Clinical practice guideline: Red blood cell transfusion in adult trauma and critical care*

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Objective: ●●●. (Crit Care Med 2009; 37:000–000) anemia; hemorrhage; critical care; trauma
KEY WORDS: transfusion; red blood cell transfusion; blood;

I. STATEMENT OF THE PROBLEM

Red blood cell (RBC) transfusion is common in critically ill and injured patients. Many studies (Table 1) (1–6) have documented the widespread use of RBC transfusion in critically ill patients and the data from these studies from diverse locations in Western Europe, Canada, the United Kingdom, and the United States reveal remarkably similar findings, with approximately 40% of patients receiving RBC transfusions, with a mean of 5 RBC units transfused per patient, and a pretransfusion hemoglobin (Hb) of 8.5 g/dL.

RBC transfusions are utilized to treat hemorrhage and anemia as well as to improve oxygen delivery to tissues. Blood transfusion is clearly indicated for the treatment of hemorrhagic shock, particularly in patients who have reached critical oxygen delivery. Independent of the mechanism of injury, hemorrhagic shock consistently represents the second leading cause of early deaths among the injured, with only central nervous system injury consistently more lethal.

However, most RBC transfusions in the intensive care unit (ICU) (90% in the CRIT Trial in the United States) are used for the treatment of anemia (Anemia and Blood Transfusion in Critical Care [ABC[1]] and Anemia and Blood Transfusion in the Critically Ill [CRIT[2]] trials). The efficacy of RBC transfusion in hemodynamically stable trauma and critically ill patients with anemia has not been demonstrated in most clinical settings. Historically, the decision to transfuse has been guided by an Hb concentration, "transfusion trigger." A reevaluation of this practice has been prompted by the growing recognition of transfusion-related complications, such as transfusion-related infections and immunosuppression, studies that demonstrate RBC transfusion may be associated with worse clinical outcomes and most evidence documenting lack of efficacy.

Although recent data suggested that critically ill patients in general can tolerate anemia to an Hb level of 7 g/dL, concerns have been raised that this level of anemia may not be well tolerated by certain critically ill or injured patients, such as those with preexisting coronary, cerebrovascular, and pulmonary disease. Finally, some clinicians retain the belief that certain conditions may require higher Hb concentrations, such as acute respiratory distress syndrome (ARDS), sepsis and multiple organ failure (MOF), traumatic brain injury and cerebrovascular diseases.

A number of prior guidelines regarding the indications for RBC transfusion have been published (Table 2) including the following:

1. American College of Physicians. Practice Strategies for Elective RBC Transfusion (7).
2. Practice Guidelines for Blood Component Therapy; American Society of Anesthesiologists 1996 (8).
3. Practice Guidelines for perioperative blood transfusion and adjuvant therapies: an updated report. American Society of Anesthesiologists 2006 (9).
4. National Institutes of Health Consensus Conference on Perioperative RBC Transfusion (10).
5. Perioperative blood transfusion for elective surgery. A national clinical guideline. Scottish Intercollegiate Guidelines Network; initially published in 2001, updated in 2004 (11, 12).
6. Guidelines for RBC and plasma transfusion for adults and children. Report of the Canadian Medical Association Expert Working Group, 1997 (13).
7. Guidelines for Transfusion in the Trauma Patient—SOP for Clinical Care 2006 (14).
8. Perioperative Blood Transfusion and Blood Conservation in Cardiac Surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists Clinical Practice Guideline, 2007 (15).

None of these guidelines specifically addresses the issue of RBC transfusion in critically ill and injured adult patients. This guideline reviews the evidence regarding RBC transfusion in adult trauma and critical illness. It will not address issues related to neonates and children.

Questions

1. What are the risks and benefits of RBC transfusion in critically ill and injured patients?
2. What are the indications for RBC transfusion? During resuscitation, during hospitalization?

*See also p. xxx.

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The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e3181b39f1b

Table 1. Results of epidemiologic studies on anemia and blood transfusion in critical care and trauma

ABC Study: Prospective multicenter observational study of ICU patients in Western Europe. Enrollment November 1999. Follow-up for 28 days or until hospital discharge. 146 ICUs with 3534 patients enrolled.

CRIT Study: Prospective multicenter observational cohort study of ICU patients in U.S. Enrollment August 2000–April 2001, within 48 hrs of ICU admission. Follow-up for 30 days, hospital discharge or death. In sum, 284 ICUs in 213 hospitals with 4892 patients enrolled.

SOAP Study: Prospective multicenter observational cohort study of ICU patients in Europe. Enrollment May 1–May 15, 2002. Follow-up until death, until hospital discharge or for 60 days. A total of 198 European ICUs with 3147 patients enrolled.

	ABC Trial (Western Europe)[1]	SOAP Study (Europe)[2]	CRIT Study (USA)[3]	Trauma Patients From CRIT Study (USA)[4]	TRICC Investigators (Canada)[5]	North Thames Blood Interest Group (UK)[6]	ABA Multicenter Trials Group (US, Canada)[7]	ATICS Study (Scotland, UK)[8,9]
n	3534	3147	4892	576	5298	1247	666	1023
Mean admission Hb, g/dL	11.3 ± 2.3	—	11.0 ± 2.4	11.1 ± 2.4	9.9 ± 2.2	—	—	—
Percentage of patients transfused in ICU	37.0%	33.0%	44.1%	55.4%	25.0%	53.4%	74.7%	39.5%
Mean transfusions per patient, units	4.8 ± 5.2	5.0 ± 5.8	4.6 ± 4.9	5.8 ± 5.5	4.6 ± 6.7	5.7 ± 5.2	13.7 ± 1.1	1.2–1.9
Mean pretransfusion Hb, g/dL	8.4 ± 1.3	—	8.6 ± 1.7	8.9 ± 1.8	8.6 ± 1.3	—	9.3 ± 0.1	7.4–7.9
Mean ICU length of stay, days	4.5	—	7.4 ± 7.3	9.4 ± 8.6	4.8 ± 12.6	—	—	2.2 (0.9–6.8)
ICU mortality	13.5%	—	13.0%	—	22.0%	21.5%	—	25%
Hospital mortality	20.2%	—	17.6%	9.9%	—	—	21.0%	—
Admission APACHE II, mean	14.8 ± 7.9	—	19.7 ± 8.2	16.9 ± 8.2	18 ± 11	18.1 ± 9.1	—	19.8 ± 7.7

ABC, anemia and blood transfusion in critical care; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; TRICC, transfusion requirements in critical care, ATICS, audit of transfusion in intensive care in Scotland.

Data are expressed as mean ± standard deviation.

[1]Vincent JL, Baron JF, Reinhart K, et al: ABC (Anemia and Blood Transfusion in Critical Care) Investigators. Anemia and blood transfusion in critically ill patients. *JAMA* 2002; 288:1499–1507.

[2]Vincent JL, Sakr Y, Sprung C, et al: Are blood transfusion associated with greater mortality rates? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study. *Anesthesiology* 2008; 108:31–39.

[3]Corwin HL, Gettinger A, Pearl RG, et al: The CRIT Study: Anemia and blood transfusion in the critically ill—Current clinical practice in the United States. *Crit Care Med* 2004; 32:39–52.

[4]Shapiro MJ, Gettinger A, Corwin H, et al: Anemia and blood transfusion in trauma patients admitted to the intensive care unit. *J Trauma* 2003; 55:269–274.

[5]Hebert 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; 340:409–417.

[6]Rao MP, Boralessa H, Morgan C, et al: Blood component use in critically ill patients. *Anesthesia* 2002; 57:530–534.

[7]Palmieri TL, Caruso DM, Foster KN, et al: Effect of blood transfusion on outcome after major burn injury: A multicenter study. *Crit Care Med* 2006; 34:1602–1607.

[8]Walsh TS, Garrioch M, Maciver C, et al: Audit of Transfusion in Intensive Care in Scotland Study Group. Red cell requirements for intensive care units adhering to evidence-based transfusion guidelines. *Transfusion* 2004; 44:1405–1411.

[9]Walsh TS, McClelland DB, Lee RJ, et al: Prevalence of ischemic heart disease at admission to intensive care and its influence on red cell transfusion thresholds: multicenter Scottish Study. *Br J Anaesth* 2005; 94:445–452.

3. What are the alternatives to RBC transfusions?
4. What practices are useful in decreasing need for rbc transfusions?

This clinical practice guideline will focus on RBC transfusion in critically ill and injured patients with anemia and hemodynamic stability and will not address the issue of RBC transfusion in uncontrolled hemorrhage further. It will also not address other blood component therapy, such as plasma, cryoprecipitate, and platelet transfusions (16).

Goals of the Guideline

1) To review the evidence regarding efficacy of RBC transfusion in trauma and critical care.
2) To review the evidence regarding risks of RBC transfusion in trauma and critical care.
3) To review indications for RBC transfusion in critically ill and injured patients.
4) To review possible alternatives to RBC transfusions.
5) To review practices that have been associated with decreased need for RBC transfusion.

II. PROCESS

The joint planning group (Eastern Association for the Surgery of Trauma [EAST] and Society of Critical Care Medicine [SCCM]) included trauma surgeons, intensivists, ICU nurse, respiratory therapist, and pharmacist.

Literature for review included the following process:

- MEDLINE, EMBASE, and Cochrane database search from 1980 through July 2006, English language;
- Articles identified and classified;
- Case reports and editorials excluded;
- Pediatric (<16 yrs of age) excluded.

A computerized search of the National Library of Medicine was undertaken. English language citations during the period of 1980 through July 2006, using the words transfusion, blood transfusion, RBC transfusion were identified from the database of journal articles. Additional references were identified by review of bibliographies of relevant published articles. Of the articles identified, those dealing with either prospective or retrospective series were selected. The following groups of articles were eliminated from analysis: 1) literature review articles; 2) wartime experiences; and 3) articles from institutions which were duplicative. The criteria for reference selection were publication in a peer-reviewed journal and English language. The articles were re-

Table 2. Prior guidelines regarding blood transfusion

1996 Practice Guidelines for blood component therapy; American Society of Anesthesiologists
"The principal conclusions of the task force are that RBC transfusions should not be dictated by a single Hb "trigger" but instead should be based on the patient's risks of developing complications of inadequate oxygenation. RBC transfusion is rarely indicated when the Hb concentration is greater than 10 g/dL and is almost always indicated when it is less than 6 g/dL."

2006 Practice Guidelines for perioperative blood transfusion and adjuvant therapies: An updated report by the American Society of Anesthesiologists task Force on Perioperative Blood Transfusion and Adjuvant Therapies. *Anesthesiology* 2006; 105:198–208
"RBCs should usually be administered when the Hb concentration is low (e.g., less than 6 g/dl in a young, healthy patient), especially when the anemia is acute. RBCs are usually unnecessary when the Hb concentration is more than 10 g/dL. These conclusions may be altered in the presence of anticipated blood loss. The determination of whether intermediate Hb concentrations (i.e., 6–10 g/dL) justify or require RBC transfusion should be based on any ongoing indication of organ ischemia, potential or actual ongoing bleeding (rate and magnitude), the patient's intravascular volume status, and the patient's risk factors for complications of inadequate oxygenation. These risk factors include a low cardiopulmonary reserve and high oxygen consumption."

Guidelines for RBC and plasma transfusion for adults and children. Report of the Canadian Medical Association Expert Working Group. 1997. [i] *CMAJ* 1997
Recommendations regarding the transfusion of red blood cells.

5. A physician prescribing transfusion of red blood cells or plasma should be familiar with the indications for and the benefits and risk from the use of these fractions.
Level of evidence: N/A
6. Documentation that supports the administration of the red blood cells or plasma should be found in the patient's chart.
Level of evidence: N/A
7. Red blood cell transfusions should be administered primarily to prevent or alleviate symptoms, signs or morbidity due to inadequate tissue oxygen delivery (resulting from a low red blood cell mass).
Level of evidence: II
8. There is no single value of hemoglobin concentration that justifies or requires transfusion; an evaluation of the patient's clinical situation should also be a factor in the decision.
Level of evidence: II
9. In the setting of acute blood loss, red blood cell transfusion should not be used to expand vascular volume when oxygen-carrying capacity is adequate.
Level of evidence II
10. Anemia should not be treated with red blood cell transfusions if alternative therapies with fewer potential risks are available and appropriate.
Level of evidence: II

Levels of evidence: The definition of the levels of evidence used to grade the recommendations in these guidelines is a modified version of that used by the Canadian Task Force on the Periodic Health Examination:
Level I: Evidence obtained from at least one properly randomized controlled trial.
Level II: Evidence obtained from well-designed controlled trials without randomization, cohort or case-control analytic studies, preferably from more than one center, or research or evidence obtained from comparisons between times or places with or without the intervention.
Level III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.
Not applicable (N/A): opinions of the EWG about issues that cannot be evaluated using accepted study designs.

[i] Guidelines for RBC and plasma transfusion for adults and children. Report of the Canadian Medical Association Expert Working Group. *Can Med Assoc J* 1997; 1;156(11 Suppl):S1–S24.

viewed and this practice management guideline developed by a joint taskforce of the EAST and the SCCM.

Assessment (Grading) of Scientific Evidence. All relevant empirical data were evaluated for clinical benefits and harms of the various interventions. Attempts were made to collect as much quality scientific data as possible. This included utilizing previously published national consensus based guidelines. Proper methods including a variety of databases and cross checking of citations were used to ensure that these standards are met and biases avoided. Reference sections of the articles identified were also utilized to gather additional articles and the Cochrane database was utilized to assure that all prospective, randomized, controlled trials were identified and collected for review. The scientific evidence assessment methods employed by the Canadian and U.S. Preventive Task Force were applied when classifying the articles identified for review (Table 3).

III. RECOMMENDATIONS SUMMARY

A. Recommendations Regarding Indications for RBC Transfusion in the General Critically Ill Patient

1. RBC transfusion is indicated for patients with evidence of hemorrhagic shock.
2. RBC transfusion may be indicated for patients with evidence of acute hemorrhage and hemodynamic instability or inadequate oxygen delivery.
3. A "restrictive" strategy of RBC transfusion (transfuse when Hb <7 g/dL) is as effective as a "liberal" transfusion strategy (transfusion when Hb <10 g/dL) in critically ill patients with hemodynamically stable anemia, except possibly in patients with acute myocardial ischemia.
4. The use of only Hb level as a "trigger" for transfusion should be avoided. Decision for RBC transfusion should be based on an individual patient's intravascular volume status, evidence of shock, duration and extent of anemia, and cardiopulmonary physiologic parameters.
5. In the absence of acute hemorrhage, RBC transfusion should be given as single units.
6. Consider transfusion if Hb is <7 g/dL in critically ill patients requiring mechanical ventilation (MV). There is no benefit of a "liberal" transfusion strategy (transfusion when Hb is <10 g/dL) in critically ill patients requiring MV.
7. Consider transfusion if Hb is <7 g/dL in resuscitated critically ill trauma patients. There is no benefit of a "liberal" transfusion strategy (transfusion when Hb is <10 g/dL) in resuscitated critically ill trauma patients.
8. Consider transfusion if Hb is <7 g/dL in critically ill patients with stable cardiac disease. There is no benefit of a "liberal" transfusion strategy

Table 3. Grading system

Grading of Evidence

Class I: Prospective randomized controlled trials (PRCTs)—the gold standard of clinical trials. Some may be poorly designed, have inadequate numbers, or suffer from other methodologic inadequacies.

Class II: Clinical studies in which the data were collected prospectively, and retrospective analyses which were based on clearly reliable data. Types of studies so classified include: observational studies, prospective cohort studies, prevalence studies, and case control retrospective studies.

Class III: Clinical studies based on retrospective data collection. Evidence used in this class includes clinical series, database or registry review, large series of case reviews, and expert opinion.

Grading of Recommendations

Level 1: The recommendation is convincingly justifiable based on the available scientific information alone. This recommendation is usually based on Class I data, however, strong Class II evidence may form the basis for a level 1 recommendation, especially if the issue does not lend itself to testing in a randomized format. Conversely, low quality or contradictory Class I data may not be able to support a level 1 recommendation.

Level 2: The recommendation is reasonably justifiable by available scientific evidence and strongly supported by expert opinion. This recommendation is usually supported by Class II data or a preponderance of Class III evidence.

Level 3: The recommendation is supported by available data but adequate scientific evidence is lacking. This recommendation is generally supported by Class III data. This type of recommendation is useful for educational purposes and in guiding future clinical research.

(transfusion when Hb is <10 g/dL) in critically ill patients with stable cardiac disease.

9. RBC transfusion should not be considered as an absolute method to improve tissue oxygen consumption in critically ill patients.
10. RBC transfusion may be beneficial in patients with acute coronary syndromes (ACSs) who are anemic (Hb ≤8 mg/dL) on hospital admission.

B. Recommendations Regarding RBC Transfusion in Sepsis
   1. The transfusion needs for each septic patient must be assessed individually because optimal transfusion triggers in sepsis patients are not known and there is no clear evidence that blood transfusion increases tissue oxygenation.

C. Recommendations Regarding RBC Transfusion in Patients at Risk for or With Acute Lung Injury (ALI) and ARDS

ALI and ARDS are common clinical sequelae of massive transfusion. Prior studies have suggested that RBC transfusion is associated with respiratory complications including ALI and ARDS that remains even after adjusting for potential confounders.

1. There are insufficient data to support Level 1 recommendations on this topic.
2. All efforts should be initiated to avoid RBC transfusion in patients at risk for ALI and ARDS after completion of resuscitation.
3. All efforts should be made to diagnose and report transfusion-related acute lung injury (TRALI) to the local blood bank because it has emerged as a leading cause of transfusion-associated morbidity and mortality, despite underdiagnosis and underreporting.
4. RBC transfusion should not be considered as a method to facilitate weaning from MV.

D. Recommendations Regarding RBC Transfusion in Patients With Neurologic Injury and Diseases
   1. There are insufficient data to support Level 1 recommendations on this topic.
   2. There is no benefit of a "liberal" transfusion strategy (transfusion when Hb is <10 g/dL) in patients with moderate-to-severe traumatic brain injury.
   3. Decisions regarding blood transfusion in patients with subarachnoid hemorrhage (SAH) must be assessed individually because optimal transfusion triggers are not known and there is no clear evidence that blood transfusion is associated with improved outcome.

E. Recommendations Regarding RBC Transfusion Risks
   1. RBC transfusion is associated with increased nosocomial infection (wound infection, pneumonia, sepsis) rates independent of other factors.
   2. RBC transfusion is an independent risk factor for MOF and SIRS.
   3. There is no definitive evidence that prestorage leukocyte depletion of RBC transfusion reduces complication rates, but some studies have shown a reduction in infectious complications.
   4. RBC transfusions are independently associated with longer ICU and hospital length of stay, increased complications, and increased mortality.
   5. There is a relationship between transfusion and ALI and ARDS.

F. Recommendations Regarding Alternatives to RBC Transfusion
   1. The rHuEpo administration improves reticulocytosis and hematocrit and may decrease overall transfusion requirements.
   2. HBOCs are undergoing investigation for use in critically ill and injured patients but are not yet approved for use in the United States.

G. Recommendations Regarding Strategies to Reduce RBC Transfusion
   1. The use of low-volume adult or pediatric blood sampling tubes is associated with a reduction in phlebotomy volumes and a reduction in blood transfusion.
   2. The use of blood conservation devices for reinfusion of waste blood with diagnostic sampling is associated with a reduction in phlebotomy volume.
   3. Intraoperative and postoperative blood salvage and alternative methods for decreasing transfusion may lead to a significant reduction in allogeneic blood usage.

4. Reduction in diagnostic laboratory testing is associated with a reduction in phlebotomy volumes and a reduction in blood transfusion.

IV. SCIENTIFIC FOUNDATION

Critically ill patients receive a large number of blood transfusions (Table 1) (17). Between 40% and 50% of all patients admitted to ICUs receive at least one allogeneic RBC unit and average close to 5 units of RBCs during their ICU admission. RBC transfusion is not risk free, and there is little evidence that routine transfusion of stored allogeneic RBCs is beneficial to hemodynamically stable critically ill patients with anemia. RBC transfusion is currently the only treatment strategy available for replacement of blood loss in patients with hemorrhagic shock (18). The largest numbers of RBC transfusions, however, are used for the treatment of anemia in critically ill and injured patients (19). A number of studies have documented that <20% of the transfusions in the ICU are used for the treatment of hemorrhagic shock.

Blood is a scarce and costly resource. Transfusion is often required in major trauma and critical illness but blood may not be readily available, and concerns remain over the potential adverse consequences of allogeneic blood transfusion (20–29). Despite evolving evidence that transfusion risks outweigh benefits in some patients, the critically ill and injured continue to receive large quantities of blood for treatment of anemia.

Anemia (defined as Hb <13 g/dL for adult males and <12 g/dL for adult nonpregnant females by the World Health Organization) is common in the ICU (30). Several studies have documented the prevalence of anemia on admission to the ICU (Table 1). The ABC study[1] was a cohort study of 3534 patients admitted to 146 Western European ICUs and found that the mean Hb at ICU admission was 11.3 g/dL, 63% had an Hb <12 g/dL, and 29% had an admission Hb <10 g/dL. A similar study in the CRIT[2] trial examined 4892 patients and documented a mean Hb at ICU admission of 11.0 g/dL. Both studies documented that anemia was more frequent and more severe in older patients and in those with longer ICU length of stay. Both studies also documented that 13% of patients had a recent history of anemia as a comorbidity. The CRIT trial documented that most RBC transfusions in the ICU (90%) were used for the treatment of anemia. Both the ABC and the CRIT studies reported that blood transfusion was associated with increased mortality in ICU patients.

Most recently, the relationship of blood transfusion to mortality was also investigated in European ICUs (31). The Sepsis Occurrence in Acutely Ill Patients (SOAP) study was a multicenter, observational study that included all adult patients admitted to 198 European ICUs between May 1 and May 15, 2002 and followed them until death, hospital discharge, or for 60 days. Patients were classified depending on whether they had received a blood transfusion at any time during their ICU stay. Of 3147 patients, 1040 (33.0%) received a blood transfusion. These patients were older (mean age = 62 yrs vs. 60 yrs; $p = .035$) and were more likely to have liver cirrhosis or hematologic cancer, to be a surgical admission, and to have sepsis. They had a longer duration of ICU stay (5.9 days vs. 2.5 days; $p < .001$) and a higher ICU mortality rate (23.0 vs. 16.3%; $p < .001$) but were also more severely ill on admission (Simplified Acute Physiology Score [SAPS] II, 40.2 vs. 34.7; $p < .001$; Sequential Organ Failure Assessment [SOFA] score, 6.5 vs. 4.5; $p < .001$). There was a direct relationship between the number of blood transfusions and the mortality rate. But in multivariate Cox regression analysis including sex and age, type of admission, main medical history (including cancer or hematologic cancer, cirrhosis, chronic lung disease), fluid balance, SAPS II, and severity of organ dysfunction on admission as measured by SOFA score, blood transfusion was not significantly associated with a worse mortality rate. Furthermore, in 821 pairs matched according to a propensity score, there was a higher 30-day survival rate in the transfusion group than in the other patients ($p = .004$). This observational study does not support the view that blood transfusions are associated with increased mortality rates in acutely ill patients.

Importantly, the SOAP study used the same approach as in the ABC study but found different results. In the ABC study, few data were collected regarding leuko-depleted blood (46% of centers indicated that they used leuko-depleted blood most of the time, 35% used it some of the time, and 19% never used it), showing simply that it was not widely used in Europe at that time. In the SOAP study, 76% of centers who replied were routinely using leuko-depleted blood, demonstrating that leuko-depleted blood is now much more commonly used across Europe. It is interesting to speculate that this may account, in part, for the differences between the previous ABC study and the more recent SOAP study.

Anemia of critical illness is a distinct clinical entity characterized by blunted erythropoietin production and abnormalities in iron metabolism identical to what is commonly referred to as anemia of chronic disease (32, 33). There are multiple causes of anemia in the critically ill and injured patients including 1) excessive phlebotomy for diagnostic laboratory testing; 2) active hemorrhage or ongoing blood loss, such as in renal failure patients requiring renal replacement therapy; and 3) underproduction or reduced erythropoiesis (34). Reduced erythropoiesis in the critically ill is related to multiple etiologies:

- Blunted erythropoietic response to low Hb (35, 36);
- Inflammatory responses (tumor necrosis factor [TNF], interleukin [IL]-1 and IL-6) (37–39);
- Increased hepcidin (peptide hormone that regulates iron metabolism in response to erythropoietic demand, iron stores, and inflammation) (40, 41);
- Iron deficiency, deficiencies of vitamins and/or factors;
- Underlying disease state (renal failure).

There are some clear benefits of RBC transfusion including the following:

- Increase in oxygen delivery ($\dot{D}o_2$) to tissues, but no evidence of increased oxygen consumption ($\dot{V}o_2$) (42–47);
- Increase cell mass and blood volume post acute hemorrhage or blood loss;
- Alleviate symptoms of anemia (dyspnea, fatigue, diminished exercise tolerance);
- Relief of cardiac effects of severe anemia with critical $\dot{D}o_2$.

There are, however, also substantial risks associated with RBC transfusion:

- Fluid overload, pulmonary edema, posttransfusion circulatory overload;
- Fever, acute transfusion reactions;
- Increased MOF (48, 49);
- Increased infection (50–56);
- Transfusion-associated immunomodulation (TRIM) (57, 58);
- Transfusion-associated leukocyte microchimerism(59–63);

- Human error—incorrect blood component (64, 65);
- TRALI (66–68);
- Transfusion-associated circulatory overload (TACO) (69, 70);
- Hypothermia, coagulopathy (dilutional), thrombocytopenia with massive transfusion.

Risks of RBC transfusion may be related to the "storage lesion" of RBCs (RBC changes that occur during ex vivo storage including reduction in deformability, altered adhesiveness and aggregability, reduction in 2,3-DPG and ATP, accumulation of bioactive compounds with proinflammatory effects which all reduce posttransfusion viability of RBCs) (71–74) donor leukocytes, inflammatory mediators, donor leukocyte microchimerism and other factors(75).

V. RECOMMENDATIONS WITH RATIONALE

A. Recommendations Regarding Indications for RBC Transfusion in the General Critically Ill Patient

1. RBC transfusion is indicated for patients with evidence of hemorrhagic shock.

Rationale. There is little Level 1 evidence that directly addresses administration of RBC transfusion to critically ill patients with hemorrhagic shock. The Advanced Trauma Life Support (ATLS) resuscitation guidelines include early empirical administration of RBC transfusion in trauma patients with evidence of hemorrhagic shock that is not corrected by 2 L of crystalloid fluid resuscitation (76). The decision to administer RBC transfusion during initial resuscitation in trauma or related to other causes of acute hemorrhage (gastrointestinal bleeding, vascular etiologies of hemorrhage, etc.) is not based on measurement of Hb concentration but on the physiologic state of the individual patient, evidence of amount of blood loss, and potential for ongoing hemorrhage. In trauma, there is recognition that there may be a need for RBC transfusion in the immediate resuscitation phase. At present, the only resuscitation fluid that is available for the treatment of hemorrhagic shock that provides $\dot{D}o_2$ is allogeneic RBC transfusion.

2. RBC transfusion may be indicated for patients with evidence of acute hemorrhage and hemodynamic instability or inadequate $\dot{D}o_2$.

Rationale. The initial treatment of acute hemorrhage and hemodynamic instability is the administration of isotonic crystalloid solutions and the rapid control of hemorrhage. Fluid resuscitation is administered to maintain arterial perfusion pressure. RBC transfusion is indicated in patients unresponsive to crystalloid resuscitation, or in those with ongoing hemorrhage. Blood lactate or base deficit measurements are sensitive tests to monitor the changes in metabolism related to hypoperfusion and extent of hemorrhagic shock, and can be evaluated on initial admission and serially thereafter (77).

3. A "restrictive" strategy of RBC transfusion (transfuse when Hb is <7 g/dL) is as effective as a "liberal" transfusion strategy (transfusion when Hb is <10 g/dL) in critically ill patients with hemodynamically stable anemia, except in patients with acute myocardial infarction (MI) or unstable myocardial ischemia.

Rationale. The Transfusion Requirements In Critical Care (TRICC) study found that critically ill patients tolerate a restrictive Hb transfusion threshold (78). This study enrolled 838 critically ill patients with euvolemia after initial treatment who had Hb concentrations <9 g/dL within 72 hrs after admission to the ICU and randomly assigned 418 patients to a restrictive strategy of transfusion, in which RBCs were transfused if the Hb concentration dropped <7 g/dL and Hb concentrations were maintained at 7 g/dL to 9 g/dL, and 420 patients were assigned to a liberal strategy, in which transfusions were given when the Hb concentration fell <10 g/dL and Hb concentrations were maintained at 10 to 12 g/dL. Overall, 30-day mortality was similar in the two groups (18.7% vs. 23.3%, $p = .11$). However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill—those with an Acute Physiology and Chronic Health Evaluation (APACHE) II score of ≤20 (8.7% in the restrictive strategy group and 16.1% in the liberal strategy group; $p = .03$)—and among patients who were <55 yrs of age (5.7% and 13.0%, respectively; $p = .02$), but not different among patients with clinically significant cardiac disease (20.5% and 22.9%, respectively; $p = .69$). The mortality rate during hospitalization was significantly lower in the restrictive strategy group (22.3% vs. 28.1%, $p = .05$). A restrictive strategy of RBC transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute MI and unstable angina.

A pilot study performed before the TRICC trial with a smaller sample size (n = 69) also documented no difference in mortality or organ dysfunction in patients randomized to a restrictive vs. liberal transfusion strategy (79). A study in eight critically ill trauma patients with anemia documented that RBC transfusion failed to increase $\dot{D}o_2$ or $\dot{V}o_2$ or mixed venous Po_2 after transfusion of 2 units of RBCs (80). Thus, RBC transfusion may not improve tissue oxygenation.

Another multicenter trial (n = 260) enrolled patients undergoing elective hip and knee replacement surgery and randomized patients to transfusion triggers that were either restrictive (8 g/dL) or liberal (10 g/dL). Participants were monitored with continuous electrocardiogram monitoring preoperatively for 12 hrs and postoperatively for 72 hrs and total cardiac ischemia time was assessed. There was no significant difference in the total cardiac ischemia time between groups and no difference in hospital length of stay. A restrictive transfusion strategy was not associated with increased cardiac ischemia in this clinical trial (81).

With the publication of the TRICC trial, RBC transfusion practices have changed in the last decade, but significant numbers of transfusions are still used in the critically ill. A number of prospective, observational, cohort studies in the ICU have documented that clinicians continue to transfuse blood for a trigger Hb of 8 g/dL to 9 g/dL and frequently prescribe 2-unit RBC transfusions (82–86). Educational efforts are ongoing. The "Guidelines for Transfusions in the Trauma Patient" (87) were developed to formulate a clinical standard operating procedure for the patients enrolled in the Inflammation and Host Response to Injury Large-Scale Collaborative Research Program. This guideline addressed RBC transfusion therapy for critically ill trauma patients after the immediate resuscitation phase and recom-

mended: "Consider RBC transfusion in critically ill patient with Hb <7 g/dL (Note, it may be desirable in selected asymptomatic, hemodynamically stable patients to avoid transfusion even if the Hb is lower than this threshold)."

4. The use of only Hb level as a "trigger" for transfusion should be avoided. Decision for RBC transfusion should be based on an individual patient's intravascular volume status, evidence of shock, duration and extent of anemia, and cardiopulmonary physiologic parameters.

Rationale. Blood should be transfused for a physiologic indication and not for a specific Hb "trigger." The effects of anemia must be separated from those of hypovolemia, although both can interfere with oxygen transport. Also, the lower limit of human tolerance to acute normovolemic anemia has not been fully established. Acute isovolemic reduction of blood Hb concentration to 5 g/dL in conscious health resting humans did not produce evidence of inadequate systemic "critical" $\dot{D}o_2$, as assessed by lack of change of $\dot{V}o_2$ and plasma lactate concentration (88). Studies have documented that acute isovolemic hemodilution to Hb 5 g/dL is associated with significant cognitive changes in normal subjects (89) but that these changes are not present with acute isovolemic hemodilution to Hb 7 g/dL (90). Further reduction of Hb level to 6 g/dL and 5 g/dL produced subtle, reversible increases in reaction time and impaired immediate and delayed memory. Supplemental oxygen reversed all of these effects of acute anemia except for decreased energy (91). It is believed that $\dot{D}o_2$ is adequate in most individuals at Hb concentrations as low as 7 g/dL. The "critical" $\dot{D}o_2$ is the value below which $\dot{D}o_2$ fails to satisfy the metabolic needs for oxygen in the human body. It has been documented that a decrease in $\dot{D}o_2$ to 7.3 ± 1.4 mL $O_2 \times kg^{-1}\ min^{-1}$ in resting, healthy, conscious humans does not produce evidence of inadequate systemic oxygenation. The critical $\dot{D}o_2$ in healthy, resting, conscious humans seems to be less than this value (92). In acute anemia, reductions in arterial oxygen content usually are well tolerated because of compensatory increases in cardiac output. The TRICC trial documented that a transfusion trigger of 7 g/dL was safe in resuscitated critically ill patients (73).

An important study in hip fracture patients (n = 8787), aged ≥60 yrs, who underwent surgical repair examined whether blood transfusion for a specific trigger Hb had any impact on patient outcome (93). The "trigger" Hb level was defined as the lowest Hb level before the first transfusion during the time period (within 7 days before surgery for preoperative transfusion and within 7 days after surgery for postoperative) or, for patients in the nontransfused group, as the lowest Hb level during the time period. Overall 30-day mortality was 4.6% (n = 402; 95% confidence interval [CI] = 4.1–5.0); overall 90-day mortality was 9.0% (n = 788; 95% CI = 8.4–9.6). A total of 42% of patients (n = 3699) received a postoperative transfusion. Among patients with trigger Hb levels between 8.0 g/dL and 10.0 g/dL, 55.6% received a transfusion, whereas 90.5% of patients with Hb levels of <8.0 g/dL received postoperative transfusions. Postoperative transfusion did not influence 30- or 90-day mortality after adjusting for trigger Hb level, cardiovascular disease, and other risk factors for death: for 30-day mortality, the adjusted odds ratio (OR) was 0.96 (95% CI = 0.74–1.26); for 90-day mortality, the adjusted hazard ratio (HR) was 1.08 (95% CI = 0.90–1.29). Similarly, 30-day mortality after surgery did not differ between those who received a preoperative transfusion and those who did not (adjusted OR = 1.23; 95% CI = 0.81–1.89). Perioperative transfusion in patients with Hb levels of ≥8.0 g/dL did not seem to influence the risk of 30- or 90-day mortality in this elderly population. At Hb concentrations of <8.0 g/dL, 90.5% of patients received a transfusion, precluding further analysis of the association of transfusion and mortality. This study in elderly trauma patients (not critically ill, but a large high-risk elderly population with extensive comorbidities) was unable to demonstrate that RBC transfusion was associated with a reduced 30- or 90-day postoperative mortality.

5. In the absence of acute hemorrhage, RBC transfusion should be given as single units.

Rationale. The treatment of anemia with RBC transfusion in a hemodynamically stable patient in most cases warrants administration of single RBC units, with careful monitoring and repeat measurement of posttransfusion Hb. This practice will assist in avoidance of overtransfusion and prevention of associated complications including transfusion-associated circulatory overload and pulmonary edema. The exception to this case may be in the patient with critical anemia (Hb at which the compensatory responses [including increased cardiac output, redistribution of regional organ blood flows, and enhanced tissue oxygen extraction [fail to preserve adequate tissue oxygenation and tissue hypoxia ensues) (94), in which ≥1 RBC unit may be indicated.

6. Consider transfusion if Hb is <7 g/dL in critically ill patients requiring MV. There is no benefit of a "liberal" transfusion strategy (transfusion when Hb is <10 g/dL) in critically ill patients requiring MV.

Rationale. Anemia occurs in virtually all critically ill patients receiving long-term MV and has been associated with increased mortality and poor outcomes (95, 96). Theoretically, the oxygen-carrying benefit of RBCs could hasten recovery from respiratory failure, and transfusions could therefore be expected to shorten the duration of MV; however, evidence to the contrary has been reported. Allogeneic RBC transfusions are administered routinely to critically ill anemia patients requiring MV, especially during increased ICU length of stay or in long-term acute care facilities. Although RBC transfusions are a physiologically rational approach to raise Hb levels, they may increase the risk of complications and have been associated with higher mortality in critically ill patients.

A retrospective subgroup analysis from the prospective multicenter observational CRIT study examined transfusion practices in a broad sample of patients receiving MV in the ICU compared with patients not receiving MV (97). Of the 4892 patients enrolled in the CRIT study, 60% were receiving MV on ICU admission or within 48 h after admission and continued for a median of 4 days. Patients receiving MV had higher baseline APACHE II scores than patients not receiving MV (22.8 ± 7.8 [mean ± standard deviation] and 14.9 ± 6.4, respectively; $p < .0001$). Despite similar baseline Hb levels (11.0 ± 2.3 g/dL and 10.9 ± 2.5 g/dL, $p = .17$), more patients

receiving MV underwent transfusions (49% vs. 33%, $p < .0001$), and they received significantly more RBCs than patients not receiving MV ($p < .0001$). The principal reason for transfusion in both groups was low Hb level (78.4% and 84.6%, respectively); however, patients receiving MV had higher pretransfusion Hb levels (8.7 ± 1.7 g/dL) than patients not receiving MV (8.2 ± 1.7 g/dL, $p < .0001$). Notably, 40.1% of all transfusions in patients receiving MV were administered after day 3 of the ICU stay, compared with 21.2% in patients not receiving MV ($p < .0001$), and a higher percentage of patients receiving MV remaining in the ICU after day 3 underwent transfusions (33.4% vs. 18.3%, $p < .0001$). Mortality was higher (17.2% vs. 4.5%, $p < .0001$) and mean hospital (15 days vs. 10 days, $p < .0001$) and ICU stays (9 days vs. 4 days, $p < .0001$) were longer in the subgroup receiving MV, without adjustment for differences in severity of illness. MV was identified as an easily identifiable early marker for allogeneic blood exposure risk in ICU patients. Although the longer ICU stays account for much of this risk, patients receiving MV also seem to undergo transfusions at higher Hb thresholds than patients not receiving MV, at least early in the ICU stay. There is no clear justification for this relatively liberal transfusion practice in patients receiving MV.

Correcting the anemia-induced decrease in $\dot{D}o_2$, using allogeneic RBC transfusions, has been hypothesized to help with increased oxygen demands during weaning from MV. However, it is also possible that transfusions hinder the process because RBCs may not be able to increase adequately $\dot{D}o_2$. An analysis of 713 patients receiving MV, representing a subgroup of patients from the larger TRICC trial, were examined (88). Baseline characteristics in the restrictive srategy group (n = 357) and the liberal strategy group (n = 356) were comparable. The average duration of MV was 8.3 ± 8.1 days and 8.3 ± 8.1 days (95% CI = −0.79–1.68; $p = .48$), whereas ventilator-free days were 17.5 ± 10.9 days and 16.1 ± 11.4 days (95% CI = −3.07–0.21; $p = .09$) in the restrictive strategy group vs. the liberal strategy group, respectively. Eighty-two percent of the patients in the restrictive strategy group were considered successfully weaned and extubated for at least 24 hrs, compared with 78% for the liberal strategy group ($p = .19$). The relative risk (RR) of extubation success in the restrictive strategy group compared with the liberal strategy group, adjusted for the confounding effects of age, APACHE II score, and comorbid illness, was 1.07 (95% CI = 0.96–1.26; $p = .43$). The adjusted RR of extubation success associated with restrictive transfusion in the 219 patients who received MV for >7 days was 1.1 (95% CI = 0.84–1.45; $p = .47$). In this study, there was no evidence that a liberal RBC transfusion strategy decreased the duration of MV in a heterogeneous population of critically ill patients (98).

A retrospective analysis of a large integrated claims database for a 5-yr period in adults requiring MV for >96 hrs (n = 4344) documented that, although Hb was >10g/dL in 75% of patients, 67% (n = 2912) received at least one transfusion (with a mean of 9.1 ± 12.0 units) of RBCs during hospitalization. In regression models adjusting for confounders, exposure to RBC transfusion was associated with a 21% increase in the risk of hospital death (95% CI = 1.0–1.48), increased length of stay (n = 6.3 days, 95% CI = 5.1–7.6) and increased cost ($48,972, 95% CI = $45,581–% = $52,478) (99).

7. Consider transfusion if Hb is <7 g/dL in resuscitated critically ill trauma patients. There is no benefit of a "liberal" transfusion strategy (transfusion when Hb is <10 g/dL) in resuscitated critically ill trauma patients.

Rationale. An analysis from a subset of the prospective, multicenter, randomized controlled trial (TRICC) compared the use of restrictive and liberal transfusion strategies in resuscitated critically ill trauma patients (100). Critically ill trauma patients with an Hb of <9 g/dL within 72 hrs of admission to the ICU were randomized to a restrictive (Hb 7 g/dL) or liberal (Hb 10 g/dL) RBC transfusion strategy. The baseline characteristics in the restrictive (n = 100) and liberal (n = 103) transfusion groups were comparable. The average Hb (8.3 ± 0.6 g/L vs. 10.4 ± 1.2 g/L; $p < .0001$) and the RBC units transfused per patient (2.3 ± 4.4 vs. 5.4 ± 4.3; $p < .0001$) were significantly lower in the restrictive group than in the liberal group. The 30-day all-cause mortality rates in the restrictive group were 10%, as compared with 9% in the liberal group ($p = .81$). The presence of multiple organ dysfunction (9.2 ± 6.3 vs. 9.0 ± 6.0; $p = .81$), the changes in multiple organ dysfunction from baseline scores adjusted for death (1.2 ± 6.1 vs. 1.9 ± 5.7; $p = .44$), and the length of stay in the ICU (9.8 ± 8.1 vs. 10.2 ± 8.7 days; $p = .73$) and hospital (31.4 ± 17.1 vs. 33.7 ± 17.7 days; $p = .34$) also were similar between the restrictive and liberal transfusion groups. This study documented that a restrictive RBC transfusion strategy seems to be safe for critically ill patients with multiple trauma. A randomized, controlled trial specifically in trauma patients is necessary to validate these findings and provide the appropriate level of evidence with regard to the efficacy of blood transfusion in this population of patients. It may be desirable in selected asymptomatic, hemodynamically stable patients to avoid blood transfusion even if the Hb is lower than the threshold of 7 g/dL. The "Guidelines for Transfusion in the Trauma Patients," published as the clinical standard operating procedure for the Large Scale Collaborative Project "Inflammation and Host Response to Injury" provided similar conclusions (Fig. 1) (101).

8. Consider transfusion if Hb is <7 g/dL in critically ill patients with stable cardiac disease. No benefit of a "liberal" transfusion strategy (transfusion when Hb is <10 g/dL) in critically ill patients with stable cardiac disease.

Rationale. An analysis of 357 critically ill patients with cardiovascular diseases in a subset of the TRICC trial with Hb concentrations of <9 gd/L within 72 hrs of admission to the ICU was reported (102). Patients were randomized to a restrictive strategy to receive allogeneic RBC transfusions at an Hb concentration of 7 g/dL (and maintained between 7 g/dL and 9 g/dL) or a liberal strategy to receive RBCs at 10 g/dL (and maintained between 10 g/dLand 12 g/dL). Baseline characteristics in the restrictive (n = 160) and the liberal groups (n = 197) were comparable, except for the use of cardiac and anesthetic drugs ($p < .02$). Decreased diuretic use in the restrictive group accounted for the observed difference in cardiac medications between groups, whereas use of epidural anesthestic medications was greater in the restrictive group. Average Hb concentrations (8.5 ± 0.6 g/L vs. 10.3 ± 0.6 g/L; $p < .01$) and RBC units transfused (2.4 ± 4.1 RBC

A Transfusion Guideline for Trauma Patient*

Inflammation and the Host Response to Injury

1. Identify critically ill patient with hemoglobin < 7 gm/dL (or Hct < 21%).
2. If hemoglobin < 7 gm/dL transfusion of PRBCs is appropriate.
   a. For patients with severe cardiovascular disease, a higher transfusion trigger may be appropriate.
3. If hemoglobin > 7 gm/dL assess the patient for hypovolemia.
   a. If the patient is hypovolemic, administer IV fluids to achieve normovolemia.
   b. If the patient is not hypovolemic, determine whether there is evidence of impaired oxygen delivery (low S_vO_2, persistent/ worsening base deficit, presence/ worsening of lactic acidosis).
4. If impaired O_2 delivery present, consider pulmonary artery catheter placement, measure cardiac output, and optimize O_2 delivery.
5. If impaired O_2 delivery not present, monitor hemoglobin as clinically indicated.

** This protocol assumes that acute hemorrhage has been controlled, the initial resuscitation has been completed, and the patient is stable in the ICU without ongoing hemorrhage.*

B Transfusion Guidelines for Trauma Patient (excludes immediate resuscitation)

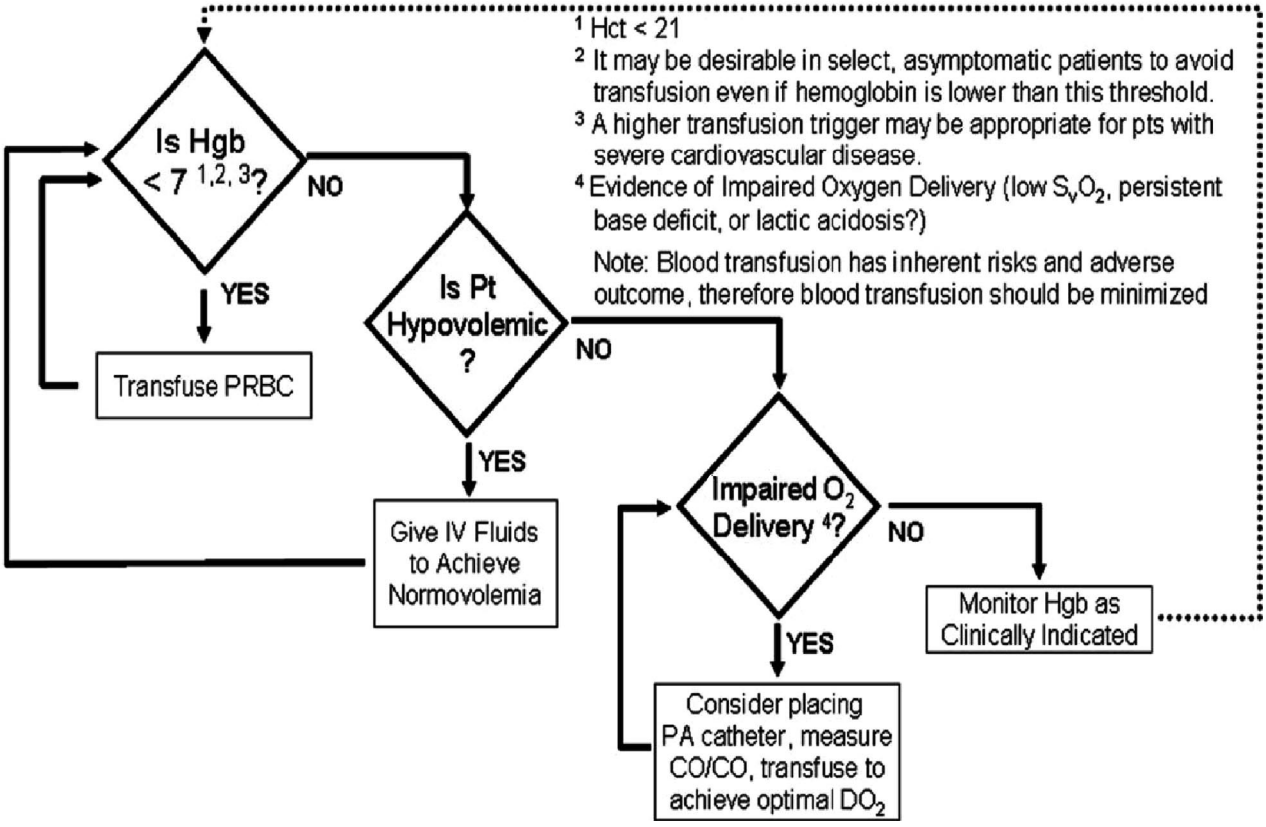

Figure 1. Summary of Transfusion Protocol from "Guidelines for Transfusion in the Trauma Patient." *J Trauma* 2006; 61:436–439.

units vs. 5.2 ± 5.0 RBC units; $p < .01$) were significantly lower in the restrictive group compared with the liberal group. All-cause mortality rates were similar in both study groups including 30-day (23% vs. 23%; $p = 1.00$), 60-day, hospital, and ICU mortality rates. Changes in multiple organ dysfunction from baseline scores were significantly less in the restrictive transfusion group overall (0.2 ± 4.2 vs. 1.3 ± 4.4; $p = .02$). In the 257 patients with severe ischemic heart disease, there were no statistically significant differences in all survival measures, but this is the only subgroup where the restrictive group had numerically lower but not significantly different survival rates compared with the patients in the liberal group. A restrictive RBC transfusion strategy generally seems to be safe in most critically ill patients with cardiovascular disease, with the possible exception of patients with acute MI and unstable angina.

A number of studies have documented the increased risk associated with RBC transfusion in patients with cardiac disease undergoing coronary artery bypass graft surgery (103–105). The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists Clinical Practice Guideline on "Perioperative Blood Transfusion and Blood Conservation in Cardiac Surgery" (106) identified six variables that identify patients at high risk for transfusion in cardiac surgery (advanced age; anemia; preoperative antiplatelet or antithrombotic drugs; reoperative or complex procedures; emergency operations; and noncardiac patient comorbidities) and recommended that perioperative interventions to reduce bleeding and postoperative blood transfusion be considered in patients at high risk for blood transfusion including a multimodality blood conservation program that is institution-based and includes transfusion algorithms.

9. RBC transfusion should not be considered as an absolute method to improve tissue $\dot{V}o_2$ in critically ill patients.

Rationale. The goal of RBC transfusions is to increase the Hb concentration, thereby improving $\dot{D}o_2$ to the tissues. To deliver oxygen to the tissues, RBCs must navigate the microcirculation, and capillary diameter may be diminished in critically ill and injured patients. Furthermore, during storage, RBCs undergo a series of biochemical and biomechanical changes that reduce their survival and function, and may impair their ability to deliver oxygen to the tissues via the microcirculation. Storage of RBCs also increased RBC adhesion to human vascular endothelium in *in vitro* and *in vivo* animal models and reduced significantly microvascular flow (107–109). In addition, accumulation of other biological byproducts of RBC preservation may be detrimental to recipients of RBC transfusion. Clinical studies aiming to determine the effect of RBC transfusion on $\dot{D}o_2$ and $\dot{V}o_2$ have demonstrated variable results (Tables 4 and 5). Of a total of 20 studies identified, it is noted that $\dot{D}o_2$ uniformly increased after RBC transfusion, but $\dot{V}o_2$ was observed to increase in only three of the studies (Table 5). There is also the possibility that RBC transfusion may be effective in altering the $\dot{D}o_2$/$\dot{V}o_2$ relationship across specific organ beds (e.g., RBC therapy in patients with coronary artery disease may decrease $\dot{V}o_2$ in the setting of restricted $\dot{D}o_2$ across a stenotic coronary artery) but this has not bee definitively determined. Furthermore, the underlying mechanism by which $\dot{V}o_2$ is not increased with RBC transfusion has not been definitively determined.

10. RBC transfusion may be beneficial in patients with ACSs who are anemic (Hb ≤8 g/dL) on hospital admission.

Rationale. The appropriate role of RBC transfusion in the treatment of patients with ischemic cardiac disease remains controversial and there is substantial variation in RBC transfusion use (110). The current evidence from published studies does not support the routine use of RBC transfusion in patients with ischemic cardiac disease, but the appropriate threshold for transfusion also remains undefined (Table 6).

A retrospective study of 78,974 Medicare beneficiaries aged ≥64 yrs who were hospitalized with acute MI (January 1994 to February 1995) categorized patients according to admission hematocrit. Patients with lower hematocrit on admission had higher 30-day mortality rates. Blood transfusion was associated with a reduction in 30-day mortality among patients with hematocrit in categories ranging from 5% to 24% (adjusted OR = 0.22; 95% CI = 0.11–0.45) to 30.1% to 33.0% (adjusted OR = 0.69; 95% CI = 0.53–0.89). Transfusion was not associated with a reduction in 30-day mortality among those with hematocrit in the higher ranges (>33%), and transfusion was associated with an increased risk of death within 30 days only among patients with hematocrit that exceeded 36%. In one of seven subgroups (among patients who survived at least 2 days), transfusion was not associated with a reduction in mortality for patients with hematocrit values of ≥30.1%. The authors concluded that blood transfusion is associated with a lower short-term mortality rate among elderly patients with acute MI if the hematocrit on admission is ≤30% and may be effective in patients with a hematocrit as high as 33.0% on admission (111).

Two large observational studies noted an association between an Hb level of <10 g/dL and increased mortality among patients with cardiovascular disease and suggested that such patients do not tolerate anemia as well as patients with other conditions (112, 113). However, in the prospective, randomized TRICC trial, within the subgroup of patients who also had ischemic heart disease, patients assigned to a restrictive transfusion strategy (target Hb = 7–9 g/dL) had a 30-day mortality rate that was 5% higher than patients assigned to the liberal transfusion strategy (target Hb = 10–12 g/dL), but this did not achieve statistical significance ($p = .38$) (114). There was a consistent trend toward higher mortality rates (≥4%) up to 60 days after admission among patients with ischemic heart disease who were treated with the restrictive transfusion strategy, but these findings were not statistically significant because the subgroup study was underpowered (n = 257) to detect such a small absolute difference in mortality rates. Furthermore, the TRICC trial documented a significantly higher rate of MI in the liberal transfusion strategy group in the full cohort analysis (12 of 420 [2.9%] in liberal group vs. three of 418 0.7% [4sqb] in the restrictive group; absolute difference between groups = 2.1; $p = .02$) (78). They concluded that a restrictive transfusion strategy seems to be safe in critically ill patients with cardiovascular disease, "with the possible exception of patients with acute myocardial infarcts and unstable angina."

Another study examined blood transfusion rates in 74,271 patients with non-ST-segment elevation ACSs who did not undergo coronary artery bypass graft (CABG) in the CRUSADE database, ad-

Table 4. RBC transfusion studies in sepsis
From: Zimmerman JL: Use of blood products in sepsis: An evidence-based review. *Crit Care Med* 2004; 32(Suppl):S542–S547.
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Study	Patients	n	RBC Transfusion	High Change, g/dL	Findings
Gilbert et al 1986 (17)	Septic adults	17	Estimated to achieve hemoglobin 10–12 g/dL	8.6 ± 1.9 to 10–12	↑ $\dot{D}o_2$; ↑ $\dot{V}o_2$ only in patients with increased lactate (thermodilution measurements)
Mink and Pollack 1990 (18)	Septic shock (2 mos–6 yrs)	8	8–10 mL/kg over 1–2 hrs	10.2 ± 0.8 to 13.2 ± 1.4	↑ $\dot{D}o_2$ but $\dot{V}o_2$ not increased (thermodilution measurements)
Lucking et al 1990 (19)	Septic children (4 mos–15 yrs with $\dot{V}o_2$ <180)	7	10–15 mL/kg over 1–3 hrs	9.3 ± 1.4 to 12.4 ± 0.7	↑ $\dot{D}o_2$ and ↑ $\dot{V}o_2$ (thermodilution measurements)
Conrad et al 1990 (20)	Septic shock (1–77 yrs)	19	591 mL over 4.2 ± 0.5 hrs	8.3 ± 0.3 to 10.7 ± 0.3	↑ $\dot{D}o_2$; but $\dot{V}o_2$ not increased (thermodilution measurements)
Steffes et al 1991 (21)	Septic adults (postoperative or posttrauma)	21 (27 studies)	1 or 2 units at 2 hrs/unit	9.3 ± 1.1 to 10.7 ± 1.5	↑ $\dot{D}o_2$ in all; ↑ $\dot{V}o_2$ only if normal lactate; ↑ intrapulmonary shunt fraction (thermodilution measurements)
Silverman and Tuna 1992 (22)	Septic adults	19	2 units	8.4 ± 0.5 to 10.6 ± 0.5 (normal pHi), 8.6 ± 0.3 to 10.8 ± 0.3 (low pHi)	↑ $\dot{D}o_2$; but $\dot{V}o_2$ not increased in patients with normal or low pHi (thermodilution measurements)
Marik and Sibbald 1993 (23)	Septic adults	23	3 units over 90–120 mins	9.0 ± 7.8 to 11.9 ± 9.0	↑ $\dot{D}o_2$ but $\dot{V}o_2$ not increased; ↓ SVR, ↑ PVR, ↑ intrapulmonary shunt; ↓ pHi with older bood (thermodilution and indirect calorimetry measurements)
Lorente et al 1993 (24)	Severe sepsis adults	16	800 mL over 90 mins	9.6 ± 0.3 to 11.6 ± 0.3	↑ $\dot{D}o_2$ but $\dot{V}o_2$ not increased; ↑ SVR, ↑ PVR; dobutamine ↑ $\dot{V}o_2$ (thermodilution measurements)
Fernandes et al 2001 (25)	Septic adults (septic shock excluded)	10 (+5 control)	1 unit over 1 hr	9.4 ± 0.5 to 10.1 ± 0.8	$\dot{D}o_2$ and $\dot{V}o_2$ not increased; ↑ PVR; no change in lactate or pHi (thermodilution and indirect calorimetry measurements)

$\dot{D}o_2$, oxygen delivery; $\dot{V}o_2$, oxygen consumption; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; pHi, gastric intramucosal pH.

mitted to U.S. hospitals since November 2001. A total of 7427 (10.3%) received transfusions during their hospitalization. Renal insufficiency and advanced age were strongly associated with the likelihood of transfusion. Patients who received transfusions had a greater risk of death (11.5% vs. 3.8%) and death or reinfarction (13.4% vs. 5.8%) than patients who did not undergo transfusion. This study documented that transfusion is common in this setting, patients who receive transfusion are sicker at baseline and experience a higher risk of adverse outcomes than their nontransfused counterparts (115).

Similarly, a retrospective analysis of 24,112 patients in three large randomized, prospective, international trials of patients with ACSs documented that 2401 (10%) of patients underwent at least one RBC transfusion during their hospitalization (116). Patients who underwent transfusion were older and had more comorbid illness at presentation and also had a significantly higher unadjusted rate of 30-day death (8.00% vs. 3.08%; $p < .001$), MI (25.16% vs. 8.16%; $p < .001$), and composite end point of death or MI (29.24% vs. 10.02%; $p < .001$) compared with patients who did not undergo transfusion. Using Cox proportional hazards modeling that incorporated transfusion

Table 5. Studies examining oxygen delivery, oxygen consumption and lactate before and after

Author and Year	Study Population	n	Amount Transfused (units)	Changes in Measurements of Posttransfusion ↑ Hb	↑ $\dot{D}o_2$	↑ $\dot{V}o_2$	↓ Lactate
Shah et al 1982	Posttrauma critically ill patients	8	1 or 2 units	Yes	No	No	NA
Kahn et al 1986	Acute respiratory failure	15	7–10 mL/kg	Yes	No	No	NA
Gilbert et al 1986	Septic	54	Δ 20 g/L	Yes	Yes	No	No
Dietrich et al 1990	Medical shock (septic/cardiac)	32	577 mL	Yes	Yes	No	No
Conrad et al 1990	Septic shock	19	Δ 3 g/dL	Yes	Yes	No	No
Ronco et al 1990	PCP pneumonia	5	1.5 units	Yes	Yes	Yes	NA
Fenwick et al 1990	ARDS	24	1.5 units	Yes	Yes	No	No
Mink et al 1990	Septic shock 2 mo–6 yrs	8	8–10 mL/kg × 1–2 hrs	Yes	Yes	No	NA
Lucking et al 1990	Septic shock 4 mos–15 yrs	7	10–15 mL/kg × 1–3 hrs	Yes	Yes	Yes	NA
Ronco et al 1991	ARDS	17	1.5 units	Yes	Yes	No	NA
Steffes et al 1991	Postoperative and posttrauma	21	1–2 units	Yes	Yes	Yes	No
Babineau et al 1992	Postoperative	31	328 ± 9 mL	Yes	Yes	No	No
Silverman et al 1992	Septic shock 21–88 yrs	21	2 units	Yes	Yes	No	No
Marik et al 1993	Septic	23	3 units	Yes	Yes	No	No
Lorente et al 1993	Septic	16	2 units	Yes	Yes	No	NA
Gramm et al 1996	Septic shock 46 ± 3 yrs	19	2 units	Yes	No	No	NA
Casutt et al 1999	Postoperative 32–81 yrs	67	368 ± 10 mL	Yes	Yes	No	NA
Fernandes et al 2001	Septic shock 18–80 yrs	10	1 units	Yes	No	No	No
Walsh et al 2004	Euvolemic anemic critically ill patients without ongoing hemorrhage	22	2 units	Yes	NA	NA	No
Suttner et al 2004	Volume-resuscitated mechanically ventilated patients	51	1 or 2 units vs. 100% Fio_2 (n = 17 each)	Yes	Yes	No	NA
Mazza et al 2005	SIRS/Sepsis	29	1–3 units	Yes	NA	NA	No

Evidence-Based Table With Summary of Results of Study

Author and Year	Study Population	n	Amount Transfused (units)	Changes in Measurements of Posttransfusion ↑ Hb	↑ $\dot{V}o_2$	↑ $\dot{V}o_2$	↓ Lactate	Comments
Shah et al 1982	Posttrauma critically ill patients	8	1 or 2 units	Yes	No	No	NA	Hemodynamic and oxygen transport parameters measured before and after RBC transfusion. Mixed venous oxygen content was measured directly by fuel cell oxygen analyzer, and standard P50 was calculated. Following transfusion of one unit of packed RBC which increased mean Hb from 9.2 ± 0.3 g/dL to 10.1 ± 0.3 g/dL ($p < .01$), there were no changes in $\dot{D}o_2$ (490 ± 80 mL/min/m^2), oxygen consumption (210 ± 30 mL/min/m^2), or mixed venous Po_2/(37 ± 2 torr). Cardiac index (4.1 ± 0.71 L/min) decreased by 0.4 L/min/m^2 ($p < .05$). Standard P50 decreased by 4.2 ± 2.4 torr post transfusion of 2 units of RBC ($p < .05$). RBC transfusion thus failed to increase $\dot{V}o_2$ in these patients, despite an increase in oxygen content.
Kahn et al 1986	Acute respiratory failure	15	7–10 mL/kg	Yes	No	No	NA	In 15 patients requiring mechanical ventilation with initial Hct ≤35%, the effect of transfusion of 7 mL/kg of RBCs on hemodynamic and $\dot{D}o_2$ variables, pulmonary venous admixture (QA/QT), and erythrocytic P50, 2,3 DPG and ATP concentrations was studied. Hemodynamics were not significantly altered by transfusion. 2,3 DPG decreased significantly from 14.5 ± 1.1 to 13.1 ± 1.5 mcmol/g Hb (mean ± SD, $p < .05$). There was no significant change in P50 or ATP. QA/QT rose significantly, from 20.1 ± 7.8 to 28.9 ± 12.3% (mean ± SD, $p < .02$). The increase in arterial oxygen content obtained by RBC transfusion was not followed by any associated decrease in cardiac work, as implied by solution of equations for oxygen delivery ($\dot{D}o_2$) and $\dot{V}o_2$.
Gilbert et al 1986	Septic	54	Δ 20 g/L	Yes	Yes	No	No	Fifty-four patients with systemic sepsis and signs of circulatory shock were prospectively investigated immediately before and after 1 of 3 therapeutic interventions chosen to increase systemic $\dot{D}o_2$: colloidal fluid loading (Group I, n = 20), blood transfusion (Group II, n = 17), or catecholamine infusion (dopamine or dobutamine, Group III, n = 17). Patients in Groups I and II with normal blood lactate concentrations (less than 2.2 mmol/L) exhibited no significant increases in systemic oxygen consumption ($\dot{V}o_2$) in response to the increases in $\dot{D}o_2$. However, significant increases in $\dot{V}o_2$ were noted in patients in Groups I and II with elevated lactate concentrations (>2.2 mmol/L). In contrast to patients in Groups I and II, patients in Group III with and without lactic acidosis exhibited significant increases in $\dot{V}o_2$ after catecholamine administration.

Table 5.—*Continued*

Author and Year	Study Population	n	Amount Transfused (Units)	Changes in Measurements of Posttransfusion				Comments
				↑ Hb	↑ $\dot{V}o_2$	↑ $\dot{V}o_2$	↓ Lactate	
Dietrich et al 1990	Medical shock (septic or cardiac)	32	577 mL	Yes	Yes	No	No	Examined the cardiovascular and metabolic response to RBC transfusion in patients with circulatory shock after volume resuscitation. Data were analyzed from 36 transfusions in 32 patients who were undergoing continuous hemodynamic monitoring. Transfusions were administered for moderate to severe anemia, mean Hgb 8.3 g/dl. The diagnoses were sepsis (19/36), cardiogenic shock (14/36), connective tissue disease (2/36), and severe hypocalcemia (1/36). Benefit from transfusion was defined as an improvement in tissue oxygen utilization (increased oxygen consumption [$\dot{V}o_2$] or decreased lactate), a decrease in myocardial $\dot{V}o_2$ (MAP × HR), or a decrease in myocardial work (left ventricular work index). Mean transfusion volume was 577 mL over 4.5 hrs. Hgb and $\dot{D}o_2$ increased by 27% and 28%, respectively, while pulmonary artery wedge pressure and cardiac index were unchanged. No significant change was noted in $\dot{V}o_2$, or lactate, after augmentation of red cell mass. An increase occurred in myocardial work indices and MAP × HR. No changes were identified when subgroups were analyzed based on diagnosis, pretransfusion Hgb, lactate, or $\dot{V}o_2$ levels. We conclude that selective increase in $\dot{D}o_2$ by augmentation of RBC mass and oxygen-carrying capacity did not improve the shock state in these volume-resuscitated patients, regardless of the etiology of the shock.
Conrad et al 1990	Septic shock	19	Δ 3 g/dL	Yes	Yes	No	No	This study investigates the effect of increasing $\dot{D}o_2$ through an isolated increase in arterial oxygen content following adequate fluid resuscitation from septic shock in humans. Nineteen patients receiving red cell transfusion (591 ± 55 SEM mL) were monitored for changes in hemodynamic and oxygen utilization variables before and after transfusion. Transfusion resulted in a significant increase in Hb (8.3 ± 0.3 to 10.7 ± 0.3 g·dL^{-1}) and $\dot{D}o_2$ (483 ± 29 to 621 ± 32 ml·min^{-1}·m^{-2}). No increase in cardiac output or pulmonary artery wedge pressure (PAWP) resulted from the transfusion. In spite of the increase in delivery, there was no increase in $\dot{V}o_2$ or decrease in lactate. An isolated increase in arterial oxygen content as a means of increasing $\dot{D}o_2$ does not improve $\dot{V}o_2$ in septic shock following adequate fluid resuscitation. Patients with a low oxygen extraction ratio (<24%) represent a subset of patients which did improve consumption with transfusion, and may represent a more severe microcirculatory disturbance not amenable to fluid loading.
Ronco et al 1990	PCP pneumonia and ARDS	5	1.5 units	Yes	Yes	Yes	NA	In five patients who had AIDS-related PCP and ARDS, oxygen delivery and consumption by calculation from thermodilution cardiac output and arterial and mixed venous oxygen contents was determined. $\dot{D}o_2$ was increased using transfusion of 2 units of RBCs over one hour. $\dot{D}o_2$ increased 22 percent (638 ± 204 to 778 ± 201 mL/min·m^2, $p \leq .006$). $\dot{V}o_2$ increased 11% (134 ± 34 to 149 ± 29 mL/min·m^2, $p \leq .02$). The oxygen extraction ratio did not change.
Fenwick et al 1990	ARDS	24	1.5 units	Yes	Yes	No	No	
Mink et al 1990	Septic shock 2 mos–6 yrs	8	8–10 mL/kg × 1–2 hrs	Yes	Yes	No	NA	Prospective examination of the effect on $\dot{V}o_2$ of improving $\dot{D}o_2$ by increasing oxygen content (CO_2) with blood transfusion in eight hemodynamically stable septic shock patients. Transfusion consisted of 8 to 10 mL/kg of packed RBC over 1 to 2 hrs. Hemodynamic and oxygen transport measurements were obtained before and after blood transfusion. Transfusion significantly ($p < .05$) increased Hgb and Hct from 10.2 ± 0.8 g/dL and 30 ± 2% to 13.2 ± 1.4 g/dL and 39 ± 4%, respectively (mean ± SD). $\dot{D}o_2$ significantly ($p < .05$) increased after transfusion (599 ± 65 to 818 ± 189 mL/min·m^2), but $\dot{V}o_2$ did not change (166 ± 68 to 176 ± 74 mL/min·m^2; NS). In pediatric septic shock patients, increasing CO_2 by blood transfusion may not increase $\dot{V}o_2$.
Lucking et al 1990	Septic shock 4 mos–15 yrs	7	10–15 mL/kg × 1–3 hrs	Yes	Yes	Yes	NA	Studied the effect of increasing systemic $\dot{D}o_2$ by packed RBC (PRBC) transfusion on $\dot{V}o_2$ in children with hyperdynamic septic shock. After routine resuscitation with volume loading and pharmacologic support, patients were studied if they had significant derangements of oxygen transport variables defined as: baseline $\dot{V}o_2$ <180 mL/min·m^2 and oxygen extraction (O_2 extr) <24%. Eight studies were performed. PRBC transfusion increased $\dot{D}o_2$ from 636 ± 167 to 828 ± 266 mL/min·m^2 ($p < .01$) without increasing cardiac index (5.2 ± 1.3 vs. 5.0 ± 1.4 L/min·m^2). $\dot{V}o_2$ increased from 112 ± 36 to 157 ± 60 mL/min·m^2 ($p < .01$) while oxygen extr was unchanged (18 ± 3% vs. 19 ± 6%). Despite initial low O_2 extr, $\dot{V}o_2$ can be increased in pediatric septic shock by an increase in $\dot{D}o_2$.

Table 5.—*Continued*

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				↑ Hb	↑ $\dot{V}o_2$	↑ $\dot{V}o_2$	↓ Lactate	
Ronco et al 1991	ARDS	17	1.5 units	Yes	Yes	No	NA	To determine whether oxygen consumption is dependent on oxygen delivery in 17 patients who had severe adult respiratory distress syndrome (ARDS), 10 of whom had increased concentrations of plasma lactate. $\dot{V}o_2$ was determined using analysis of respiratory gases while increasing $\dot{D}o_2$ using blood transfusion. $\dot{V}o_2$ did not change after transfusion (from 227 ± 83 to 225 ± 82 ml/min, p less than or equal to 0.38). $\dot{D}o_2$ increased from 1043 ± 468 mL/min (24%, $p \leq .001$). Even in the ten patients who had increased concentration of plasma lactate and metabolic acidosis, $\dot{V}o_2$ remained constant after increasing oxygen delivery (pre transfusion, 224 ± 101 ml/min; post transfusion, 225 ± 99 mL/min; $p \leq .83$). These data have >99% power of detecting a change in $\dot{V}o_2$ of 20 mL/min after transfusion. Directly measured $\dot{V}o_2$ remains constant and independent of increases in $\dot{D}o_2$.
Steffes et al 1991	Postoperative and posttrauma	21	1–2 units	Yes	Yes	Yes	No	Twenty-one septic patients, postsurgical or posttrauma, Serum lactic acid concentrations, $\dot{D}o_2$, and $\dot{V}o_2$ were measured before and after transfusion therapy. Overall, the $\dot{D}o_2$ increased from 532 ± 146 to 634 ± 225 (SD) mL/min.m^2 ($p < .001$), and the $\dot{V}o_2$ increased from 145 ± 39 to 160 ± 56 mL/min·m^2 ($p = .02$). These changes occurred with an Hgb increase from 9.3 ± 1.1 to 10.7 ± 1.5 g/dL ($p < .001$). The patients were grouped by their pretransfusion serum lactic acid values. In those patients with normal (<1.6 mmol/dL) serum lactic acid (n = 10), $\dot{D}o_2$ increased from 560 ± 113 to 676 ± 178 mL/min·m^2 ($p < .02$), and $\dot{V}o_2$ increased from 150 ± 25 to 183 ± 46 mL/min·m^2 ($p < .02$). However, in the increased serum lactic acid group (n = 17), $\dot{V}o_2$ was not significantly changed after transfusion (143 ± 46 to 146 ± 58 mL/min·m^2) despite increased $\dot{D}o_2$ (515 ± 163 to 609 ± 251 mL/min·m^2, $p < .01$).
Babineau et al 1992	Postoperative	31	328 ± 9 mL	Yes	Yes	No	No	The impact on $\dot{V}o_2$ of PRBC transfusions administered for Hb< 10 g/dL in 30 surgical ICU patients who were euvolemic and hemodynamically stable. Transfusion had a negligible effect on $\dot{V}o_2$. 58% of all transfusions failed to change $\dot{V}o_2$ by >10% and could therefore be considered of questionable benefit.
Silverman et al 1992	Septic shock 21–88 yrs	21	2 units	Yes	Yes	No	No	To determine the efficacy of dobutamine infusions and RBC transfusions on splanchnic tissue oxygen utilization by measuring gastric pHi. Physiologic parameters and pHi measurements via the use of a gastric tonometer were obtained in 21 septic patients before and after the administration of a dobutamine infusion (5 micrograms/kg/min) or the transfusion of 2 RBC units. Subsets of measurements with normal (>7.32) and with low (<7.32) pHi were separately analyzed for each intervention. In the dobutamine low pHi group, pHi increased significantly from 7.16 ± 0.03 to 7.24 ± 0.03 (n = 9, $p < .05$). In contrast, pHi failed to increase in the RBC low pHi subgroup (7.16 ± 0.05 to 7.17 ± 0.04 [n = 10, $p > .80$]). Dobutamine, rather than RBC transfusions, should be administered to reverse gastric intramucosal acidosis.
Marik et al 1993	Septic	23	3 units	Yes	Yes	No	No	23 critically ill patients with sepsis undergoing mechanical ventilation. Systemic oxygen uptake was measured by indirect calorimetry and calculated by the Fick method. Gastric intramucosal pH as measured by tonometry was used to assess changes in splanchnic oxygen availability. Measurements were made before transfusion of 3 units of RBCs. These were then repeated immediately following transfusion, as well as 3 hrs and 6 hrs later. There was no increase in systemic oxygen uptake measured by indirect calorimetry in any of the patients studied for up to 6 hrs post transfusion (including those patients with an elevated arterial lactate concentration). However, the calculated systemic oxygen uptake increased in parallel with the $\dot{D}o_2$ in all the patients. More importantly, we found an inverse association between the change in gastric intramucosal pH and the age of the transfused blood ($r = -.71$; $p < .001$). In those patients receiving blood that had been stored for >15 days, the gastric intramucosal pH consistently decreased following the RBC transfusion. This study failed to demonstrate a beneficial effect of RBC transfusion on measured systemic oxygen uptake in patients with sepsis. Patients receiving old transfused RBCs developed evidence of splanchnic ischemia. We postulate that the poorly deformable transfused RBCs cause microcirculatory occlusion in some organs, which may lead to tissue ischemia in some organs.

Table 5.—*Continued*

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Lorente et al 1993	Septic	16	2 units	Yes	Yes	No	NA	Prospective, randomized, interventional crossover study to investigate whether increasing $\dot{D}o_2$ by increasing hematocrit results in increases in oxygen uptake ($\dot{V}o_2$) in septic patients. A total of 16 ICU patients with Hb <10 g/dL. Patients received, in random order, an infusion of dobutamine (10 micrograms/kg/min) and a blood transfusion (800 mL of packed RBCs in 90 mins). Hemodynamic and oxygen transport variables were determined before and after each treatment, allowing at least 20 mins during the infusion of dobutamine to achieve the steady state. Changes in $\dot{D}o_2$ and $\dot{V}o_2$ induced by each intervention were measured. Dobutamine significantly increased $\dot{D}o_2$ (48.5 ± 6.9%; $p = .0001$) and $\dot{V}o_2$ (21.7 ± 3.3%; $p = .0001$). Blood transfusion increased $\dot{D}o_2$ (21.4 ± 4.3%; $p = .005$) but $\dot{V}o_2$ did not change significantly (2.2 ± 4.1%). Correlation coefficients for the percent changes of $\dot{D}o_2$ and $\dot{V}o_2$ ($r^2 = .67$, $p = .001$ for dobutamine; and $r^2 = 21$, $p = .07$ for blood transfusion) were significantly different for each treatment ($p = .0001$). Blood transfusion does not significantly increase $\dot{V}o_2$, despite significant changes in $\dot{D}o_2$.
Gramm et al 1996	Septic shock 46 ± 3 y	19	2 units	Yes	No	No	NA	The role of isolated blood transfusion as a means toward improving oxygen transport was evaluated in 19 critically ill septic patients. ICU therapies were unchanged during transfusion and hemodynamic profiles with serum lactate levels were obtained before and after packed RBCs were given. Blood transfusions in these patients did not cause a change in hemodynamic status. Arterial lactate was normal before and after transfusion was administered. Oxygen uptake failed to increase with RBC transfusion, corresponding to increased arterial and mixed venous oxygen content. In the presence of sepsis, patients having oxygen delivery and uptake above normal without evidence of ischemia (normal lactate) do not increase oxygen consumption by raising the Hb.
Casutt et al 1999	Postoperative 32–81 yrs	67	368 ± 10 mL	Yes	Yes	No	NA	To determine factors influencing the individual effects of blood transfusions regarding $\dot{D}o_2$ and $\dot{V}o_2$ in 67 cardiovascular surgery patients with 170 transfusion events. Measurements were performed before and after a blood transfusion, separated by 302 ± 13 mins (mean ± SEM). The individual increase in cardiac index resulting from a blood transfusion was inversely related to cardiac index before transfusion ($p < .001$), $\dot{D}o_2$ index before transfusion ($p < .001$), and $\dot{V}o_2$ index before transfusion ($p < .001$). The individual increase in $\dot{D}o_2$ index was inversely related to $\dot{V}o_2$ index before transfusion ($p < .001$). The individual increase in $\dot{V}o_2$ index was inversely related to $\dot{V}o_2$ index before transfusion ($p < .001$). Individual changes in cardiac index, $\dot{D}o_2$ index, and $\dot{V}o_2$ index were not significantly related to preoperative ejection fraction (25%–87%), age (32–81 yrs), and pretransfusion Hb concentration (5.0–11.8 g/dL). In adult patients after cardiovascular surgery, $\dot{D}o_2$- and $\dot{V}o_2$-related variables predict the individual response to blood transfusions better than do patient characteristics such as preoperative ejection fraction, age, and pretransfusion Hb concentration. Including oxygen delivery and $\dot{V}o_2$, variables into the transfusion decision, thus, may enable a more individual use of allogeneic blood in specific situations.
Fernandes et al 2001	Septic shock 18–80y	10	1 unit	Yes	No	No	No	This study evaluates the hemodynamic and oxygen utilization effects of Hb infusion in 15 critically ill septic patients requiring mechanical ventilation whose Hb was <10 g%. Ten patients (APACHE II: 25.5 ± 7.6) received an infusion of 1 unit of packed RBC over 1 hr while sedated and paralyzed. The remaining five control patients (APACHE II: 24.3 ± 6.0) received a 5% albumin solution (500 mL) over 1 hr. Hemodynamic data, gastric tonometry and calorimetry were obtained before and immediately after RBC transfusion or 5% albumin infusion. RBC transfusion was associated with an improvement in left ventricular systolic work index (38.6 ± 12.6 to 41.1 ± 13.0 g/min/m2; $p = 0.04$). In the control group there was no significant change in the left ventricular systolic work index (37.2 ± 14.3 to 42.2 ± 18.9 g/min/m2). An increase in pulmonary vascular resistance index (203 ± 58 to 238 ± 49 dyne/cm^5/m^2; $p = .04$) was also observed, while no change was produced by colloid infusion (237 ± 87.8 to 226.4 ± 57.8 dyne/cm^5/m^2). Oxygen utilization did not increase either by Fick equation or by indirect calorimetry in either group. Gastric intramucosal pH increased only in the control group but did not reach statistical significance. Hb increase did not improve either global or regional oxygen utilization in anemic septic patients. Furthermore, RBC transfusion may hamper right ventricular ejection by increasing the pulmonary vascular resistance index.

Table 5.—*Continued*

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Walsh et al 2004	Euvolemic anemic critically ill patients without ongoing hemorrhage	22	2 units	Yes	NA	NA	No	Compared leukodepleted RBCs that were either ≤5 days (n = 10) or ≥20 days (n = 12) after donation. No differences in indices of tissue hypoxia (gastric to $Paco_2$ gap, gastric intramucosal pH by automated gas tonometry, arterial pH or arterial lactate).
Suttner et al 2004	Volume-resuscitated mechanically ventilated patients	51	1 or 2 units vs. 100% Fio_2 (n = 17 each)	Yes	Yes	No	NA	Transfusion of stored allogeneic RBCs was effective only in improving systemic $\dot{D}o_2$ index, whereas 100% oxygen ventilation improved systemic oxygen transport and skeletal muscle Po_2 ($Ptio_2$). This improved oxygenation status was most likely due to an increase in convective oxygen transport with a large driving gradient for diffusion of plasma-dissolved oxygen into the tissue.
Mazza et al 2005	SIRS sepsis	29	1–3 units	Yes	NA	NA	No	Hb levels, mixed venous oxygen saturation, and lactate levels were collected before RBC transfusion (pre-T) and up to 1 hr after transfusion (post-T). These variables were analyzed through a paired Student's *t* test, and results were considered significant if $p < .05$. 29 patients (17 male, 12 female) with ages of 61.9 ± 15.1 (mean ± SD) yrs (range = 21–85 yrs) and a mean APACHE II score of 12.5 ± 3.75 (7–21) were transfused with a mean of 1.41 packed red cell units. A significant increase in Hb levels was reached by blood transfusion, from 8.14 ± 0.64 g/dL (pre-T) to 9.4 ± 0.33 g/dL (post-T), with $p < .001$. However, this was not accompanied by a significant change in lactate levels, from 1.87 ± 1.22 mmol/L (pre-T) to 1.56 ± 0.28 mmol/L (post-T), with $p = .28$, or in mixed venous oxygen saturation, from 64.3 ± 8.52% (pre-T) to 67.4 ± 6.74% (post-T), with $p = .13$. The results were similar even in patients with Hb levels of <8.0 g/dL (n = 9). These results suggest that RBC transfusions, in spite of leading to a significant increase in Hb levels, are not associated with an improvement in tissue oxygenation in patients with SIRS/sepsis and Hb levels < 9 g/dL.

APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; RBC, red blood cell; SIRS, systemic inflammatory response syndrome.

as a time-dependent covariate, transfusion was associated with an increased hazard for 30-day death (HR = 2.92; 95% CI = 2.55–3.35). The predicted probability of 30-day death was higher with transfusion at nadir hematocrit values of >25%. These authors concluded that RBC transfusion in the setting of ACSs is associated with higher mortality, and this relationship persists after adjustment for other predictive factors and timing of events. They suggested caution regarding the routine use of RBC transfusion to maintain arbitrary Hb levels in stable patients with ischemic heart disease.

Another retrospective cohort study aimed to further clarify the impact of blood transfusions on short-term mortality and morbidity in anemic patients (370 of 1410) presenting with ACS and non-ST elevation MI and admitted to a monitored bed of a tertiary care Department of Veterans Affairs hospital, and found no transfusion benefit (117). Transfusion was associated with a significant increase in 30-day recurrent MI or death (OR = 3.05; 95% CI = 1.80–5.17; $p < .001$). This relationship persisted after adjusting for significant univariate predictors: hypotension on presentation, pulmonary edema, and increased troponin-I levels (OR = 2.57; 95% CI = 1.41–4.69; $p < .001$).

A prospective database study examined the effect of RBC transfusion in patients with acute MI (n = 2358) (118). Cox regression models were used to determine the association between RBC transfusion and 6-mo outcomes, incorporating transfusion as a time-dependent variable. The models adjusted for baseline variables, propensity for transfusion, and nadir Hb previous to the transfusion. A total of 192 patients (8.1%) received RBC transfusion. Six-month mortality rates were higher in patients receiving transfusion (28.1% vs. 11.7%, $p < .0001$). The adjusted HR for mortality was 1.9 in transfused patients (95% CI = 1.3–2.9). Interaction between RBC transfusion and nadir Hb with respect to mortality ($p = .004$) was significant. Stratified analyses showed a protective effect of transfusion in patients with nadir Hb ≤8 g/dL (adjusted HR = 0.13; 95% CI = 0.03–0.65; $p = .013$). By contrast, transfusion was associated with increased mortality in patients with nadir Hb >8 g/dL (adjusted HR = 2.2; 95% CI = 1.5–3.3; $p < .0001$). Similar results were obtained for the composite end point of death/MI/heart failure (p for interaction = .04). The authors concluded that RBC transfusion in patients with acute MI and Hb ≤8 g/dL may be appropriate. The increased mortality observed in transfused patients with nadir Hb >8 g/dL underscores the clinical difficulty of balancing risks and benefits of RBC transfusion in the setting of ACS.

Using data from the CRUSADE initiative (January 2004 to December 3005) from 44,242 patients with non-ST segment elevation acute coronary syndromes (NSTE ACS), the association between transfusion and outcomes as a function of nadir hematocrit (hematocrit = ≤24%, 24.1%–27%, 27.1%–30%, >30%) was examined (119). Overall, 22.2% of patients with NSTE ACS were anemic and 10.4% received a transfusion.

Table 6. Studies on RBC transfusion and outcome in ischemic heart disease

	Year of Publication	Study Design	n	Patients	Primary Results
Hebert	1997	Retrospective		Critically ill patients with cardiac disease, as part of a retrospective assessment of transfusion practices in Canadian ICUs	Increased survival with transfusion when Hb <9.5 g/dL No difference in mortality
Hebert	2001	Prospective, subgroup analysis	357	Subgroup of patients with cardiac disease from the TRICC trial	Increased organ dysfunction with transfusion
Wu	2001	Retrospective	Approx 79,000	Patients aged ≥64 yrs who had been hospitalized with a disgnosis of acute MI, Medicare database	Increased survival with transfusion
Rao	2004	Retrospective	Approx 24,000	Meta-analysis of data that had been collected as part of the GUSTO IIb, PURSUIT and PARAGON B trials of patients with ACS	Increased mortality, combined death or MI Decreased mortality in STEMI
Sabatine	2005	Retrospective		Data from 16 ACS studies	Increased mortality in non ST-elevation ACS
Yang	2005	Retrospective	85,111 total cohort; 74,271 no CABG	Patients with nonST-segment elevation acute coronary syndromes	Increased mortality, combined death or MI
Singla	2007	Prospective database		Patients with anemia and suspected ACS receiving transfusion, using data prospectively collected as part of an ongoing registry	Increased mortality, recurrent MI
Aronson	2008	Prospective database	2358	Patients with acute MI	Increased mortality in patients with nadir Hb >8g/dL; decreased mortality in patients with nadir Hb <8g/dL
Alexander	2008	Prospective database	44242	Patients with nonST-segment elevation acute coronary syndromes	Increased mortality in patients with nadir Hematocrit >30%; decreased mortality in patients with nadir Hematocrit ≤24%

ACS, acute coronary syndrome; MI, myocardial infarction; CABG, coronary artery bypass graft.
Adapted, in part, from: Gerber DR. Transfusion of packed red blood cells in patients with ischemic heart disease. *Crit Care Med* 2008; 36:1068–1074.

Likelihood of transfusion rose from 1% when nadir hematocrit was >30% when nadir hematocrit was ≤24%. The threshold for transfusion was a median nadir hematocrit of 25.7% (interquartile range = 23.8%–27.5%). Inhospital mortality was higher in lower nadir hematocrit groups. In those with a nadir hematocrit of ≤24%, transfusion tended to have a beneficial impact on mortality (hematocrit = ≤24%; adjusted OR = 0.68 [0.45–1.02]). In the median range, transfusion had a neutral impact on mortality (hematocrit = 24%–27%; adjusted OR = 1.01 [0.79–1.30]). Although rare, those transfused with nadir hematocrit of 27% to 30% (adjusted OR = 1.18 [0.92–1.50]) or hematocrit of >30% (adjusted OR = 3.47 [2.30–5.23]) had higher mortality. This study documented that anemia and transfusion are common in the care of NSTE ACS patients. The observed association between transfusion and adverse outcomes was neutral in the nadir hematocrit range where transfusions are most often given and trends strongly to benefit when nadir hematocrit is ≤24%.

These studies document that the risk vs. benefit of transfusion in patients presenting with ACSs needs further careful assessment. Rather than primarily focusing on blood transfusion in ACSs, physicians should administer all therapies that have been shown to be effective to reduce mortality and limit infarction size, such as aggressive cardiac revascularization and β blockade. Given the limitations of these prior studies, a randomized trial of transfusion strategies is warranted to resolve the disparity in results in the above referenced studies in ACSs, acute MI, and ischemic cardiac disease. Randomized trials are also needed to confirm the safety of transfusion in patients with ischemic cardiac disease.

B. Recommendations Regarding RBC Transfusion in Sepsis

1. The transfusion needs for each septic patient must be assessed individually because optimal transfusion triggers in sepsis patients are not known and there is no clear evidence that blood transfusion increases tissue oxygenation.

Rationale. The optimal Hb for patients with severe sepsis and septic shock has not yet been defined. Most studies of blood transfusion in sepsis have failed to demonstrate any differences in clinically significant outcomes. In general, RBC transfusion in septic and other critically ill patients increases $\dot{D}o_2$ but does not usually increase $\dot{V}o_2$ (Tables 4 and 5) (120).

In a study investigating the efficacy of RBC transfusion in septic patients (n = 15) randomized to transfusion of 1 unit RBCs or 500 mL of 5% albumin, there was no improvement in $\dot{D}o_2$ or $\dot{V}o_2$ post transfusion, measured by the Fick method or indirect calorimetry. No change in gastric tonometry indices was noted post transfusion. Blood transfusion was associated with a significant increase in pulmonary vascular resistance and decreased right ventricular ejection fraction, reflecting pulmonary hypertension (121).

Another study evaluated the effects of RBC transfusion in patients with SIRS or sepsis who presented with Hb of <9 g/dL at ICU admission (122). Hb levels, mixed venous oxygen saturation, and lactate levels were collected before RBC transfusion and up to 1 hr after transfusion. Twenty-nine patients aged 61.9 ± 15.1 yrs (range = 21–85 yrs) and a mean APACHE II score of 12.5 ± 3.75 (7–21) were transfused with a mean of 1.41 units packed RBCs. A significant increase in Hb levels was reached by blood transfusion, from 8.14 ± 0.64 g/dL (pre transfusion) to 9.4 ± 0.33 g/dL (post transfusion), with $p < .001$. However, this was not accompanied by a significant change in lactate or mixed venous oxygen saturation. The results were similar even in patients with Hb levels of <8.0 g/dL (n = 9). These results suggest that RBC transfusions, in spite of a significant increase in Hb, are not associated with an improvement in tissue oxygenation in patients with SIRS/sepsis and Hb levels of <9 g/dL.

Another prospective, randomized, double-blind pilot study aimed at investigating the effects of transfusion of 2 units of "fresh" (≤5 days) or "stored" (≥20 days) prestorage leuko-depleted and plasma-depleted RBCs in ventilated euvolemic critically ill patients (n = 22) with anemia (Hb concentration ≤9 g/dL). They determined that, at 5 hrs, neither "fresh" nor "stored" RBC transfusions were associated with an improvement in tissue oxygenation as measured by automated gas tonometry (123). This study further supported the evidence regarding lack of efficacy of RBC transfusion in the critically ill (124, 125).

The evidence-based Surviving Sepsis Guidelines 2008 for the management of severe sepsis and septic shock (126) has two recommendations for RBC transfusion, with the first recommendation a) relevant during the initial resuscitation, and the second recommendation b) after tissue hypoperfusion has resolved:

a. We suggest that during the first 6 hrs of resuscitation of severe sepsis or septic shock, if $Sc\dot{V}o_2$ or $s\dot{V}o_2$ of 70% or 65%, respectively, is not achieved with fluid resuscitation to the central venous pressure target, then transfuse packed RBCs to achieve a hematocrit of ≥30% and/or administer a dobutamine infusion (up to a maximum of 20 μg/kg/min) to achieve this goal (grade 2C).

This first recommendation is based on one single-center study and the efficacy of blood transfusion in sepsis was not the primary goal of the study. The protocol of "early goal-directed therapy (EGDT)" used in this single-center study targeted an increase in mixed venous oxygen saturation to ≥70%. This was achieved by sequential institution of initial fluid resuscitation, then packed RBC transfusions, and then inotropes (dobutamine). The EGDT group received significantly more fluid resuscitation and RBC transfusion in the first 6 hrs of treatment. This protocol was associated with a significant improvement in survival (127). It is not possible to separate what, if any, independent impact RBC transfusion had in this treatment algorithm of EGDT for sepsis. Furthermore, the study was neither adequately powered nor designed to test the specific effect of the single variable of blood transfusion on morbidity and mortality in sepsis (128).

b. Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardiac ischemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, or lactic acidosis, we recommend that RBC transfusion occur when Hb decreases to <7 g/dL to target a Hb of 7.0 g/dL to 9.0 g/dL in adults (grade 1B).

The evidence-based Practice Parameters for Hemodynamic Support of Sepsis in Adult Patients (2004 Update) (129) recommended that Hb concentration should be maintained at >8 g/dL, and between 8 and 10 g/dL. In patients with low cardiac output, mixed venous oxygen desaturation, lactic acidosis, widened gastric-arterial Pco_2 gradients, or significant cardiac or pulmonary disease, transfusion to a higher concentration of Hb may be desirable.

Additional prospective studies are clearly warranted to advance our knowledge in this important area and unify these disparate recommendations.

c. Recommendations Regarding RBC Transfusion in Patients at Risk for or With ALI and ARDS

ALI and ARDS are common clinical sequelae of massive transfusion. Prior studies have suggested that RBC transfusion is associated with respiratory complications including ALI and ARDS, even after adjusting for potential confounders. Whether the association between transfusion and ALI/ARDS reflects a causal relationship is not known (130). But, in light of this evidence, the following recommendations are made:

1. All efforts should be initiated to avoid RBC transfusion in patients at risk for ALI and ARDS after completion of resuscitation.

Rationale. Multiple RBC transfusions have long been considered a risk factor for ALI and ARDS (131, 132). In the TRICC trial, the best level of evidence available, it was noted that ARDS was more common in patients randomized to the liberal transfusion strategy group compared with the restrictive group (48 of 420 [11.4%] in the liberal group vs. 32 of 418 [7.7%] in the restrictive group; $p = .06$; absolute difference between groups = 3.8, 95% CI = −0.1–7.8) (78).

An observational, prospective, cohort study examined 688 ICU patients with sepsis, trauma, aspiration, or hypertransfusion, and 221 (32%) patients developed ARDS with a 60-day mortality rate of 46%. Significant predictors for ARDS on multivariate analyses included direct pulmonary injury (adjusted OR = 3.78, 95% CI = 2.45–5.81), hematologic failure (adjusted OR = 1.84, 95% CI = 1.05–3.21), and hematocrit >37.5% (adjusted OR = 1.77, 95% CI = 1.14–2.77). RBC transfusion was associated with ARDS (adjusted OR = 1.52, 95% CI = 1.00–2.31, $p = .05$). Significant predictors for mortality in ARDS included age (adjusted OR = 1.96, 95% CI = 1.50–2.53), APACHE III score (adjusted OR = 1.78, 95% CI = 1.16–2.73), trauma (adjusted OR = 0.075, 95% CI = 0.006–0.96), corticosteroids before ARDS (adjusted OR = 4.65, 95% CI = 1.47–14.7), and arterial pH <7.22 (adjusted OR = 2.32, 95% CI = 1.02–5.25). Packed RBC transfusions were associated with increased mortality in ARDS (adjusted OR = 1.10 per unit transfused; 95% CI = 1.04–1.17) with a significant dose-dependent response ($p = .02$). The authors concluded that RBC transfusion was associated with an increased development of and increased mortality in ARDS (133).

In trauma, a number of studies have also confirmed an association with transfusion and ALI/ARDS. A prospective cohort study of 102 consecutive ICU patients with severe trauma divided patients into three predetermined groups on the basis of the total number of units of PRBCs received in the initial 24 hrs. A significant association was identified between acute exposure to transfused blood and the development of ARDS. Twenty-one percent of patients who received 0 to 5 units of packed RBCs developed ARDS, compared with 31% of those patients who received 6 to 10 units of packed RBCs and 57% of those who received >10 units of packed RBCs ($p = .007$). The association between the amount of transfused blood and the development of ARDS remained significant in a multivariable logistic regression model accounting for differences in severity of illness, type of trauma, race, gender, and base deficit ($p = .002$; OR = 14.4; 95% CI = 3.2–78.7). Patients who received more units of packed RBCs during the first 24 hrs also had a higher hospital mortality rate ($p = .03$). This study concluded that severely injured trauma patients who require administration of packed RBCs, the amount of transfused blood is independently associated with both the development of ARDS and hospital mortality (134).

Another study evaluated the association between delayed RBC transfusion and serious, well-defined respiratory complications (ventilator-associated pneumonia [VAP] and ARDS) or death in a cohort of ICU admissions with less severe (Injury Severity Score [ISS] of <25) blunt trauma who received no transfusion within the initial 48 hrs after admission. Patients with blunt injury and ISS of <25 admitted to the ICU over a 7-yr period were identified from the registry and excluded if, within 48 hrs from admission, they received any Tx or if they died. VAP was defined as quantitative bronchoalveolar lavage culture ($\geq 10^5$ colonies/mL), and ARDS was defined only in part in accordance with the American-European Consensus Conference on ARDS (128) (Pao_2/Fio_2 ratio <200 torr [<●●● kPa], no congestive heart failure, diffuse bilateral infiltrates, and peak airway pressure >50 cm H_2O). A population of 9126 patients with blunt injury were admitted to the ICU, and 5260 (58%) met the study criteria (72% male). Mean values for age, ISS, and Glasgow Coma Scale (GCS) score were 39, 12, and 14, respectively. There were 778 (15%) who received delayed Tx. Frequencies of VAP, ARDS, and death were 5%, 1%, and 1%, respectively. Logistic regression analysis identified age, base excess, Chest Abbreviated Injury Scale (AIS) score, ISS, and any transfusion as significant predictors for VAP; Chest AIS score and transfusion as significant predictors for ARDS; and age and transfusion as significant predictors for death. Delayed transfusion was independently associated with VAP, ARDS, and death in trauma patients regardless of injury severity. These data support a judicious transfusion policy after resuscitation and emphasize the need for reducing transfusion to the lowest safe Hb level (135).

Another study aimed to identify independent risk factors for the development of ARDS in blunt trauma patients and to examine the contributions of each factor to ARDS development. Patients with ARDS were identified from the registry of a Level I trauma center over a 4.5-yr period. Records were reviewed for demographics, injury characteristics, transfusion requirements, and hospital course. A total of 4397 ICU patients sustained blunt trauma and survived >24 hrs and 200 (4.5%) developed ARDS. Stepwise logistic regression demonstrated age of >65 yrs, ISS of >25, hypotension on admission, 24-hr transfusion requirement >10 units, and pulmonary contusion as independent risk factors. The risk factors providing the greatest contribution to ARDS development were ISS of >25 (receiver operating characeristic [ROC] area = 0.72) and pulmonary contusion (ROC area = 0.68) followed by 24-hr transfusion requirement of >10 units (ROC area = 0.56), admission hypotension (ROC area = 0.57), and age >65 yrs (ROC area = 0.54). The frequency of ARDS in patients receiving >10 units of transfusion was 45% (136).

Additional studies have confirmed that RBC transfusion is an independent risk factor for ALI and ARDS (137–140).

2. All efforts should be made to diagnose and report TRALI to the local blood bank because it has emerged as a leading cause of transfusion-associated morbidity and mortality, despite underdiagnosis and underreporting.

Rationale. TRALI is a clinical syndrome that presents as acute hypoxemia and noncardiogenic pulmonary edema during or after blood transfusion. The National Heart, Lung and Blood Institute convened a working group to identify areas of research needed in TRALI and identified the need for a common definition (141). This group defined TRALI as new acute lung injury occurring during or within 6 hrs after a transfusion, with a clear temporal relationship to the transfusion, and not explained by another ALI risk factor. Another important concept is that ALI temporally associated with multiple transfusions can be TRALI, because each unit can carry one or more of the possible causative agents: antileukocyte antibody; biologically active substances; and other yet unidentified agents. The reported prevalence of TRALI varies and includes an estimate of one in 5000 blood and blood components, one in 2000 plasma-containing components, one in 7900 units of fresh-frozen plasma, and one in 432 units of whole blood-derived platelets (142–146). TRALI has emerged as a leading cause of transfusion-related morbidity and mortality (147).

3. RBC transfusion should not be considered as a method to facilitate weaning from MV.

Rationale. MV is an easily identifiable early marker for allogeneic blood exposure risk in ICU patients. In a retrospective subgroup analysis from the prospective, multicenter, observational CRIT study, it was identified that 60% of the 4892 patients received MV on ICU admission or within 48 hrs after admission for a median of 4 days. Despite similar baseline Hb levels (11.0 ± 2.3 g/dL and 10.9 ± 2.5 g/dL, $p = .17$), more patients receiving MV underwent transfusions (49% vs. 33%, $p < .0001$), and received significantly more RBCs per patient than patients not receiving MV ($p < .0001$). The principal reason for transfusion in both groups was low Hb level (78.4% and 84.6%, respectively); however, patients receiving MV had higher pretransfusion Hb levels (8.7 ± 1.7 g/dL) than patients not receiving MV (8.2 ± 1.7 g/dL, $p < .0001$). Notably, 40.1% of all transfusions in patients receiving MV were administered after day 3 of the ICU stay, compared with 21.2% in patients not receiving MV ($p < .0001$), and a higher percentage of patients receiving MV remaining in the ICU after day 3 received transfusions (33.4% vs. 18.3%, $p < .0001$) (148).

Although the longer ICU stays in these patients account for much of the risk for transfusion, patients receiving MV also seem to receive RBCs at higher Hb thresholds than patients not receiving MV, at least early in the ICU stay. There is lack of justification for this relatively liberal transfusion practice in ICU patients receiving MV. Although prior studies have identified anemia as an independent risk factor for prediction of extubation failure (149, 150), none have demonstrated that RBC transfusion for treatment of anemia is associated with improved weaning from mechanical ventilation.

Correcting the decrease in $\dot{D}o_2$ from anemia using allogeneic RBC transfusions has been hypothesized to help with increased oxygen demands during weaning from mechanical ventilation (151). However, it is also possible that transfusions hinder the weaning process because RBCs may not be able to adequately increase $\dot{D}o_2$ related to changes in RBC function reported to occur during storage (152). In addition, complications, such as pulmonary edema from volume overload or an increased rate of nosocomial infections from transfusion-associated immune suppression, may directly prolong the length of time a patient receives MV or decreases weaning success (153). In the ICU, pulmonary edema occurs frequently after blood transfusion (154–156).

In a cohort analysis of the TRICC trial, 713 patients receiving MV (representing a subgroup of patients from the larger trial) were randomized to either a restrictive transfusion strategy, receiving allogeneic RBC transfusions at an Hb concentration of 7.0 g/dL (and maintained between 7.0 g/dL and 9.0 g/dL), or to a liberal transfusion strategy, receiving RBCs at 10.0 g/dL (and maintained between 10.0 g/dL and 12.0 g/dL). Baseline characteristics in the restrictive group (n = 357) and the liberal group (n = 356) were comparable. The average durations of MV were 8.3 ± 8.1 days and 8.3 ± 8.1 days (95% CI around difference = −0.79–1.68; p = .48), whereas ventilator-free days were 17.5 ± 10.9 days and 16.1 ± 11.4 days (95% CI around difference = −3.07–0.21; p = .09) in the restrictive group vs. the liberal group, respectively. No differences in ventilator weaning were identified, with 82% of the patients in the restrictive group considered successfully weaned and extubated for at least 24 hrs, compared with 78% for the liberal group (p = .19). The RR of extubation success in the restrictive group compared with the liberal group, adjusted for the confounding effects of age, APACHE II score, and comorbid illness was 1.07 (95% CI = 0.96–1.26; p = .43). The adjusted RR of extubation success associated with restrictive transfusion in the 219 patients who received MV for >7 days was 1.1 (95% CI = 0.84–1.45; p = .47). In this study, there was no evidence that a liberal RBC transfusion strategy decreased the duration of MV in a heterogeneous population of critically ill patients (157).

D. Recommendations Regarding RBC Transfusion in Patients With Neurologic Injury and Diseases

1. There is no benefit of a "liberal" transfusion strategy (transfusion when Hb is <10 g/dL) in patients with moderate-to-severe traumatic brain injury.

Rationale. Despite clear evidence in critical care that blood transfusion has an adverse impact on outcome, many neurocritical care and neurosurgical textbooks still recommend transfusion of patients with traumatic brain injury (TBI) and other intracranial disorders to a hematocrit of 30%. A poor functional outcome and greater risk of mortality are well established when patients with TBI are also hypoxic, hypotensive, or develop brain ischemia (158). The relationship between anemia and these complications is not well established. RBC transfusion has been used in TBI to prevent cerebral ischemia by maximizing oxygen-carrying capacity post blood loss and dilution with crystalloid fluid replacement. Although many practitioners have commonly utilized Hb thresholds for transfusion in these patients, the rationale for this practice has largely been centered on older studies. There is little evidence to support this practice, and the ultimate effects of transfusion on neurologic and functional outcome have not been well studied.

A subgroup analysis of 67 patients from the TRICC trial who sustained TBI reported 30-day all-cause mortality rates of 17% in the restrictive group vs. 13% in the liberal group (risk difference = 4.1; 95% CI = 13.4–21.5, p = .64). The development of multiple organ dysfunction and changes in Multiple Organ Dysfunction Scores were similar between the restrictive and liberal transfusion groups. Median ICU lengths of stay were similar between groups. Although limited by small sample size, this analysis was unable to detect significant improvements in mortality with a liberal as compared with a restrictive transfusion strategy in critically ill trauma victims with moderate-to0severe TBI (159).

A retrospective review of patients with severe TBI (n = 169) examined the outcome measures of GCS, Glasgow Outcome Score (GOS), and Ranchos Los Amigos Score (RLA) at hospital discharge (D/C); and GOS and Functional Independence Measures at follow-up (160). Univariate analysis showed that lowest measured hematocrit was associated with lower D/C GCS, D/C GOS, and RLA scores. In contrast, linear regression showed that more days with hematocrit <30% was associated with improved neurologic outcomes measured by GOS (R^2 = .424, p < .001), GCS (R^2 = .381, p < .001), and RLA (R^2 = .392, p < .001) scores on D/C. Both transfusion and lowest measured hematocrit values were significantly associated with all lower outcome scores on D/C. Additional factors with adverse impact on outcome were head AIS, ISS, hyperglycemia, and hypotension. Long-term outcomes were only significantly associated with head AIS. The use of blood transfusion for treatment of anemia in this study was not associated with improved outcome.

One study documented that RBC transfusion was associated with an increase in local brain tissue oxygen partial pressure in 74% of volume-resuscitated patients (n = 35) with SAH or TBI (161). This mean increase seemed to be independent of cerebral perfusion pressure, arterial oxygen saturation (Sao_2), and Fio_2. An additional study in 60 hemodynamically stable patients with severe TBI and pretransfusion Hb of <10 g/dL examined the influence of RBC transfusion on cerebral oxygenation (162). Transfusion was associated with a significant increase in brain tissue partial pressure of oxygen ($Ptio_2$) measured by intracranial catheters during a 6-hr period, with a peak at 3 hrs in 78.3% of the patients. However, no relationship was observed between cerebral oxygenation, cerebral perfusion pressure, and Hb increments. All patients with low baseline cerebral oxygenation ($Ptio_2$ <15 mm Hg) showed an increment in $Ptio_2$ with blood transfusion. These preliminary findings require validation, and additional studies investigat-

ing the impact on outcome, particularly neurologic outcome, are necessary.

Patients with severe TBI should not have a different transfusion threshold than other critical care patients. Additional prospective studies are needed to evaluate the effects of anemia and RBC transfusion in TBI.

2. Decisions regarding blood transfusion in patients with SAH must be assessed individually because optimal transfusion triggers are not known and there is no clear evidence that blood transfusion is associated with improved outcome.

Rationale. Although higher-goal Hb and more RBC transfusions are associated with no different or worse outcomes in general critical care patients, there are few data on blood transfusion and outcomes after SAH. Blood transfusion in SAH patients is used most commonly for the treatment of anemia.

In one study, the authors retrospectively reviewed a prospective observational database including hospital records, computerized tomography (CT) scans, and pre- and postoperative four-vessel angiograms, in which the management methods used in 441 patients undergoing surgery for ruptured cerebral aneurysms were described. A total of 270 patients (61.2%) received an RBC transfusion during their hospital stay. After adjustment for Hunt and Hess grade, SAH grade on CT scans, delay between rupture and surgery, smoking status, and intraoperative aneurysm rupture, a worse outcome was more likely in patients who received intraoperative blood (OR = 2.44, 95% CI = 1.32–4.52; 120 patients). Intraoperative RBC transfusion did not influence subsequent angiographically confirmed vasospasm (OR = 0.92, 95% CI = 0.6–1.4). Worse outcome also was observed in patients who received blood postoperatively (OR = 1.81, 95% CI = 1.21–2.7), but not after adjustments were made for confounding variables (OR = 1.48, 95% CI = 0.83–2.63). Angiographic vasospasm was observed in 217 patients and, after adjusting for confounding variables, was more frequent among patients who received postoperative RBC transfusion (OR = 1.68, 95% CI = 1.02–2.75). Among patients with angiographically confirmed vasospasm, there was a tendency to have received more blood than in those with no vasospasm; however, a clear dose-dependent response was not observed. These authors concluded that development of angiographically confirmed vasospasm after SAH is associated with postoperative RBC transfusion and worse outcome is associated with intraoperative RBC transfusion. Before blood is transfused, patients with SAH should be assessed carefully to determine whether they are symptomatic because of anemia (163).

Another study reviewed the daily Hb levels of 103 patients with aneurysmal SAH. Cerebral infarction was diagnosed by CT scan. Multivariate analysis adjusted for Hunt and Hess grade, age, and angiographic vasospasm. Of 103 patients, the mean age was 55.3 ± 14.5 yrs, 63% were women, and 29% were Hunt and Hess grades 4 and 5; Hb values steadily declined from 12.6 ± 1.7 g/dL the day of SAH to 10.4 ± 1.2 g/dL by day 14. Patients who died had lower Hb than survivors on days 0, 1, 2, 4, 6, 10, 11, and 12 ($p \leq .05$). Higher mean Hb was associated with reduced odds of poor outcome (OR = 0.57 per g/dL; 95% CI = 0.38–0.87; $p = .008$) after correcting for Hunt and Hess grade, age, and vasospasm. Higher day 0 Hb (OR = 0.7 per g/dL; 95% CI = 0.5–0.99; $p = .05$) and mean Hb (OR = 0.57 per g/dL; 95% CI = 0.38–0.87; $p = .009$) predicted a lower risk of cerebral infarction independent of vasospasm. There were no associations between Hb and other prognostic variables. This study concluded that SAH patients with higher initial and mean Hb values had improved outcomes (164).

Based on the divergent findings in these two studies, the efficacy and safety of blood transfusions to increase Hb in patients with SAH warrants further study.

E. Recommendations Regarding RBC Transfusion Risks

1. RBC transfusion is associated with increased nosocomial infection (wound infection, pneumonia, sepsis) rates independent of other factors.

Rationale. Many studies have documented the association between blood transfusion and infection (Table 7) (165–175). Studies in critical care patients have documented a similar association. All of these studies, however, are confounded by indication for RBC transfusion and difficulty in controlling for differences in severity of illness. Although there is clearly an association between RBC transfusion and adverse outcome in critical care, causality has not been established.

A recent meta-analysis demonstrated the relationship between allogeneic blood transfusion and postoperative bacterial infection (176). Twenty peer-reviewed studies published from 1986 to 2000 were included. Criteria for inclusion included a clearly defined control group (nontransfused) compared with a treated (transfused) group, using stepwise multivariate logistic regression analysis. In addition, a subgroup of publications that included only the traumatically injured patient was included in a separate meta-analysis in this publication. The total number of subjects included in this meta-analysis was 13,152 (5215 in the transfused group and 7937 in the nontransfused group). The common OR for all articles included in this meta-analysis evaluating the association of allogeneic blood transfusion to the prevalence of postoperative bacterial infection was 3.45 (range = 1.43–15.15), with 17 of the 20 studies demonstrating a $p \leq .05$. The common OR of the subgroup of trauma patients was 5.263 (range = 5.03–5.43), with all studies showing a $p < .05$ (.005–.0001). These results demonstrate that allogeneic blood transfusion is associated with a greater risk of postoperative bacterial infection in the trauma patient. The risk of bacterial infection post transfusion seems to be greater in the trauma population than elective surgery patients.

A retrospective evaluation similarly demonstrated an association between RBC transfusion, nosocomial infections, and worse outcomes in critically ill patients (n = 1717), independent of survival probability or patient age (177). A second validation study was performed prospectively and only included nosocomial infections that occurred after transfusion (178). In both studies, transfusion decisions were made independently of patient study inclusion. Of the 2085 patients enrolled, 21.5% received RBC transfusions. The posttransfusion nosocomial infection rate was 14.3% in 428 evaluable patients, significantly higher than that observed in nontransfused patients (5.8%; $p < .0001$, chi-square). In a multivariate analysis controlling for patient age, maximum storage age, and number of RBC transfusions, only the number of transfusions was independently associated with nosocomial infec-

Table 7. Studies examining association of RBC transfusions with mortality and morbidity in critically ill observational studies

Study: First Author, Year	Population	Design	Number	Outcomes
Ciesla, 2005 (113)	Trauma	Prospective cohort	1,344	Increased multiorgan failure
Gong, 2005 (106)	ICU patients	Prospective cohort	688	Increased risk of ARDS
Lebron, 2005 (109)	Liver transplant	Retrospective cohort	241	Increased early postoperative renal failure
Shorr, 2005 (107)	ICU patients	Prospective cohort	3,502	Increased ICU acquired bacteremia
Silverboard, 2005, (112)	Trauma	Prospective cohort	102	Increased risk of ARDS
Smith, 2004 (108)	Subarachnoid hemorrhage	Prospective cohort	441	Worse outcome with intraoperative transfusions
Vincent, 2004 (5)	ICU patients	Prospective cohort	1,136	Increased ICU, hospital and 28-day mortality, increased organ dysfunction
Leal-Noval, 2003 (104)	Cardiac surgery	Prospective cohort	103	Increased ICU LOS, mechanical ventilation, and pneumonia
Malone, 2003 (98)	Trauma	Prospective cohort	15,534	Increased mortality
Chelemer, 2002 (100)	CABG	Prospective cohort	533	Increased bacterial infections
Claridge, 2002 (110)	Trauma	Prospective cohort	1,593	Increased infection
Corwin, 2002 (4)	ICU	Prospective cohort	4,892	Increased ICU and hospital LOS Increased complications
Taylor, 2002 (95)	ICU	Retrospective cohort	1,717	Increased nosocomial infections, ICU LOS, and mortality
Vamvakas, 2002 (111)	Cardiac surgery	Retrospective cohort	416	Increased postoperative ventilation associated with volume of RBC supernatant
Leal-Noval, 2001 (96)	Cardiac surgery	Prospective cohort	738	Increased ICU LOS, mechanical ventilation, and pneumonia
Chang, 2000 (97)	Colorectal surgery	Retrospective cohort	282	Increased postoperative infection, increased mortality
Carson, 1999 (101)	Hip fracture	Retrospective cohort	9,598	Increased risk of serious bacterial infection and pneumonia
Offner, 1999 (105)	Trauma	Prospective cohort	61	Increased infection
Vamvakas, 1999 (103)	Cardiac surgery	Retrospective cohort	416	Increased postoperative infection (5%/unit)
Carson, 1998 (141)	Hip fracture	Retrospective cohort		No change in mortality or morbidity
Moore, 1997 (102)	Trauma	Prospective cohort	513	Increased multiple organ failure
Martin, 1994 (99)	ICU	Retrospective cohort	698	Increased mortality

ARDS, acute respiratory distress syndrome; LOS, length of stay; ICU, intensive care unit; RBC, red blood cell.
From Tinmouth A, et al: Clinical consequences of red cell storage in the critically ill. *Transfusion* 2006; 46:201–202.

tion (OR = 1.097; 95% CI = 1.028–1.171; $p = .005$). When corrected for survival probability, the risk of nosocomial infection associated with RBC transfusions remained statistically significant ($p < .0001$). Leukoreduction tended to reduce the nosocomial infection rate but not significantly. Mortality and length of stay (ICU and hospital) were significantly higher in transfused patients, even when corrected for illness severity. Although these data provide evidence of a strong relationship between RBC transfusion and infections, causality remains unproven.

2. RBC transfusion is an independent risk factor for MOF and SIRS.

Rationale. A number of studies have documented the association between blood transfusion, MOF, and SIRS in trauma patients. Sauaia, Moore, and colleagues were the first to determine that blood transfusion is a consistent risk factor for postinjury MOF, independent of other shock indices, such as admission lactate and base deficit (179). A 55-mo inception cohort single-institution study of 513 consecutive trauma patients admitted to the trauma ICU with an ISS of >15 who were >16 yrs and who survived >48 hrs was performed. A dose-response relationship between early blood transfusion and the later development of MOF was identified. Despite the inclusion of other indices of shock, blood transfusion was identified as an independent risk factor in 13 of the 15 multiple logistic regression models tested; the ORs were high, especially in the early MOF models (180). Additional studies confirmed this (181, 182) and also documented that age of transfused blood was an independent risk factor for postinjury MOF (183). A 12-yr prospective study of postinjury MOF demonstrated a decreasing prevalence of MOF over the study period, despite an increasing MOF risk. Improvements in MOF outcomes in this study were attributed to improvements in trauma and critical care and were associated with decreased use of blood transfusion during trauma resuscitation (184).

A prospective, observational study examined transfusion practices in patients (n = 120) admitted to a single Level 1 academic trauma center. Patients had a mean age of 34.1 ± 16.0 yrs, a mean ISS of 21.5 ± 9.5, and were equally distributed by major injury type (48% blunt, 52% penetrating). In sum, 104 patients (87%) received a total of 324 transfusions, 20 (6%) of which were given in the emergency room, 186 (57%) in the surgical ICU, 22 (7%) postsurgical ICU, and 96 (30%) in the operating room. The mean volume of blood per patient transfused was 3144 ± 2622 mL. A total of 101 patients received an allogeneic transfusion (mean volume = 3126 ± 2639 mL) and ten patients received an autotransfusion (844 ± 382 mL). The mean pretransfusion Hb level was 9.1 ± 1.4 g/dL. Transfusion volumes correlated with ISS ($p = .011$). Patients with an admission Hb ≤12 g/dL or age >55 yrs were at significant risk for transfusions ($p < .001$ and $p = .035$, respectively). An admission Hb ≤12 g/dL and any mention of long bone orthopedic operations or laparotomy or

thoracotomy were associated with increased risk of blood transfusion during the first week of admission. Logistic regression analysis identified transfusion of >4 units of blood as a significant risk factor for SIRS. After 1 wk of ICU stay, ISS of >20 and blunt injury were associated with increased risk of transfusion. This study concluded that trauma patients are heavily transfused with allogeneic blood throughout the course of their hospital stay and transfusions are administered at relatively high pretransfusion Hb levels (mean = 9 g/dL). Transfusion of >4 units of blood is an independent risk factor for SIRS (185).

3. There is no definitive evidence that prestorage leukocyte reduction of RBC transfusion reduces complication rates, but some studies have shown a reduction in infectious complications.

Rationale

Residual leukocytes contaminating units of packed RBCs have been incriminated through the induction of anergy and/or a potentiated inflammatory response, leading to the possibility that leukoreduced RBC transfusion might mitigate these effects. A number of countries have implemented a policy of universal leukoreduction of their blood supply, but the potential role of leukoreduction in decreasing mortality and infection is unclear.

Two meta-analyses of randomized, controlled trials evaluated the efficacy and effectiveness of RBC leukoreduction in reducing postoperative infection, mortality, and cancer recurrence (186). The pooled relative risk ratio (RR) of developing an adverse postoperative outcome with either leukoreduced or nonleukoreduced blood was calculated, using a random effects model. To better estimate the efficacy of leukoreduction, a second analysis of transfused patients only was conducted. Ten trials met the inclusion criteria and eight provided separate data for patients randomized and transfused. The mean percentage of patients randomized but not transfused was 34%. For postoperative infection, the overall pooled RR was 0.76 (95% CI = 0.54–1.08) for the "all patients randomized" analysis. For the "only patients transfused" analysis, the pooled RR became clinically and statistically significant (RR = 0.60; 95% CI = 0.38–0.93). For mortality, the pooled RR for the "all patients randomized" analysis was 0.71 (95% CI = 0.45–1.13) and 0.61 (95% CI = 0.36–1.04) for the "only patients transfused" analysis. When analyzing either all patients randomized or all patients transfused, there was no statistically significant difference in cancer recurrence rates (one study only). This study demonstrated that patients who were transfused leukoreduced RBCs might benefit from a decrease in postoperative infections. Including all patients randomized, regardless of whether or not they were actually transfused, diluted the observed clinical benefit of leukoreduction.

A retrospective before-and-after cohort study was conducted from August 1998 to August 2000 in 23 academic and community hospitals throughout Canada, enrolling 14,786 patients who received RBC transfusions after cardiac surgery or repair of hip fracture, or who required intensive care after a surgical intervention or multiple trauma (187). Universal prestorage leukoreduction program was introduced by two Canadian blood agencies. A total of 6982 patients were enrolled during the control period and 7804 patients were enrolled after prestorage leukoreduction. Unadjusted in-hospital mortality rates were significantly lower after the introduction of leukoreduction compared with the control period (6.19% vs. 7.03%, respectively; $p = .04$). Compared with the control period, the adjusted odds of death post leukoreduction were reduced (OR = 0.87; 95% CI = 0.75–0.99), but serious nosocomial infections did not decrease (adjusted OR = 0.97; 95% CI = 0.87–1.09). The frequency of posttransfusion fevers decreased significantly after leukoreduction (adjusted OR = 0.86; 95% CI = 0.79–0.94), as did antibiotic use (adjusted OR = 0.90; 95% CI = 0.82–0.99). The authors concluded that a national universal leukoreduction program is potentially associated with decreased mortality as well as decreased fever episodes and antibiotic use after RBC transfusion in high-risk patients. A major limitation of these studies, however, is that any individual patient may receive both leukoreduced and nonleukoreduced RBC units.

A single-center, double-blind, randomized controlled trial of leukoreduced vs. standard, nonleukoreduced RBC transfusions in injured patients receiving transfusion within 24 hrs of injury was performed in 268 patients (188). Rates of infectious complications were similar in subjects receiving leukoreduced transfusions (30%) or standard transfusions (36%) (RR = 0.84 [0.55–1.3]) and there was no statistically significant effect of leukoreduced RBC transfusion on mortality (RR = 1.20 [0.74–1.9]), febrile episodes (RR = 1.01 [0.89–1.2]), or organ dysfunction scores (5.9 vs. 6.6; $p = .29$). Thus, prestorage leukoreduction of allogeneic RBCs had a small, but nonsignificant effect on the rate of infectious complication in this high-risk population requiring transfusion. There was no effect on the rates of febrile episodes, mortality, length of stay, or severity of organ dysfunction.

Rates of ALI (RR = 1.06, 95% CI = 0.69–1.640) and ARDS (RR = .96, 95% CI = 0.48–1.91) were not statistically different between intervention arms early after injury. Similarly, no statistically significant effect of leukoreduced transfusion on rates of ALI (RR = .88, 95% CI = 0.54–1.44) or ARDS (RR = .95, 95% CI = 0.58–1.57) was observed to occur late after injury. There was no significant difference in the number of ventilator-free days or in other ventilator parameters between intervention arms. No statistically significant effect of leukoreduced blood on plasma levels of surfactant protein-D or von Willebrand factor antigen was identified. Prestorage leukoreduction had no effect on the incidence or timing of lung injury or on plasma measures of systemic alveolar and endothelial inflammation in a population of trauma patients requiring transfusion. The relationship between transfusion and lung injury is not obviously explained by mechanistic pathways involving the presence of transfused leukocytes (189).

In a cohort analysis of this randomized trauma study, although leukoreduction removes >99.9% of donor leukocytes, it failed to prevent or even substantially reduce the likelihood of developing transfusion-associated microchimerism (190). Some studies suggested that universal leukoreduction has further reduced the already low risk of transfusion-associated-graft vs. host disease in immunocompetent recipients and has altered the profile of posttransfusion purpura cases (191).

4. RBC transfusions are independently associated with longer ICU and hospital lengths of

stay, increased complications, and increased mortality.

Rationale. Many studies have documented the association between RBC transfusion and increased mortality in trauma and ICU patients (Table 7), and increased length of stay (192–196). Blood transfusions were also associated with increased mortality in the two large, prospective, multicenter studies quantifying the prevalence of anemia and the use of RBC transfusions in critically ill patients (ABC and CRIT trials) (197, 198). These data have led many to conclude that blood transfusion for the treatment of anemia should be minimized whenever possible.

5. There is a relationship between transfusion and ALI and ARDS.

Rationale

In recent years, TRALI has developed from an almost unknown transfusion reaction to the most common cause of transfusion-related major morbidities and fatalities. A clinical definition of TRALI was established in 2004, based on acute respiratory distress, noncardiogenic lung edema temporal association with transfusion and hypoxemia. Histologic findings reveal lung edema, capillary leukostasis, and neutrophil extravasation. However, the pathogenesis of TRALI remains controversial. Leukocyte antibodies, present in fresh-frozen plasma and platelet concentrates from multiparous donors, and neutrophil-priming agents released in stored cellular blood components have been considered to be causative (199). TRALI is an immune-mediated transfusion reaction that can cause severe complications or even death. It is now the leading cause of transfusion-related death in the United States. Knowledge of the TRALI syndrome is necessary to enable early diagnosis and treatment. It should be taken into consideration at any time when cardiopulmonary instability occurs after transfusion of blood products, which is a frequent event in ICUs. TRALI remains a clinical diagnosis supported by serologic studies if these are available. Against the background of this potentially life-threatening complication, every single indication to transfuse blood products needs to be scrutinized (200).

F. Recommendations Regarding Alternatives to RBC Transfusion

1. The rHuEpo administration improves reticulocytosis and hematocrit and may decrease overall transfusion requirements.

Rationale. Recent data have shown that RBC transfusions in critically ill patients can be decreased with rHuEpo therapy during their ICU stay (201, 202). Strategies to increase the production of RBCs are complementary to other approaches to reduce blood loss in the ICU and decrease the transfusion threshold in the management of critically ill patients.

The EPO-1 study (203) was the first to examine whether the administration of rHuEpo to critically ill patients in the ICU would reduce the number of RBC transfusions. This prospective, randomized, double-blind, placebo-controlled, multicenter trial was performed in ICUs at three academic tertiary care medical centers (n = 160). Patients were randomized to receive either rHuEpo or placebo. The study drug (300 units/kg of rHuEpo or placebo) was administered by subcutaneous injection beginning on ICU day 3 and continuing daily for a total of 5 days. The subsequent dosing schedule was every other day for a minimum of 2 wks or until ICU discharge. Subjects with ICU lengths of stay >2 wks were treated up to a total of 6 wks (42 days) post randomization. The cumulative number of units of RBCs transfused was significantly less in the rHuEPO group than in the placebo group ($p < .002$, Kolmogorov-Smirnov test). The rHuEPO group was transfused with a total of 166 units of RBCs vs. 305 units of RBCs transfused in the placebo group. The final hematocrit concentration of the rHuEPO patients was significantly greater than the final hematocrit concentration of placebo patients (35.1 ± 5.6 vs. 31.6 ± 4.1; $p < .01$, respectively). A total of 45% of patients in the rHuEPO group received a blood transfusion between days 8 and 42 or died before study day 42 compared with 55% of patients in the placebo group (RR = 0.8; 95% CI = 0.6–1.1). There were no significant differences between the two groups either in mortality or in the frequency of adverse events. The administration of rHuEPO to critically ill patients was effective in raising their hematocrit concentrations and in reducing the total number of units of RBCs.

The EPO-2 study (204) assessed the efficacy of a weekly dosing schedule of rHuEpo to decrease the occurrence of RBC transfusion in critical care patients. A prospective, randomized, double-blind, placebo-controlled, multicenter trial was conducted between December 1998 and June 2001 in medical, surgical, or medical/surgical ICU in each of 65 participating institutions in the United States. A total of 1302 patients who had been in the ICU for 2 days and were expected to be in the ICU at least 2 more days and who met the eligibility criteria were enrolled in the study; 650 patients were randomized to rHuEpo and 652 were randomized to placebo. Study drug (40,000 units of rHuEpo) or placebo was administered by subcutaneous injection on ICU day 3 and continued weekly for patients who remained in the hospital, for a total of three doses. This was a significantly reduced rHuEpo dose compared with the EPO-1 study. Patients in the ICU on study day 21 received a fourth dose. Patients receiving rHuEpo were less likely to undergo transfusion (60.4% placebo vs. 50.5% rHuEpo; $p < .001$; OR = 0.67; 95% CI = 0.54–0.83). There was a 19% reduction in the total units of RBCs transfused in the rHuEpo group (1963 units for placebo vs. 1590 units for rHuEpo) and reduction in RBC units transfused per day alive (ratio of transfusion rates = 0.81; 95% CI = 0.79–0.83; $p = .04$). Increase in Hb from baseline to study end was greater in the rHuEpo group (mean [standard deviation], 1.32 (2) g/dL vs. 0.94 [1.9] g/dL; $p < .001$). Mortality (14% for rHuEpo and 15% for placebo) and adverse clinical events were not significantly different. A statistically significant reduction in mortality in the trauma cohort was noted. In critically ill patients, weekly administration of 40,000 units of rHuEpo reduced allogeneic RBC transfusion and increased Hb.

Another double-blind, placebo-controlled study in anemic critically ill adults randomized patients (n = 73) 2:1 to rHuEpo, 40,000 IU, administered subcutaneously once weekly (n = 48) or matching placebo (n = 25) for up to 4 wks. Serum erythropoietin concentration and hematologic variables (percentage reticulocytes [RETI], Hb, and total RBC counts) were measured, and area under the serum concentration-time curve from time 0 to the last blood sampling time at time t (t = 120, 144, or 168 hrs) post dose (AUC0-Tlast) for these three variables was determined. Mean serum

erythropoietin concentrations in placebo patients were slightly higher than typical physiologic levels of erythropoietin in healthy subjects, although not appropriate for the degree of anemia in these patients. Overall, exposure of endogenous erythropoietin in the placebo group (in terms of AUC0-Tlast) was only about 20% of exposure to exogenous erythropoietin in the rHuEpo group. Baseline Hb levels were the same in both groups (9.9 g/dL). Mean change in Hb level from baseline through day 29 was 1.9 g/dL and 1.6 g/dL in the epoetin alfa and placebo groups, respectively. Mean AUC(RETI)0-Tlast was higher with rHuEpo than with placebo and was related to the AUC of erythropoietin. There were no apparent differences in AUC(Hb)0-Tlast and AUC(RBC)0-Tlast between rHuEpo and placebo groups, which was most likely due to bleeding and transfusion events. The rHuEpo was safe and well tolerated, with a rate of treatment-emergent complications similar to that seen with placebo. The rHuEpo, once weekly, augmented the erythropoietic response in critically ill patients as indicated by the increased erythropoietin levels and larger AUC(RETI)0-Tlast in treated patients (205).

Another study assessed the efficacy of two dosing schedules of rHuEpo to increase hematocrit and Hb and reduce exposure to allogeneic RBC transfusion in critically ill patients. This was a prospective, randomized, multicenter trial in 13 ICUs with 148 patients. Patients were assigned randomly to receive intravenous iron saccharate alone (control group), intravenous iron saccharate, and subcutaneous rHuEpo 40,000 units once per week (group A), or intravenous iron saccharate and subcutaneous rHuEpo 40,000 units three times per week (group B). The rHuEpo was given for a minimum of 2 wks or until discharge from the ICU or death. The maximum duration of therapy was 3 wks. The cumulative number of RBC units transfused, the average numbers of RBC units transfused per patient and per transfused patient, the average volume of RBCs transfused per day, and the percentage of transfused patients were significantly higher in the control group than in groups A and B. No significant difference in RBC transfusions was observed between groups A and B. The mean increases in hematocrit and Hb from baseline to final measurement were significantly greater in group B than in the control group. The mean increase in hematocrit was significantly greater in group B than in group A. The mean increase in hematocrit in group A was significantly greater than that in control individuals, whereas the mean increase in Hb did not differ significantly between the control group and group A. Administration of rHuEpo to critically ill patients significantly reduced the need for RBC transfusion. The magnitude of the reduction did not differ between the two dosing schedules, although there was a dose response for hematocrit and Hb to rHuEpo in these patients (206).

The EPO-3 study (207), a multicenter, placebo-controlled trial, randomized ICU patients (n = 1460) to either placebo or 40,000 units rHuEpo weekly for up to three doses. The patients were followed up to 140 days to assess drug safety. Unlike earlier investigations with rHuEpo in critical care, this protocol included a formal guideline, suggesting that blood transfusions not be given unless the Hb concentration fell to the range of 7 to 9 mg/dL. Patients were also prospectively stratified based on admitting diagnosis (trauma, nontrauma surgical, medical). The placebo and intervention populations were well matched with respect to baseline characteristics, and the mean APACHE II score was 20 in both groups. More than half were admitted post trauma, although one fourth were medical patients. Overall, there was no difference in transfusion rates between the rHuEpo and placebo groups. This may have been related to inadequate rHuEpo dosing and inadequate iron supplementation, which is necessary to achieve a maximal rHuEpo response. When stratified by admitting diagnosis, there was no evidence of a beneficial effect of rHuEpo on transfusion utilization. The mean pretransfusion Hb concentration in each group was similar, but the Hb concentration increased more quickly in patients in rHuEpo patients *data*.

In the EPO-3 study, the 28-day mortality rate was significantly lower in the rHuEpo group, and this was driven by improved outcome in the trauma patients who received rHuEpo (6.7% in placebo-treated trauma patients vs. 3.5% in rHuEpo-treated trauma patients, $p < .05$). Even after adjusting for covariates, rHuEpo use was associated with a significant reduction in mortality (adjusted HR = 0.37; 95% CI = 0.19–0.72). This was confirmed after examining other trauma-related variables that may have impacted on outcome (208). These findings were nearly identical to the findings reported in the trauma subpopulation in the prior EPO-2 trial in the ICU. As compared with placebo, rHuEpo was associated with a significant increase in the prevalence of thrombotic events (HR = 1.41; 95% CI = 1.06–1.86, $p = .008$). *Post hoc* analyses showed that the prevalence of thrombotic vascular events in the epoetin alfa group as compared with the placebo group was increased among patients who did not receive heparin at baseline (20.3% vs. 12.8%; HR = 1.58; 95% CI = 1.09–2.28; $p = .008$) but not among those who received heparin at baseline (12.3% vs. 10.2%; HR = 1.16; 95% CI = 0.75–1.80; $p = .41$). An increase in the prevalence of thrombotic events was not noted in the previous trials (EPO-1 and EPO-2). There are significant limitations to the thrombotic event data that were collected in this study (EPO-3) related to the lack of standardized detection strategies (thrombotic events were captured as serious adverse events) and prevention strategies for thromboembolism (>60% of the trauma cohort did not receive venous thromboembolism prophylaxis on study day 1). In addition, no standardized venous thromboembolism risk factors were assessed, thereby limiting comparative analysis.

The efficacy of rHuEpo in chronically critically ill patients admitted to a long-term acute care facility (LTAC) was examined in a prospective, randomized, double-blind, placebo-controlled multicenter trial (n = 86). Study drug (rHuEpo 40,000 units) or a placebo was administered by subcutaneous injection before day 7 of LTAC admission and continued weekly for up to 12 doses. The baseline Hb level was higher in the rHuEpo group (9.9 ± 1.15 g/dL vs. 9.3 ± 1.41 g/dL, $p = .02$) as was the pretransfusion Hb level (8.0 ± 0.5 g/dL vs. 7.5 ± 0.8 g/dL, $p = .04$). On day 84, patients receiving rHuEpo received fewer RBC transfusions (median units per patient 0 vs. 2, $p = .05$), and the ratio of RBC transfusion rates per day alive was 0.61 with 95% CI = 0.2–1.01, indicating a 39% relative reduction in transfusion burden for the rHuEpo group compared with placebo. There was also a trend on day 84 toward a reduction in the total units of RBCs transfused in the rHuEpo group (113 units of placebo vs. 73 units of rHuEpo). Patients receiving rHuEpo were also less likely to be transfused (64% placebo vs. 41% rHuEpo, $p = .05$; adjusted OR = 0.47, 95% CI = 0.19–1.16). Most of the transfusion benefit of rHuEpo occurred

by study day 42. Increase in Hb from baseline to final was greater in the rHuEpo group (1.0 ± 2 g/dL vs. 0.4 ± 1.7 g/dL, $p < .001$). Mortality rate (19% rHuEpo, 29.5% placebo, $p = .17$; RR = 0.55, 95% CI = 0.21–1.43) and serious adverse clinical events (38% rHuEpo, 32% placebo, $p = .65$) were not significantly different between the two groups. In patients admitted to an LTAC, administration of weekly rHuEpo resulted in a significant reduction in exposure to allogeneic RBC transfusion during the initial 42 days of rHuEpo therapy, with little additional benefit achieved with therapy to 84 days. Despite receiving fewer RBC transfusions, patients treated with rHuEpo achieve a higher Hb level (209).

Potential adverse events related to rHuEpo including venous thromboembolism and cancer outcomes have recently been reviewed. Erythropoiesis-stimulating agents (ESAs) are approved as an alternative to blood transfusions for treating anemia secondary to chemotherapy in patients with cancer. Recently, ESAs have been a source of controversy and confusion in the oncology community. This began when two European trials—the Breast Cancer Erythropoietin Survival Trial (BEST) and the Advanced Head-and-Neck Cancer Treated with Radiotherapy (ENHANCE) Study—raised safety concerns about decreased overall survival and increased venous thromboembolic events. In 2004, the U.S. Food and Drug Administration (FDA) convened its Oncologic Drugs Advisory Committee (ODAC) to review the data and reassess the risks and benefits of ESAs in patients with cancer. On May 10, 2007, ODAC reconvened when five trials (BEST, ENHANCE, AMG-20010103, AMG-20000161, and EPO-CAN-20) showed decreased overall survival. The briefing document noted that studies demonstrating detrimental effects on survival and/or tumor outcomes used an unapproved treatment regimen designed to maintain Hb levels of >12 g/dL (210, 211).

The American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH) Guidelines for the use of ESAs in cancer were recently expanded to address use of darbepoetin and thromboembolic risk associated with these agents. For patients with chemotherapy-associated anemia, the evidence-based guideline continues to recommend initiating an ESA as Hb approaches, or falls below, 10 g/dL, to increase Hb and decrease transfusions. ESA treatment continues to be recommended for patients with low-risk myelodysplasia for similar reasons. There is no evidence showing increased survival as a result of ESA treatment. Conclusive evidence is lacking that, absent clinical circumstances necessitating earlier treatment, initiating ESAs at Hb levels >10 g/dL either spares more patients from transfusion or substantially improves their quality of life. Starting doses and dose modifications based on response or lack thereof should follow the package insert. Continuing ESAs >6 to 8 wks in the absence of response, assuming appropriate dose increase has been attempted in nonresponders as per US FDA-approved label, does not seem to be beneficial, and ESA therapy should be discontinued. The Guideline recommends monitoring iron stores and supplementing iron intake for ESA-treated patients. ESAs should be used cautiously with chemotherapy or in clinical states associated with elevated risk for thromboembolic complications. The Guideline also cautions against ESA use for patients with cancer who are not receiving chemotherapy because recent trials reported increased thromboembolic risks and decreased survival under these circumstances (212, 213).

2. HBOCs are undergoing investigation for use in critically ill and injured patients but are not yet approved for use in the United States.

Rationale. The many limitations and risks of transfusions of packed RBCs in critically ill patients have facilitated interest in developing alternative agents for $\dot{D}o_2$. Over the past decades, a number of HBOCs have been in development. However, at present there is no currently FDA-approved HBOC that provides both oxygen transport and volume in place of allogeneic RBC transfusion. Oxygen carrier products have several advantages compared with packed RBCs, including a prolonged shelf-life, lack of a cross-matching requirement, lower viscosity, and minimal infectious risks or concerns about immunogeneicity. These products may also deliver more oxygen per unit mass than an equivalent amount of Hb from RBCs, providing the potential to sustain life in certain clinical situations. A number of problems remain, including short biological half-life, which may limit the application to times when the patient is most acutely anemic (i.e., in the intraoperative or immediate perioperative phase) or for emergent use, vasoactivity (214) and concern regarding possible risks of MI and death examined in a recent meta-analysis (215). There is concern, however, that heterogeneity in HBOCs and controls in these studies preclude combining in a meta-analysis, and lack of information on criteria used to diagnose MIs within these trials was a limitation as well. Nevertheless, a safe, effective alternative therapy providing $\dot{D}o_2$ characteristics comparable to RBCs could have significant impact in the care of critically ill patients. Oxygen carriers have several potential clinical applications in the management of perioperative blood loss, trauma, acute normovolemic hemodilution, traumatic brain injury, and blood replacement in patients who refuse or have contraindications to transfusions or RBCs (216–218).

Two HBOCs are undergoing clinical trials. PolyHeme (human HBOC derived from outdated human RBCs) has been studies in Phase II and Phase III in-hospital clinical trials (219–221). A U.S. multicenter prehospital trial in trauma patients was recently completed in which severely injured patients with major blood loss (systemic blood pressure <90 mm Hg) were randomized to initial field resuscitation with crystalloid vs. HBOC. During the hospital phase, the control group was further resuscitated with stored RBCs, whereas the study group received HBOC (up to 6 units) in the first 12 hrs. The primary study end point was 30-day mortality, and secondary end points included reduction in allogenic RBCs, Hb levels <5 g/dL, transfusion of uncrossmatched RBCs, and MOF (222, 223). A total of 714 patients were enrolled at 29 urban Level I trauma centers (79% men; mean age = 37.1 yrs). Injury mechanism was blunt trauma in 48%, and median transport time was 26 mins. There was no significant difference between day 30 mortality in the as-randomized (13.4% PolyHeme vs. 9.6% control) or per-protocol (11.1% PolyHeme vs. 9.3% control) cohorts. Allogeneic blood use was lower in the PolyHeme group (68% vs. 50% in the first 12 hrs). The prevalence of MOF was similar (7.4% PolyHeme vs. 5.5% control). Adverse events (93% vs. 88%; $p = .04$) and serious adverse events (40% vs. 35%; $p = .12$), as anticipated, were frequent in the PolyHeme and control groups, respectively. Although MI was reported by the investigators more frequently in the PolyHeme

group (3% PolyHeme vs. 1% control), a blinded committee of experts reviewed records of all enrolled patients and found no discernible difference between groups. This study documented that patients resuscitated with PolyHeme, without stored blood for up to 6 units in 12 hrs post injury, had outcomes comparable with those for the standard of care. Although there were more adverse events in the PolyHeme group, the benefit/risk ratio of PolyHeme is favorable when blood is needed but not available (224). Hemopure (bovine HBOC) has completed Phase II and Phase III in-hospital clinical trials, which confirmed the reduction of allogeneic transfusion requirement (225, 228).

G. Recommendations Regarding Strategies to Reduce RBC Transfusion

1. The use of low-volume adult or pediatric blood sampling tubes is associated with a reduction in phlebotomy volumes and a reduction in blood transfusion.

Rationale. Phlebotomy for diagnostic testing is a contributing cause of anemia in trauma and critical care. Multiple studies have documented daily phlebotomy volumes from 40 to 70 mL/day. A number of strategies to reduce blood loss related to phlebotomy are available, including the use of reduced volume blood sampling tubes, such as pediatric or low-volume adult tubes, and reduction in laboratory testing by elimination of automatic daily laboratory orders. Additional strategies include point-of-care and in-line bedside microanalysis, minimization of diagnostic sample waste, minimization of routine multiple daily phlebotomies, and blood salvage (229, 230).

A prospective study examined phlebotomy volume in 96 medical ICU patients with ICU length of stay of >3 days (231). Diagnostic blood loss declined from a median of 41 mL on day 1 to <20 mL after 3 wks and contributed 17% (median) to total blood loss during the entire ICU stay. Acute renal failure, fatal outcome, and an SAPS of >38 on admission were associated with a 5.8-, 7.0-, and 2.8-fold increase in total blood loss. The ABC trial[1] was a prospective, observational blood sampling study. The mean ± standard deviation volume per blood draw was 10.3 ± 6.6 mL, with an average total volume of 41.1 ± 39.7 mL during the 24-hr period. There was a positive correlation between organ dysfunction and the number of blood samples drawn ($r = .34$; $p < .001$) and total volume drawn ($r = .28$; $p < .001$). Similarly, Nguyen and colleagues (232) also documented that the volume of blood drawn daily for laboratory studies was 40.3 ± 15.4 mL (49.0 ± 11.3 mL in septic patients vs. 36.7 ± 14.9 mL in nonseptic patients, $p = .04$). A prior study documented a mean volume of 41.5 mL of blood drawn a day and a total volume of 762.2 mL in 50 ICU patients, with a mean phlebotomy rate of 3.4 times daily, all contributing to their anemia and blood transfusion requirements (233).

A recent study in 140 public and private institutions documented significant overcollection of the instrument analytic volume necessary for laboratory testing, ranging from 8- to 12-fold higher volume for complete blood counts and electrolyte panels in ICU patients (234). Specimen collection container size was directly associated with overcollection. Therefore, the use of smaller collection tubes can help reduce autologous blood wastage. The use of pediatric-sized blood collection tubes for diagnostic laboratory testing was associated with a 46.8% reduction in volume of blood drawn (120.2 mL total; 32.3 mL/day vs. 226.1 mL total; 55.6 mL/day). Sufficient blood was available for performance of all laboratory tests ordered at the time of phlebotomy. Although substitution of pediatric-sized tubes does not address the problem of excessive use of laboratory tests, smaller tubes may reduce the severity of phlebotomy-induced anemia in adults without compromising laboratory test procedures (235, 236). Another option is the use of low-volume adult sampling tubes if the hospital laboratory cannot convert to the use of pediatric-sized blood collection tubes.

2. The use of blood conservation devices for reinfusion of waste blood with diagnostic sampling is associated with a reduction in phlebotomy volume.

Rationale. The use of a blood conservation device to minimize diagnostic phlebotomy blood loss in critically ill patients has been documented to be efficacious. A prospective, randomized, controlled trial in 100 medical ICU patients confirmed that a device incorporated into the arterial pressure monitoring system resulted in significant blood conservation (237). The volume of blood drawn and discarded from arterial catheters was significantly lower in the blood conservation group (blood conservation device: 5.7 ± 7.5 mL; control: 96.4 ± 88.5 mL; $p < .0001$), as was the total volume of blood discarded (blood conservation device: 19.4 ± 47.4 mL; control: 103.5 ± 99.9 mL; $p < .0001$). Univariate and multiple regression analysis demonstrated discarded blood volume to be a significant and independent predictor of the decline in Hb concentration, and has been validated in other studies (238).

A recent survey of arterial blood sampling practices in 280 ICUs throughout England and Wales found that few measures were taken to reduce diagnostic blood loss from arterial sampling in adult patients (239). The average volume of blood withdrawn to clear the arterial catheter before sampling was 3.2 mL, which was subsequently returned to the patient in only 18.4% of ICUs. Specific measures to reduce the blood sample size through the routine use of pediatric sample tubes in adult patients occurred in only 9.3% of ICUs. In pediatric ICUs, the average volume withdrawn was 1.9 mL, which was routinely returned in 67% of units. These arterial blood sampling practices identified in this survey contribute to iatrogenic anemia in ICU patients.

Most recently, a survey of Australian ICUs documented that only 16% of units return deadspace blood volume from in-line arterial sets and no ICU routinely used pediatric blood collection tubes. Using a highly conservative phlebotomy protocol, median phlebotomy-associated blood loss was reduced by over 80% (40 mL vs. 8 mL, $p < .001$) (240). Neonatal and pediatric critical care have embraced these practices, and recent studies have documented a significant reduction in RBC transfusion by use of a point-of-care technology including a novel bedside laboratory monitor that returned analyzed blood to the patient (241, 242).

3. Intraoperative and postoperative blood salvage and alternative methods for decreasing transfusion may lead to a significant reduction in allogeneic blood usage.

Rationale. A randomized, controlled trial in patients with penetrating torso injury requiring a laparotomy for hemor-

rhagic shock examined the efficacy of blood salvage. Patients who had hypotension either prehospital or on arrival were assigned randomly to two groups: allogeneic blood transfusion (control, n = 23) vs. cell saver (CS, n = 21, intraoperative blood salvage with transfusion of both allogeneic and autologous blood). The primary outcome was exposure to allogeneic blood up to the first 24 hrs post injury. The groups were equivalent in demographic details, injury patterns, and injury severity. The mean volume of salvaged blood reinfused in the CS group was 1493 mL (range = 0–2690 mL). The mean number of units of allogeneic blood transfused in the first 24 hrs in the control group was 11.17 compared with 6.47 in the CS group (p = .008). Enteric injury had been sustained in 17 (75%) of 23 of the control group and 18 (85%) of 21 of the CS group (p = NS). Survival in the control group was 8 (35%) of 23 compared with 7 (33.3%) of 21 in the CS arm (p = NS). Patients with documented postoperative sepsis were significantly more likely to die compared with those without sepsis (p = .04); however, those patients in the CS arm were no more likely to develop sepsis compared with those who received allogeneic blood alone. In this randomized, controlled trial for patients with penetrating abdominal injuries, intraoperative blood salvage led to a significant reduction in allogeneic blood usage with no discernible effect on rates of postoperative infection or mortality (243). Intraoperative blood salvage has also been associated with a significant reduction in blood transfusion requirements in emergency surgery for spine trauma (244), orthopedic and abdominal trauma surgery (245).

Intraoperative cell salvage was also documented to be effective in reducing blood transfusion in a prospective, randomized trial of 263 adults undergoing elective coronary artery bypass surgery. Transfusion rates were lower in the cell salvage group (OR = 0.43, 95% CI = 0.23–0.80) and the mean number of units of allogeneic blood transfused was lower (0.68 ± 1.55 unitsvs. 1.07 ± 1.56 units) p value (246). Similar trials have validated these findings (247). Furthermore, postoperative cell salvage, such as retransfusion of thoracic drainage blood, may also be used as a strategy to reduce allogeneic blood transfusion in the perioperative period. The cost-effectiveness of cell salvage and alternative methods of minimizing perioperative allogeneic blood transfusion (such as acute normovolemic hemodilution) have been documented in a systematic review (248).

The Consensus Document on Alternatives to Allogeneic Blood Transfusion was developed from five scientific societies including the Spanish societies of anesthesiology (SEDAR), critical care medicine and coronary units (SEMICYUC), hematology and hemotherapy (AEHH), blood transfusion (SETS) and thrombosis and hemostasis (SETH) sponsored and participated in the development of a "Spanish Consensus Statement on Alternatives to Allogeneic Transfusions: the Seville document" (249).

VI. FUTURE INVESTIGATION

Well-controlled clinical trials regarding the use of RBC transfusion in acute resuscitation of critically ill and injured patients are needed, but these are difficult to control because of difficulty with blinding, no gold standard regarding the end points of resuscitation, and the need for strict control of resuscitation protocols. Particularly in the use of blood transfusion in acute resuscitation for hemorrhagic shock, other issues directly impact on patient outcome, especially prompt cessation of hemorrhage.

In addition, prospective, randomized, clinical trials examining the efficacy of blood transfusion for the treatment of anemia in critically ill and injured patients are necessary. The optimal Hb in critically ill patients is unknown. Furthermore, whether a transfusion trigger vs. a physiologic indication for blood transfusion should be utilized in critically ill and injured patients is unknown, particularly in those with significant cardiac and respiratory comorbidities and at high risk of death. There is an urgent need for prospective studies to determine the optimal transfusion threshold for ACS and to determine the role of transfusion in acute resuscitation in septic shock patients.

Data regarding the lack of efficacy of blood transfusion in improving $\dot{D}o_2$ in critically ill and injured patients is also of concern. Additional studies investigating the issues regarding age of blood, i.e., whether "fresh" (decreased storage time) blood is more efficacious than "old" (increased storage time) blood will be extremely important in all future studies. Additional methods to increase Hb concentration including the use of HBOCs and recombinant erythropoietin also require further study in critically ill and injured patients, particularly with regard to dosing and potential adverse effects. Studies to further investigate the pathophysiology of anemia in critical illness and determine potential novel treatment strategies are important. Further studies regarding iron deficiency and iron supplementation are also warranted (250).

Answering these questions will require systematic approaches to the problem in the context of coordinated research efforts. Multicentered studies should be instituted to achieve the large numbers of patients who will be needed to complete the studies in a timely fashion and to assure utility of the technique across a variety of patient populations and physician practices.

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