optimal RBC transfusion strategy for patients undergoing cardiac surgery. The Transfusion Requirements in Younger Patients Undergoing Cardiac Surgery (TRICS-IV) trial, currently underway, compares the two transfusion strategies in moderate to high-risk patients aged 65 years and younger to ensure that the benefits of a restrictive strategy also apply to this younger high-risk patient population.[47]

Question 5: Should critically ill patients with an isolated elevation of serum troponin levels without other evidence of cardiac ischemia be treated with a restrictive or a permissive RBC transfusion strategy?

5. In critically ill patients with isolated elevation of serum troponin without other evidence of cardiac ischemia, we suggest a restrictive RBC transfusion strategy over a permissive RBC transfusion strategy (Conditional Recommendation, Very Low Certainty of Evidence).

Justification

No data are available regarding RBC transfusion thresholds for critically ill patients with isolated elevated troponin levels without evidence of cardiac ischemia, defined as clinical symptoms, ECG changes, or both consistent with ischemia.[48] Despite the absence of

TABLE 5] Pooled Analysis Comparing Restrictive vs Permissive Strategies in Patients Who Have Undergone Cardiac Surgery

Outcome	Relative Risk (95% CI)	Absolute Risk (95% CI)
30-d mortality	1.12 (0.95-1.32)	8 more per 1,000 (3 fewer-21 more)
ICU length of stay	NA	MD 0.12 d more (0.03 more-0.21 more)
Hospital length of stay	NA	MD 0.02 d lower (0.19 lower-0.15 higher)
Infections	1.07 (0.94-1.22)	6 more per 1,000 (5 fewer-19 more)
Cardiac adverse events	1.00 (0.75-1.32)	0 fewer per 1,000 (14 fewer-18 more)
Renal adverse events	1.03 (0.86-1.23)	2 more per 1,000 (7 fewer-12 more)
Thromboembolism	0.82 (0.36-1.88)	2 fewer per 1,000 (8 fewer-10 more)
Pulmonary adverse events	1.05 (0.89-1.24)	6 more per 1,000 (14 fewer-30 more)

MD = mean difference; NA = not applicable.

evidence, the panel identified this as an important clinical question and formulated a recommendation using the collective experience approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluations criteria, considering several factors. First, no universally agreed-on definition for elevated troponin exists. This is attributable to the availability of various troponin assays for clinical use, resulting in variability in both reported units and accepted normal troponin values.[49] Moreover, troponin levels represent a test value, rather than a specific clinical diagnosis, particularly in critically ill patients, in whom elevated troponin levels may indicate diverse conditions unrelated to ACS.[50-53] Considering the heterogeneity of conditions leading to elevated troponin levels in the absence of acute cardiac ischemia, the risk-benefit assessment regarding RBC transfusion strategy will depend on individual clinical circumstances. In general, we suggest adopting a restrictive RBC transfusion strategy as the first-line approach. However, the decision to transfuse should consider various clinical factors, including vasculopathy, intravascular volume status, troponin level and rate of rise, biventricular cardiac function, myocardial strain or trauma, renal dysfunction, sepsis, and surrogates of end-organ perfusion. In certain circumstances, clinicians may choose to transfuse RBCs to increase oxygen-carrying capacity.

What Others Are Saying

To our knowledge, no recommendations from other professional societies have been published.

Question 6: Should critically ill patients with septic shock with end-organ hypoperfusion be treated with RBC transfusion in addition to usual care or usual care alone?

6. In patients with septic shock and end-organ hypoperfusion, we suggest against adding permissive RBC transfusion thresholds to usual care (Conditional Recommendation, Low Certainty of Evidence).

Remarks: Studies evaluating protocol-driven approaches to goal-directed therapy in septic shock were not considered in the evidence review.

Justification

Sepsis care has evolved over the last 2 decades, with usual care including prompt antibiotic and fluid administration and hemodynamic stabilization. Moreover, RBC transfusion practices in septic shock have shifted[54,55] toward a restrictive approach.[39,56,57] Consequently, the addition of RBC transfusions to usual care, aiming for higher hemoglobin levels, implies a permissive transfusion strategy, whereas usual care adheres to a restrictive approach. Studies evaluating RBC transfusions as part of a resuscitation bundle were not included, because the effect of transfusions could not be isolated from the effect of other bundle elements.

This recommendation is informed by three RCTs and long-term follow-up of an RCT cohort.[16,19,30,32] Two of the RCTs focused on general critically ill patients, whereas one RCT included patients with cancer, all of whom had septic shock, with higher RBC transfusion rates in the permissive groups compared with the restrictive groups (evidence profile 5, supplementary material).

Transfusion Requirements in Septic Shock (TRISS), the largest study including > 1,000 patients, reported similar 30-day mortality rates in the permissive (35%) and restrictive (33%) approaches.[30] In patients with cancer, lower, albeit not statistically significant, 30-day mortality (hazard ratio, 0.74; 95% CI, 0.53-1.04; $P = .08$) and ICU mortality rates (33.6% vs 43.7%; $P = .071$) were reported in the permissive compared with the restrictive group,[19] findings consistent with a smaller study in general critically ill patients.[16] The pooled analysis showed no significant difference between permissive and restrictive RBC transfusion strategies in terms of ICU mortality (RR, 0.84; 95% CI, 0.62-1.13) or 30-day mortality (RR, 0.93; 95% CI, 0.72-1.21). Longer-term follow-up at 1 year reported mortality rates of 55.8% in the permissive group and 53.5% in the restrictive cohort (RR, 0.97; 95% CI, 0.85-1.09; $P = .62$).[32] No difference was found in terms of ICU and hospital LOS between both strategies.

Given that the studies evaluating adverse transfusion reactions were not powered a priori to detect such events, the number of events was very low. No strategy was superior regarding the need for renal replacement, cardiac, or pulmonary complications (Table 6).[19,30] Overall, although the data show that the permissive strategy might result in benefit, it does not exclude possible harm because the RR crosses the null threshold. In the absence of clear benefit and with similar rates of adverse effects, neither strategy is deemed clinically favorable. However, a restrictive approach results in fewer RBC units transfused, optimizing resource use and decreasing costs.[30]

TABLE 6] Pooled Analysis Comparing Permissive vs Restrictive Strategies in Patients With Septic Shock

Outcome	Relative Risk (95% CI)	Absolute Risk (95% CI)
ICU mortality	0.84 (0.62-1.12)	71 fewer per 1,000 (169 fewer-58 more)
30-d mortality	0.93 (0.72-1.21)	27 fewer per 1,000 (108 fewer-81 more)
Adverse transfusion reactions	0.33 (0.01-8.15)	1 fewer per 1,000 (2 fewer-11 more)
Need for renal replacement therapy	0.98 (0.61-1.57)	2 fewer per 1,000 (34 fewer-50 more)
Cardiac complications	0.60 (0.27-1.31)	11 fewer per 1,000 (19 fewer-8 more)
Pulmonary complications	1.05 (0.60-1.82)	10 more per 1,000 (77 fewer-159 more)

What Others Are Saying

The recommendation to not add a permissive RBC transfusion strategy to usual care aligns with the most recent ESICM and the Surviving Sepsis Campaign guidelines.[37,58]

Research Priorities

Future studies including populations typically underrepresented in sepsis trials, such as patients with malignancies (solid and hematologic), liver disease, and chronic coronary disease, are welcome. Additionally, further evidence is needed regarding the benefits of RBC transfusions in severe hypoxemia or tissue hypoperfusion.

Additional Considerations

The statements on cost, equity, acceptability, feasibility, and implementation were consolidated, given the significant overlap across various Population, Intervention, Comparator, and Outcome questions.

Cost

Economic considerations are important when deciding on RBC transfusion strategies for critically ill patients. In the United States, the hospital cost of an RBC unit is approximately $207,[59] with administrative, logistic, and labor costs totaling up to $1,183.[60,61] A restrictive strategy spares 36% of patients from RBC transfusions, reduces the number of RBC units transfused by 50%, and reduces costs by 33% compared with a permissive approach.[28,30]

Cost-effectiveness analysis of RBC transfusions in patients undergoing cardiac surgery revealed that expenses from surgery to the third postoperative month were slightly higher in the permissive group than in the restrictive group, driven by RBC costs. However, the differences in quality-adjusted life-years were negligible. Therefore, the restrictive strategy in these patients was considered cost-effective.[62]

Although a definitive evaluation of cost-effectiveness is challenging because of limited studies in the critically ill population, a restrictive approach is deemed cost-effective overall and among most subpopulations because no significant impact on overall mortality in any major subgroups was observed, except for ACS. Therefore, in the general critically ill population, in the absence of benefit resulting from a permissive strategy, a restrictive strategy would be considered a preferred option under most circumstances.

Equity

Access to RBC transfusions is influenced by geographic location and resource allocation. A restrictive RBC transfusion strategy can reduce inequity by ensuring that individuals most in need of RBCs receive them. This may be even more relevant during major blood shortages or in rural areas with limited resources. Moreover, in countries with higher rates of blood-borne infections, a restrictive approach will reduce exposure. However, the impact of provider biases on transfusion practices in settings of limited RBC availability remains unclear.

Acceptability and Feasibility

The evidence suggested that most practitioners and centers have adopted a restrictive RBC transfusion strategy, indicating stakeholder acceptability.[63] However, some patients may reject transfusions based on personal values or religious beliefs.[64] The panel believed that implementing restrictive transfusion strategies is feasible through behavior modification interventions, including education, institutional guidelines, and audit and feedback. Furthermore, additional blood conservation strategies, such as reduced laboratory testing, optimization of perioperative antiplatelet and anticoagulation regimens, intraoperative blood conservation, and small-volume blood sampling, are crucial. These interventions have demonstrated effectiveness in reducing the odds of transfusion,

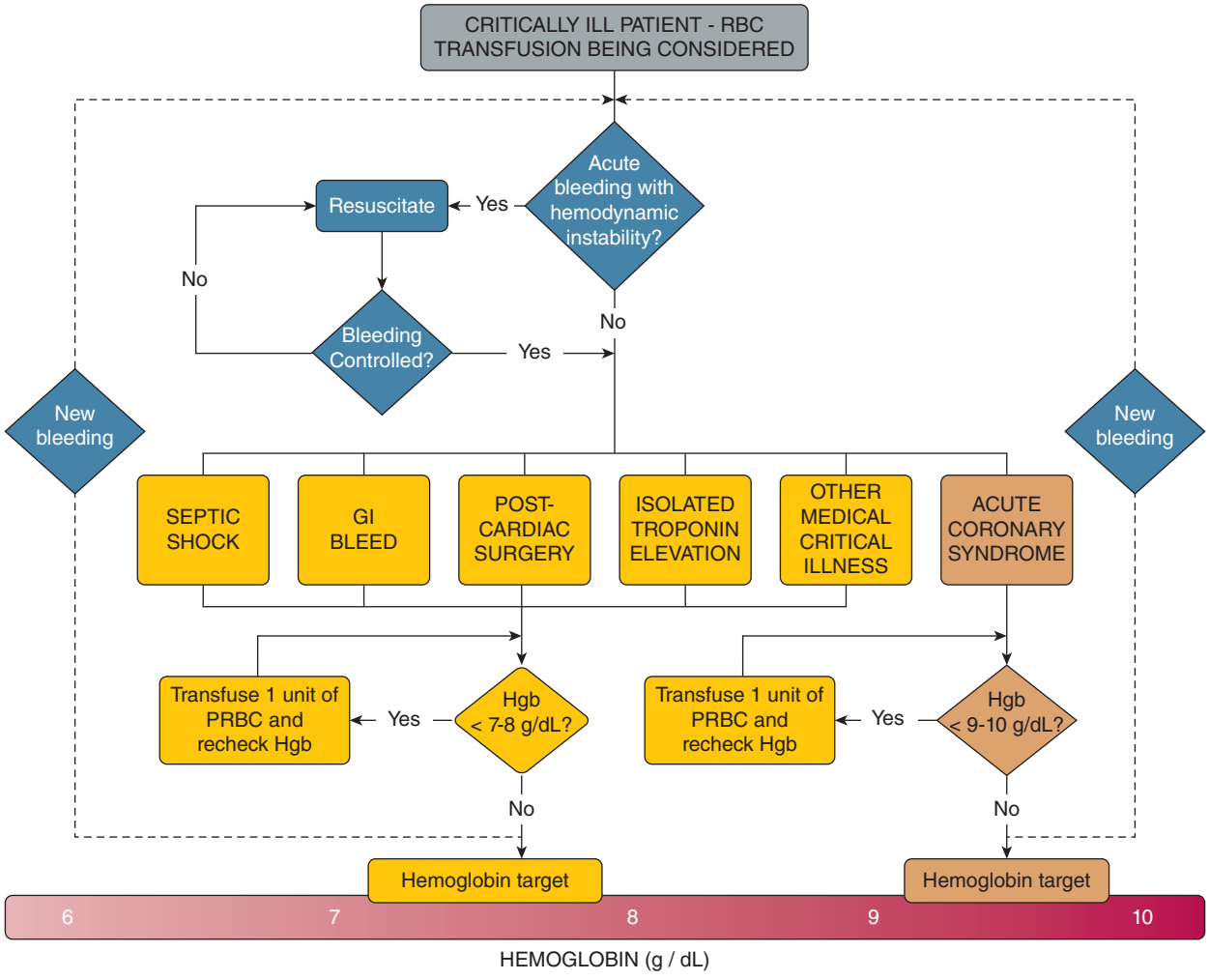

Figure 1 – *Suggested approach to RBC transfusion in critically ill patients. Hgb = hemoglobin; PRBC = packed RBC.*

inappropriate transfusion rates, and the number of RBC units transfused per patient.[65-67]

Implementation

For patients reluctant to accept transfusions based on personal values or religious beliefs, a thorough discussion with the patient or surrogate should occur before deciding to transfuse. As soon as an RBC transfusion is decided on, the optimal implementation strategy encompasses a restrictive approach and transfusing one RBC unit at a time. This threshold and single-unit recommendation does not apply to patients actively bleeding at a rate exceeding the ability to transfuse single units or await hemoglobin test results safely. The recommendation can be applied to patients whose acute bleeding has subsided. If acute bleeding occurs during a patient's stay, this approach should be suspended and then reapplied after bleeding is controlled (Fig 1).

The panel suggested conducting audits or observational studies using hospital databases to understand current practices. Proven implementation strategies to overcome barriers to changing transfusion include academic detailing, audit-feedback approaches, standard order sets, computerized order entry decision support, reminders, and alerts. These approaches require resources, leadership, and clinical oversight.[68-72]

Summary

In the United States, approximately 5 million patients are admitted to the ICU annually, and one-quarter of them receive RBC transfusions during their stay.[1-3,73] Most clinical trials support a restrictive transfusion strategy, showing no significant differences in mortality or adverse outcomes overall and in all patient subgroups, except for critically ill patients with ACS.[20,22,23]

Adopting a restrictive strategy could decrease the number of patients receiving RBC transfusions by approximately 40%.[38] On a large scale, this could represent sparing 0.5 million patients from RBC transfusions.

A limitation of this guideline is the quality of the evidence, which ranged from moderate to very low. For conditions like ACS and septic shock, the number of studies was small, and the inferences were not strong. No studies specifically addressed critically ill patients with elevated troponin levels. Moreover, the studies did not assess additional aspects of the transfusion process (storage age, donor characteristics, processing, storage solutions). These guidelines provide an opportunity for institutions to develop local policies, monitor their impact on transfusion practices, and to create a framework to longitudinally optimize RBC use.

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Additional information: The e-Appendix, e-Figures, and e-Tables are available online under "Supplementary Data."

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