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Summary of Blood Utilization Literature, 1999 to 2014

PRIMARY EVIDENCE

Hebert PC, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; 340:409-17.

The “TRICC trial”: Investigators enrolled 838 critically ill patients who, once euvolemic, had hemoglobin concentrations of less than 9.0 g per deciliter. They randomly assigned 418 patients to a restrictive strategy of transfusion (transfused if the hemoglobin concentration dropped below 7.0 g per deciliter with target of 7.0 to 9.0 g per deciliter) and 420 patients to a liberal strategy (transfusion given when the hemoglobin concentration fell below 10.0 g per deciliter with target 10.0 to 12.0 g per deciliter). A restrictive strategy of red-cell transfusion was 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 myocardial infarction and unstable angina.

Taylor RW, et al. Impact of allogenic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient. *Crit Care Med* 2002; 30:2249 – 2254

Investigators evaluated 1717 patients admitted to the medical-surgical-trauma intensive care unit. After severity adjustment, the nosocomial infection rates for the transfusion group and the nontransfusion group were 15.38% and 2.92%, respectively ($p < .005$). There was a dose-response pattern; for each unit of packed red blood cells transfused, the odds of developing nosocomial infection were increased by a factor of 1.5.

Shorr AF, et al. Red blood cell transfusion and ventilator-associated pneumonia: A potential link? *Crit Care Med* 2004;32(3):666-74.

284 ICUs in the US were studied from August 2000 to April 2001. VAP was defined as arising 5 or more days of mechanical ventilation. Transfusions given during the ICU stay and before the onset of VAP were tracked prospectively. Of 4892 subjects, 1518 received mechanical ventilation and did not have preexisting pneumonia. VAP was diagnosed in 311 (20.5%) patients. Multivariant analysis revealed that transfusion independently increased the risk for VAP (odds ratio, 1.89; 95% CI, 1.33-2.68). The effect of transfusion on late onset VAP was more pronounced (odds ratio, 2.16; 95%

CI, 1.27-3.66) and demonstrated a positive dose-response relationship (p=0.0223 for trend test).

Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, MacIntyre NR, Shabot MM, Duh MS, Shapiro MJ. The CRIT Study: Anemia and blood transfusion in the critically ill--current clinical practice in the United States. *Crit Care Med* 2004;32(1):39-52

Prospective, multicenter, observational cohort study of ICU patients in US. Total of 4892 patients were enrolled in the study. The number of RBC transfusions a patient received during the study was independently associated with longer ICU and hospital lengths of stay and an increase in mortality. Patients who receive transfusions were also more likely to experience a complication. Baseline hemoglobin was related to the number of RBC transfusions, but it was not an independent predictor of LOS or mortality.

Hill GE, Frawley WH, Griffith KE, Forestner JE, Minei JP. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a meta-analysis. *J Trauma* 2003;54(5):908-14

Meta-analysis of 20 peer reviewed articles from 1986-2000 with a total number of subjects of 13,152 (5214 in transfused group and 7937 in non-transfused group). The common odds ratio for all articles included in the meta-analysis evaluating the association of ABT to the incidence of postoperative bacterial infection was 3.45 (range 1.43-15.15), with 17 of the 20 studies demonstrating a value of $p < \text{or} = 0.05$. These results provide overwhelming evidence that ABT is associated with a significantly increased risk of post-operative bacterial infection in the surgical patient. The common odds ratio of the trauma subgroup was 5.263 (range 5.03-5.43) with all studies showing a value of $p < 0.05$ (0.005-0.0001). These results demonstrate that ABT is associated with a greater risk of post-operative bacterial infection in the trauma patient when compared with those receiving ABT during or after elective surgery.

McIntyre LA, et al. Effect of a liberal versus restrictive transfusion strategy on mortality in patients with moderate to severe head injury. *Neurocrit Care* 2006;5(1):4-9.

This was a subgroup analysis of 67 critically ill patients from the TRICC trial who sustained a closed head injury. Investigators were unable to detect significant improvements in mortality with a liberal as compared to restrictive transfusion strategy in critically ill trauma victims with moderate to severe head injury.

Aronson D, et al. Impact of red blood cell transfusion on clinical outcomes in patients with acute myocardial infarction. *Am J Cardiol* 2008 Jul 15;102(2):115-9.

Transfusion was associated with increased mortality in patients with nadir hemoglobin >8 g/dL (adjusted HR 2.2, 95% CI 1.5 to 3.3; $p < 0.0001$). Similar results were obtained for the composite end point of death/MI/heart failure. Authors concluded that RBC transfusion in patients with acute MI and hemoglobin ≤ 8 g/dL may be appropriate.

Shishehbor MK, et al. Impact of blood transfusion on short- and long-term mortality in patients with ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 2009;2(1):46-53.

Investigators evaluated 30-day, 6-month, and 1-year all-cause mortality among 4,131 STEMI patients enrolled in the GUSTO IIb trial. Patients were categorized according to whether they received a blood transfusion during hospitalization. Cox proportional hazards survival models with transfusion as a time-dependent covariate were conducted for the whole and for the propensity-matched groups. The investigators observed that death at 30 days (13.7% vs. 5.5%), 6 months (19.7% vs. 6.9%), and 1 year (21.8% vs. 8.7%) was significantly higher for transfused patients than for nontransfused patients, respectively. After adjusting for over 25 baseline characteristics, nadir hemoglobin, and propensity score for transfusion, and using transfusion as a time-dependent covariate, transfusion remained significantly associated with increased risk of mortality at 30 days (hazard ratio [HR]: 3.89, 95% CI: 2.66 to 5.68, $p < 0.001$), 6 months (HR: 3.63, 95% CI: 2.67 to 4.95, $p < 0.001$), and 1 year (HR: 3.03, 95% CI: 2.25 to 4.08, $p < 0.001$). The authors concluded that blood transfusion is independently associated with increased short- and long-term mortality in the setting of STEMI.

Carson JL, et al. Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery. *N Engl J Med* 2011;365:2453-62

The investigators enrolled 2016 patients who were 50 years of age or older, all of whom had either a history of cardiovascular disease or significant risk factors for cardiovascular disease, and all of whom had hemoglobin levels below 10 g per deciliter after hip-fracture surgery. Patients were randomly assigned to a liberal transfusion strategy (a hemoglobin threshold of 10 g per deciliter) or a restrictive transfusion strategy (symptoms of anemia or at physician discretion for a hemoglobin level of < 8 g per deciliter). A liberal transfusion strategy did not reduce rates of death or inability to walk independently on 60-day follow-up or reduce in-hospital morbidity.

Villanueva C, et al. Transfusion Strategies for Acute Upper Gastrointestinal Bleeding. *N Engl J Med* 2013;368:11-21.

The investigators enrolled 921 patients with severe acute upper gastrointestinal bleeding and randomly assigned 461 of them to a restrictive strategy (transfusion for hemoglobin below 7 g per deciliter) and 460 to a liberal strategy (transfusion for hemoglobin below 9 g per deciliter). As compared with a liberal transfusion strategy, a restrictive strategy significantly improved outcomes in patients with acute upper gastrointestinal bleeding.

Shorr AF et al. Red blood cell transfusion and ventilator-associated pneumonia: a potential link? *Crit Care Med*. 2004; 32: 666-74

284 ICUs in the US were studied from August 2000 to April 2001. VAP was defined as arising 5 or more days of mechanical ventilation. Transfusions given during the ICU stay and before the onset of VAP were tracked prospectively. Of 4892 subjects, 1518 received mechanical ventilation and did not have preexisting pneumonia. VAP was diagnosed in 311 (20.5%) patients. Multivariate analysis revealed that transfusion independently increased the risk for VAP (odds ratio, 1.89; 95% CI, 1.33-2.68). The effect of transfusion on late onset VAP was more pronounced (odds ratio, 2.16; 95% CI, 1.27-3.66) and demonstrated a positive dose-response relationship (p=0.0223 for trend test).

deGast-Bakker DH, et al. Safety and Effects of Two Red Blood Cell Transfusion Strategies in Pediatric Cardiac Surgery Patients: a Randomized Controlled Trial. *Intensive Care Med*. 2013. 39: 2011-2019.

Randomized controlled trial in the pediatric ICU setting. 107 patients with non-cyanotic congenital heart disease (6wks to 6 years old). 103 underwent corrective surgery on cardiopulmonary bypass. Patients randomized prior to surgery into two groups with specific transfusion thresholds: Hb 10.8g/dl and Hb 8.0 g/dl. Measurements: length of stay in hospital, length of stay in PICU, duration of ventilation, incidence of adverse events and complications related to randomization. Results: In the restrictive transfusion group, mean volume of transfused RBC was 186 ml per patient and in the liberal group 258 ml per patient. Hospital LOS shorter for restrictive versus liberal group (median 8 vs 9 p=0.047). All other outcome measures were equal for the two groups. Conclusion: a restrictive blood transfusion strategy in non-cyanotic congenital heart defect patients

undergoing elective cardiac surgery during the entire perioperative period is safe, leads to shorter LOS.

Sherwood MW, et al. Patterns and Outcomes of Red Blood Cell Transfusion in Patients Undergoing Percutaneous Coronary Intervention. *JAMA*. 2014; 311: 836-843.

Retrospective cohort study of all patient visits from the CathPCI Registry at US hospitals from July 2009 to March 2013 that included, PCI, excluding those with missing data on bleeding complications or who underwent in-hospital coronary artery bypass graft surgery (N=2,248,711 visits). Transfusion rates in the overall population and by hospitals (N=1431) were the primary outcomes. The association of transfusion with MI, stroke, and death after accounting for patient's propensity for transfusion was measured. The overall rate of transfusion was 2.14% (95% CI, 2.13%-2.16%) and quarterly transfusion rates slightly declined from July 2009 to March 2013 (from 2.11% to 2.04%; $p < 0.001$). Variation in hospital risk-standardized rates of transfusion persisted after adjustment and hospitals showed variability in their transfusion thresholds. Receipt of transfusion was associated with MI (4.5% vs. 1.8%; odds ratio (OR) 2.60), stroke (2.0% vs. 0.2%; OR 7.72) and in-hospital death (12.5% vs 1.2%; OR 4.63), irrespective of bleeding complications. Conclusions and Relevance: Among patients undergoing a PCI at US hospitals, there was considerable variation in blood transfusion practices, and receipt of transfusion was associated with an increased risk of in-hospital adverse cardiac events.

Robertson CS, et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury. A randomized control trial. *JAMA*. 2014; 312: 36-47.

To compare the effects of erythropoietin and 2 hemoglobin transfusion thresholds (7 and 10 g/dL) on neurological recovery after traumatic brain injury.

Randomized clinical trial of 200 patients (erythropoietin, n = 102; placebo, n = 98) with closed head injury who were unable to follow commands and were enrolled within 6 hours of injury at neurosurgical intensive care units in 2 US level I trauma centers between May 2006 and August 2012. The study used a factorial design to test whether erythropoietin would fail to improve favorable outcomes by 20% and whether a hemoglobin transfusion threshold of greater than 10 g/dL would increase favorable outcomes without increasing complications. Erythropoietin or placebo was initially dosed daily for 3 days and then weekly for 2 more weeks (n = 74) and then the 24- and 48-hour doses were stopped for the remainder of the patients (n = 126). There were 99 patients assigned to a hemoglobin transfusion threshold of 7 g/dL and 101 patients assigned to 10 g/dL. Interventions included

intravenous erythropoietin (500 IU/kg per dose) or saline. Transfusion threshold maintained with packed red blood cells.

Outcomes and measures used were the Outcome Scale score dichotomized as favorable (good recovery and moderate disability) or unfavorable (severe disability, vegetative, or dead) at 6 months postinjury.

There was no interaction between erythropoietin and hemoglobin transfusion threshold. Compared with placebo (favorable outcome rate: 34/89 [38.2%; 95% CI, 28.1% to 49.1%]), both erythropoietin groups were futile (first dosing regimen: 17/35 [48.6%; 95% CI, 31.4% to 66.0%], $P = .13$; second dosing regimen: 17/57 [29.8%; 95% CI, 18.4% to 43.4%], $P < .001$). Favorable outcome rates were 37/87 (42.5%) for the hemoglobin transfusion threshold of 7 g/dL and 31/94 (33.0%) for 10 g/dL (95% CI for the difference, -0.06 to 0.25 , $P = .28$). There was a higher incidence of thromboembolic events for the transfusion threshold of 10 g/dL (22/101 [21.8%] vs 8/99 [8.1%] for the threshold of 7 g/dL, odds ratio, 0.32 [95% CI, 0.12 to 0.79], $P = .009$).

In patients with closed head injury, neither the administration of erythropoietin nor maintaining hemoglobin concentration of greater than 10 g/dL resulted in improved neurological outcome at 6 months. The transfusion threshold of 10 g/dL was associated with a higher incidence of adverse events. These findings do not support either approach in this setting.

Janssen SJ et al. Allogeneic Blood Transfusions and Postoperative Infections After Lumbar Spine Surgery. *Spine J.* 2015 Feb 11. pii: S1529-9430(15)00108-4. doi: 10.1016/j.spinee.2015.02.010. [Epub ahead of print] Author information • 1 Department of Orthopaedic Surgery, Spine Service, Massachusetts General Hospital - Harvard Medical School, Room • 2 Department of Orthopaedic Surgery, Spine Service, Massachusetts General Hospital - Harvard Medical School,

Allogeneic blood transfusions have an immunomodulating effect and previous studies in other fields of medicine demonstrated an increased risk of infections after administration of allogeneic blood transfusions. **PURPOSE:** Our primary null hypothesis is that exposure to allogeneic blood transfusion in patients undergoing lumbar spine surgery is not associated with postoperative infections after controlling for patient and treatment characteristics. Secondly, we assessed if there was a dose-response relationship per unit of blood transfused. **STUDY DESIGN/SETTING:** Retrospective cohort study from a tertiary care spine referral center. **PATIENT SAMPLE:** 3,721 Patients who underwent laminectomy and/or arthrodesis of the lumbar spine. **OUTCOMES MEASURES:** Postoperative infection, including: pneumonia, endocarditis, meningitis, urinary tract infection, central venous line infection, surgical site infection, and sepsis, within 90 days after lumbar spine surgery. **METHODS:** Multivariable logistic regression analyses were used to assess the relationship of perioperative allogeneic blood transfusion with specific and overall postoperative infections accounting for age, duration of surgery, duration of hospital stay,

comorbidity status, preoperative hemoglobin, sex, type of operation, multilevel treatment, operative approach, and year of surgery. RESULTS: The adjusted odds ratio for exposure to allogeneic blood transfusion from multivariable logistic regression analysis was: 2.6 for any postoperative infection (95% confidence interval [CI]: 1.7 - 3.9, $P < 0.001$); 2.2 for urinary tract infections (95% CI: 1.3 - 3.9, $P = 0.004$); 2.3 for pneumonia (95% CI: 0.96 - 5.3, $P = 0.062$); and 2.6 for surgical site infection requiring incision and drainage (95% CI: 1.3 - 5.3, $P = 0.007$). Secondary analyses demonstrated no dose-response relationship between the number of blood units transfused and any of the postoperative infections. Due to the low number of endocarditis (1 case, 0.031%), meningitis (1 case, 0.031%), central venous line infection (1 case, 0.031%), and sepsis (14 cases, 0.43%), we abstained from multivariable analysis. CONCLUSIONS: Conscious of the limitations of this retrospective study, our data suggests an increased risk of surgical site infection, and urinary tract infection, and overall postoperative infections, but not pneumonia, after exposure to allogeneic blood transfusion in patients undergoing lumbar spine surgery. These findings should be taken into account when considering blood transfusion and developing transfusion policies for patients undergoing lumbar spine procedures

MASSIVE TRANSFUSION:

Holcomb JB et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015 Feb 3;313(5):471-82.

IMPORTANCE: Severely injured patients experiencing hemorrhagic shock often require massive transfusion. Earlier transfusion with higher blood product ratios (plasma, platelets, and red blood cells), defined as damage control resuscitation, has been associated with improved outcomes; however, there have been no large multicenter clinical trials. OBJECTIVE: To determine the effectiveness and safety of transfusing patients with severe trauma and major bleeding using plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio. DESIGN, SETTING, AND PARTICIPANTS: Pragmatic, phase 3, multisite, randomized clinical trial of 680 severely injured patients who arrived at 1 of 12 level I trauma centers in North America directly from the scene and were predicted to require massive transfusion between August 2012 and December 2013.

INTERVENTIONS: Blood product ratios of 1:1:1 (338 patients) vs 1:1:2 (342 patients) during active resuscitation in addition to all local standard-of-care interventions (uncontrolled). MAIN OUTCOMES AND MEASURES: Primary outcomes were 24-hour and 30-day all-cause mortality. Prespecified ancillary outcomes included time to hemostasis, blood product volumes transfused, complications, incidence of surgical procedures, and functional status. RESULTS: No significant differences were detected in mortality at 24 hours (12.7% in 1:1:1 group vs 17.0% in 1:1:2 group; difference, -4.2% [95% CI, -9.6% to 1.1%]; $P = .12$) or at 30 days (22.4% vs 26.1%, respectively;

difference, -3.7% [95% CI, -10.2% to 2.7%]; P = .26). Exsanguination, which was the predominant cause of death within the first 24 hours, was significantly decreased in the 1:1:1 group (9.2% vs 14.6% in 1:1:2 group; difference, -5.4% [95% CI, -10.4% to -0.5%]; P = .03). More patients in the 1:1:1 group achieved hemostasis than in the 1:1:2 group (86% vs 78%, respectively; P = .006). Despite the 1:1:1 group receiving more plasma (median of 7 U vs 5 U, P)

CONCLUSIONS AND RELEVANCE: Among patients with severe trauma and major bleeding, early administration of plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio did not result in significant differences in mortality at 24 hours or at 30 days. However, more patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 hours. Even though there was an increased use of plasma and platelets transfused in the 1:1:1 group, no other safety differences were identified between the 2 groups

EVIDENCE THAT SUPPORTS THE PRACTICE OF PREADMISSION TESTING (PAT) FOR ANEMIA WITH PRE-SURGICAL TREATMENT OF ANEMIA OUTSIDE OF TRANSFUSION

Viola J1 , et al.. Preoperative Anemia Increases Postoperative Complications and Mortality Following Total Joint Arthroplasty. *J Arthroplasty*. 2015 Jan 10. pii: S0883-5403(15)00012-1. doi: 10.1016/j.arth.2014.12.026. [Epub ahead of print].

Single-institution, large case-controlled study examines the association between preoperative anemia and adverse outcomes following total joint arthroplasty (TJA). We collected data from our institutional database of patients who underwent primary and aseptic revision TJA. Only 2576 patients had anemia preoperatively, and 10,987 patients had hemoglobin within the normal range. Multivariate analysis was used to determine the effect of preoperative anemia on the incidence of medical complications, infection, LOS and mortality. Anemic patients had a higher rate of complications (odds ratio 2.11), namely cardiovascular 26.5% versus 11.8%, and genitourinary 3.9% versus 0.9%. Our study confirms that patients with preoperative anemia are likely to exhibit a higher incidence of postoperative complications following TJA. Preoperative optimization may be needed in an effort to reduce these complications.

Carson JL et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet*. 1996; 348: 1055-1060.

The hemoglobin concentration at which risk for death or serious morbidity occurs was investigated using a retrospective cohort of 1958 patients who underwent surgery and declined blood transfusion. The primary outcome variable was 30 day mortality. Cardiovascular disease was defined as a history of angina, myocardial infarction, congestive heart failure, or peripheral vascular disease. In patients with preoperative hemoglobin levels of 12g/dl or greater the mortality rate of 1.3%, whereas patients with preoperative hemoglobin levels of less than 6g/dl had a mortality rate of 33.3%. The authors concluded that the low preoperative hemoglobin substantially increases the risk of death and serious morbidity.

PRACTICE GUIDELINES PUBLISHED GREATER THAN 5 YEARS AGO

Nuttall GA, Brost BC, Connis RT, Gessner JS, Hill C, Harrison CR, Miller RD, Nickinovich DG, Nussmeier NA, Rosenberg AD, and Spence R. 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* 2004; 198-208.

1. Preoperative evaluation for risk of blood transfusion and need of adjuvant therapies includes a) review of patient's medical records, b) conducting family or patient interview, c) review of selected laboratory tests to include hemoglobin/hematocrit, and coagulation profiles if appropriate and available.
2. Preoperative preparation to include preoperative anemia assessment, discontinuation of anticoagulation therapy for sufficient time prior to surgery but weighing the risk of thrombosis to bleeding.
3. Erythropoietin may be used in certain populations (renal insufficiency, anemia of chronic disease)
4. Strong agreement that rbc's should be transfused when Hb < 6 g/dl and strongly agree rbc unnecessary > 10 g/dl.
5. Strong agreement that when autologous blood is required (Jehovah's Witness) that normovolemic hemodilution and intraoperative blood recovery (cell saver devices) useful.
6. Decision as to whether to transfuse greater than 6 g/dl and less than 10 g/dl of Hb should be based on ongoing indication of organ ischemia, rate and magnitude of ongoing hemorrhage, intravascular volume status of patient, and risk factors for inadequate oxygenation to include low cardiopulmonary reserve and high oxygen consumption.

7. Red blood cells should be transfused to maintain organ perfusion and crystalloids or colloids should be used to maintain intravascular volume.

PRACTICE GUIDELINES PUBLISHED IN LAST 5 YEARS

Carson JL, et al. Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB. *Ann Intern Med* 2012;157:49-58.

Authors made the following recommendations:

- 1: A restrictive strategy (7 to 8 g/dL) in stable patients (high-quality evidence).
- 2: A restrictive strategy in patients with preexisting cardiovascular disease, considering transfusion for patients with symptoms or a hemoglobin level of 8 g/dL or less (moderate-quality evidence).
- 3: Cannot recommend for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with the acute coronary syndrome (low-quality evidence).

Napolitano LM, et al. Clinical practice guideline: Red blood cell transfusion in adult trauma and critical care. *Crit Care Med* 2009; 37:3124 –3157

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

1. RBC transfusion is indicated for patients with evidence of hemorrhagic shock (Level 1).
2. RBC transfusion may be indicated for patients with evidence of acute hemorrhage and hemodynamic instability or inadequate oxygen delivery. (Level 1)
3. A “restrictive” strategy of RBC transfusion (transfuse when Hb \leq 7 g/dL) is as effective as a “liberal” transfusion strategy (transfusion when Hb \leq 10 g/dL) in critically ill patients with hemodynamically stable anemia, except possibly in patients with acute myocardial ischemia. (Level 1)

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. (Level 2)
5. In the absence of acute hemorrhage RBC, transfusion should be given as single units. (Level 2)
6. Consider transfusion if Hb \leq 7 g/dL in critically ill patients requiring mechanical ventilation (MV). There is no benefit of a “liberal” transfusion strategy (transfusion when Hb \leq 10 g/dL) in critically ill patients requiring MV. (Level 2)
7. Consider transfusion if Hb \leq 7 g/dL in resuscitated critically ill trauma patients. There is no benefit of a “liberal” transfusion strategy (transfusion when Hb \leq 10 g/dL) in resuscitated critically ill trauma patients. (Level 2)
8. Consider transfusion if Hb \leq 7 g/dL in critically ill patients with stable cardiac disease. There is no benefit of a “liberal” transfusion strategy (transfusion when Hb \leq 10 g/dL) in critically ill patients with stable cardiac disease. (Level 2)
9. RBC transfusion should not be considered as an absolute method to improve tissue oxygen consumption in critically ill patients. (Level 2)
10. RBC transfusion may be beneficial in patients with acute coronary syndromes (ACS) who are anemic (Hb \leq 8 g/dL) on hospital admission. (Level 3)

B. Recommendations Regarding RBC Transfusion in Sepsis

1. There are insufficient data to support Level 1 recommendations on this topic.
2. The transfusion needs for each septic patient must be assessed individually since optimal transfusion triggers in sepsis patients are not known and there is no clear evidence that blood transfusion increases tissue oxygenation. (Level 2)

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. (Level 2)
3. All efforts should be made to diagnose and report transfusion-related ALI (TRALI) to the local blood bank because it has emerged as a leading cause of transfusion-associated morbidity and mortality, despite underdiagnosis and underreporting. (Level 2)
4. RBC transfusion should not be considered as a method to facilitate weaning from MV. (Level 2)

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 \leq 10 g/dL) in patients with moderate-to-severe traumatic brain injury. (Level 2)
3. Decisions regarding blood transfusion in patients with subarachnoid hemorrhage (SAH) must be assessed individually since optimal transfusion triggers are not known and there is no clear evidence that blood transfusion is associated with improved outcome. (Level 3)

E. Recommendations Regarding RBC Transfusion Risks

1. There are insufficient data to support Level 1 Recommendations on this topic.
2. RBC transfusion is associated with increased nosocomial infection (wound infection, pneumonia, sepsis) rates independent of other factors. (Level 2)
3. RBC transfusion is an independent risk factor for MOF and SIRS. (Level 2)
4. 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. (Level 2)

5. RBC transfusions are independently associated with longer ICU and hospital length of stay, increased complications, and increased mortality. (Level 2)

6. There is a relationship between transfusion and ALI and ARDS. (Level 2)

F. Recommendations Regarding Alternatives to RBC Transfusion

1. There are insufficient data to support Level 1 recommendations on this topic.

2. Recombinant human erythropoietin (rHuEpo) administration improves reticulocytosis and hematocrit and may decrease overall transfusion requirements. (Level 2)

3. Hemoglobin-based oxygen carriers (HBOCs) are undergoing investigation for use in critically ill and injured patients but are not yet approved for use in the United States. (Level 2)

G. Recommendations Regarding Strategies to Reduce RBC Transfusion

1. There are insufficient data to support Level 1 recommendations on this topic.

2. 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. (Level 2)

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

4. Intraoperative and postoperative blood salvage and alternative methods for decreasing transfusion may lead to a significant reduction in allogeneic blood usage. (Level 2)

5. Reduction in diagnostic laboratory testing is associated with a reduction in phlebotomy volumes and a reduction in blood transfusion. (Level 2)

Ferraris VA et al. 2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines. *Ann Thorac Surg* 2011; 91: 944-82.

1. Three important preoperative risk factors are linked to bleeding and blood transfusion: a) advanced age (age \geq 70 years); b) low RBC volume due to preoperative anemia or small body habitus or both, and c) urgent or complex operations usually associate with prolonged cardiopulmonary bypass time and non CABG procedures.

2. Preoperative interventions:

- a. P2Y12 platelet receptor inhibitor drugs should be discontinued prior to operative coronary artery vascularization, if possible Class I(B) evidence
- b. E-aminocaproic acid (Amicar) and tranexamic acid (Cyklokapron) reduce total blood loss and decrease number of patients who require blood transfusion Class I(A) evidence
- c. Antithrombin III concentrates are indicated to reduce plasma transfusions in patients with ATIII mediated heparin resistance immediate before cardiopulmonary bypass Class I(A) evidence.

3. Blood Conservation:

- a. The use of minicircuits (reduced priming volume in the minimized CPB circuit) reduces hemodilution and are indicated for blood conservation Class I(A) evidence
- b. The use of modified ultrafiltration is indicated for blood conservation and reducing postoperative blood loss in adult and pediatric cardiac operations using CPB Class 1(A) evidence

4. Transfusion Triggers

- a. With hemoglobin levels below 6 g/dl, rbc transfusion is reasonable since this can be lifesaving. Class Iia evidence
- b. Transfusion is reasonable in most postoperative patients whose hemoglobin is less than 7 g/dl but no high level evidence supports this recommendation (Level of evidence C)
- c. During CPB with moderate hypothermia, transfusion of rbc for Hb \leq 6g/dl is reasonable except for those patients at risk for decreased cerebral oxygen delivery (history of CVA, cerebral vascular illness, diabetes, carotid stenosis) where higher Hb levels may be justified (Level of evidence C).

5. Blood Salvage Interventions

a. Routine use of red cell salvage using centrifugation is helpful in cardiac operations using CBP Class I(A) evidence

6. Management of blood resources

b. A multidisciplinary approach involving multiple stakeholders, institutional support, enforceable transfusion, algorithms, supplemented with point of care testing and all of the already mentioned efficacious blood conservation interventions limits blood transfusion and provides optimal blood conservation for cardiac operations Class I(A) evidence.

Malloy PC et al. Consensus Guidelines for Periprocedural Management of Coagulation Status and Hemostasis Risk in Percutaneous Image-Guided Interventions. *J Vasc Interv Radiol.* 2009; 20: S240-S249.

Recommendations from the Society of Interventional Radiology Standards of Practice Committee. They note that recommendations from the open surgical experience may not be applicable to interventional procedures due to the lack of direct visualization and the inability of access to prompt vascular control in interventional cases.

Articles on Storage Lesion and Immune Modulation

Sparrow RL. Red blood cell storage and transfusion-related immunomodulation. *Blood Transfus.* 2010; 8 Suppl 3: s26-s30.

Many of the physical changes that occur to RBCs during storage appear to be similar to those that occur to diseased RBCs (malaria, sickle cell disease, thalassemia), in which disturbances in vascular function are key morbidities. These changes include altered membrane surface receptors and cytoskeletal structures that maintain shape, deformability, and aggregability.

Transfusion-related immunomodulation (TRIM) has emerged as a concept to potentially explain the numerous clinical observations that suggest that RBC transfusion is associated with increased proinflammatory or immunosuppressive effects that may increase morbidity in at least some patients. The predominant mechanism for TRIM likely depends on an interplay of genetic predisposition and illness in the patient. Platelets and vascular endothelial cells also potentially contribute to “response” as both cell types are highly responsive to inflammatory signals. When activated, these cells release significant amounts of bioactive mediators. Stored RBCs

are also exposed to the cell debris that accumulates in the suspension fluid during storage. Although, the widespread practice of prestorage leukocyte reduction, it does not eliminate the biochemical and morphological changes occurring as a result of storage and aging.

The "two insult" model of post-transfusion injury proposes that the first insult (the patients underlying inflammatory condition) primes the immune cells and endothelium and frank inflammation is triggered by the second inflammatory insult (the transfusion).

Blumberg N, Heal JM. Effects of transfusion on immune function. Cancer recurrence and infection. *Archives of Pathology and Laboratory Medicine*. 1994, 118(4): 371-379.

The paradigm related to the immunologic consequences of allogeneic blood transfusions has been extended from humoral allosensitization to the effects of transfusion on cellular immune function. This includes downregulation of effector cells, activation of latent viral infection and the prolonged circulation of donor immunocompetent cells, as seen in graft-vs-host disease. There are now extensive data showing conclusively that allogeneic transfusions are associated with increases in recurrence rates (80% in colorectal cancer) and postoperative bacterial infections (as much as 200% to 1000% in some studies). Whether these associations are causal or not remains in doubt. Based on animal and clinical studies, we believe these associations are likely, in part, due to immune dysregulation caused by transfusion, perhaps augmented by the effects of hemorrhage, anesthesia, and surgical stress. The most likely mechanism underlying transfusion-induced immunosuppression is anergy due to presentation of large amounts of antigen through the intravenous route. This favors presentation of antigen by "nonprofessional" antigen-presenting cells, a situation that usually leads to anergy or tolerance rather than immune activation. Two additional hypothetical mechanisms proposed for immune dysregulation after allogeneic transfusion are (1) prolonged circulation of donor cells causing subclinical graft-vs host disease, and (2) reactivation of immunosuppressive viruses latently present in recipient white blood cells. Results of some initial interventional studies, employing autologous transfusions or removing white blood cells from allogeneic donor blood suggest that relatively simple, cost-effective strategies to ameliorate these complications may be at hand.

Vamvakas EC¹, Blajchman MA. Transfusion-related immunomodulation (TRIM): an update. *Blood Rev*. 2007 Nov; 21(6): 327-48.

Allogeneic blood transfusion (ABT)-related immunomodulation (TRIM) encompasses the laboratory immune aberrations that occur after ABT and their established or purported clinical effects. TRIM is a real biologic phenomenon resulting in at least one established beneficial clinical effect in humans, but the existence of deleterious clinical TRIM effects has not yet

been confirmed. Initially, TRIM encompassed effects attributable to ABT by immunomodulatory mechanisms (e.g., cancer recurrence, postoperative infection, or virus activation). More recently, TRIM has also included effects attributable to ABT by pro-inflammatory mechanisms (e.g., multiple-organ failure or mortality). TRIM effects may be mediated by: (1) allogeneic mononuclear cells; (2) white-blood-cell (WBC)-derived soluble mediators; and/or (3) soluble HLA peptides circulating in allogeneic plasma. This review categorizes the available randomized controlled trials based on the inference(s) that they permit about possible mediator(s) of TRIM, and examines the strength of the evidence available for relying on WBC reduction or autologous transfusion to prevent TRIM effects.

Blajchman MA. Immunomodulation and blood transfusion. *Am J Ther.* 2002 Sep-Oct;9(5):389-95.

Over the past three decades, evidence from a variety of sources has suggested that allogeneic blood transfusions can induce clinically significant immunosuppression in recipients. This clinical syndrome is referred to in the transfusion medicine literature as transfusion-associated immunomodulation (TRIM) and has been linked to an improved clinical outcome in the setting of renal transplantation. Possible deleterious TRIM-associated effects include increased prevalence of cancer recurrence and postoperative bacterial infections. The recognition that TRIM can increase morbidity and mortality in allogeneically transfused individuals has become a major concern for those involved in transfusion medicine. Whether TRIM predisposes recipients to increased risk for cancer recurrence and/or bacterial infections is still not proven, however. In contrast to the available clinical data, studies in experimental animal models suggest that TRIM is an immunologically mediated biologic effect associated with the infusion of allogeneic leukocytes, which can be ameliorated by prestorage leukoreduction. Although considerable data have been accumulated in an attempt to unravel the clinically adverse effects of TRIM, the precise mechanism of TRIM has yet to be elucidated. Further studies, both basic and applied, to establish the clinically relevant manifestations of TRIM as well as the mechanism(s) are urgently required.

ARTICLES ON IATROGENIC BLOOD LOSS IN HOSPITALS

Salisbury AC et al. Diagnostic blood loss from phlebotomy and hospital-acquired anemia during acute myocardial infarction. *Arch Intern Med.* 2011; 171: 1646-1653.

Blood loss due to phlebotomy can be another important cause of anemia both in general care areas and ICU. The normal daily production of RBCs in a healthy adult is 0.25 ml/kg, about a half a liter per week. Diagnostic phlebotomy can result in a mean daily loss of 70 ml per day in the ICU patient which may outpace the ability to naturally replenish in the critically ill patient. This study of 17676 cardiac patients from 57 hospitals, researchers found that for every 50 mL of blood collected, the risk of moderate to severe hospital-acquired anemia increased 18%. Suggestions on how to mitigate this loss include use of pediatric sample tubes when possible and non-invasive hemoglobin monitoring for anemia.

Vincent et al. Anemia and Blood Transfusion in Critically Ill Patients. *JAMA*. 2002; 299: 1499-1507.

Prospective observational study conducted in November 1999 with a blood sampling study and a blood transfusion study. The blood sampling study included 1136 patients from 145 western European ICUs. Patients were followed for 28 days or until discharge, transfer or death. The mean volume per blood draw was 10.3 mL (SD 6.6 mL) with after 24 hour total 41.1 mL (SD 39.7 mL). For matched patients in the propensity analysis, the 28 day mortality was 22.7% among patients with transfusions and 17.1% among those without (p=0.02); Kaplan-Meier log-rank test confirmed the difference.

Dang D et al. *J Obstet Gynaecol Res*. 2015 Feb 6. doi: 10.1111/jog.12657. [Epub ahead of print] Umbilical cord milking reduces need for red cell transfusions and improves neonatal adaptation in preterm infants: Meta-analysis.

AIM: To assess effects of umbilical cord milking (UCM) on early blood pressure stabilization, hemoglobin (Hb), as well as incidence of transfusion and complications in preterm infants. METHODS: This meta-analysis was conducted by searching the Pubmed, EMBASE and Cochrane Library (until July 2014) databases. Any clinical trials, including randomized control trials, comparing UCM to immediate cord clamping (ICC) were analyzed. RESULTS: Six studies were included in this meta-analysis. In total, 292 preterm infants were treated with UCM, while 295 received ICC. Compared to ICC, UCM increased initial Hb significantly by 1.84 g/dL (weighted mean difference; 95%CI: 0.91-2.76;)

Schiergens TS. Impact of perioperative allogeneic red blood cell transfusion on recurrence and overall survival after resection of colorectal liver metastases. *Dis Colon Rectum*. 2015 Jan;58(1):74-82. Impact of perioperative allogeneic red blood cell transfusion on recurrence and overall survival after resection of colorectal liver metastases.

BACKGROUND: Perioperative allogeneic red blood cell transfusion has been conclusively shown to be associated with adverse oncologic outcomes after resection of nonmetastatic colorectal adenocarcinoma. **OBJECTIVE:** The aim of the study was to identify risk factors for a perioperative transfusion and to assess the effects of transfusion on survival after curative-intended resection of hepatic metastases in patients featuring stage IV colorectal cancer.

DESIGN: This was an observational study with a retrospective analysis of a prospective data collection. **SETTING:** The study was conducted at a tertiary care center. **PATIENTS:** A total of 292 patients undergoing curative-intended liver resection for colorectal liver metastases were included in the study. **MAIN OUTCOME MEASURES:** Univariate and multivariate analyses were performed identifying factors influencing transfusion, recurrence-free survival, and overall survival. **RESULTS:** A total of 106 patients (36%) received allogeneic red blood cells. Female sex ($p = 0.00004$), preoperative anemia ($p = 0.001$), major intraoperative blood loss ($p < 0.00001$), and major postoperative complications ($p = 0.02$) were independently associated with the necessity of transfusion. Median recurrence-free and overall survival were 58 months. Allogeneic red blood cell transfusion was significantly associated with reduced recurrence-free survival (32 vs 72 months; $p = 0.008$). It was reduced further by administration of >2 units (27 months; $p = 0.02$). Overall survival was not significantly influenced by transfusion (48 vs 63 months; $p = 0.08$). When multivariately adjusted for major intraoperative blood loss and factors univariately associated, namely comorbidities, tumor load, and positive resection margins, transfusion was an independent predictor for reduced recurrence-free survival ($p = 0.03$).

LIMITATIONS: These include the retrospective and observational design, as well as the impossibility to prove causality of the association between transfusion and poor outcome. **CONCLUSIONS:** In patients undergoing liver resection for colorectal liver metastases, perioperative transfusion is independently associated with earlier disease recurrence. This emphasizes appropriate blood management measures, including the conservative correction of preoperative anemia, the use of low transfusion triggers, and the minimization of intraoperative blood loss

CONTINUOUS HEMOGLOBIN MONITORING:

Frasca D et al. Continuous monitoring of haemoglobin concentration after in-vivo adjustment in patients undergoing surgery with blood loss. *Anaesthesia*. 2015 Feb 13. doi: 10.1111/anae.13028. [Epub ahead of print]

Non-invasive monitoring of haemoglobin concentration provides real-time measurement of haemoglobin concentration (SpHb) using multi-wavelength pulse co-oximetry. We hypothesised that in-vivo adjustment using the mean of three haemoglobinometer (HemoCue®) measurements from an arterial blood sample at the first SpHb measurement (HCueART) would increase the accuracy of the monitor. The study included 41 adults for a total of 173 measurements of haemoglobin concentration. In-vivo adjusted SpHb was automatically calculated by the following formula: in-vivo adjusted SpHb = unadjusted SpHb - (SpHb - HCueART). The accuracy of in-vivo adjusted SpHb was compared with SpHb retrospectively adjusted using the same formula, except for haemoglobin level which was assessed at the central laboratory and then compared with all other available invasive methods of haemoglobin measurement (co-oximetry, HbSAT; arterial HemoCue, HCueART; capillary HemoCue, HCueCAP). Compared with laboratory measurement of haemoglobin concentration, bias (precision) for unadjusted SpHb, in-vivo adjusted SpHb, retrospectively adjusted SpHb, HbSAT, HCueART and HCueCAP were -0.4 (1.4), -0.3 (1.1), -0.3 (1.1), -0.6 (0.7), 0.0 (0.4) and -0.5 (1.2) g.dl⁻¹ , respectively. In-vivo adjustment of SpHb values using the mean of three arterial HemoCue measurements improved the accuracy of the device similar to those observed after a retrospective adjustment using central laboratory haemoglobin level.

OTHER GREAT RESOURCES:

Hicks LK et al. Five hematologic tests and treatments to question. Abstract Choosing Wisely. Blood. 2014 Dec 4;124(24):3524-8. doi: 10.1182/blood-2014-09-599399.

Choosing Wisely(®) is a medical stewardship initiative led by the American Board of Internal Medicine Foundation in collaboration with professional medical societies in the United States. The American Society of Hematology (ASH) released its first Choosing Wisely(®) list in 2013. Using the same evidencebased methodology as in 2013, ASH has identified 5 additional tests and treatments that should be questioned by clinicians and patients under specific, indicated circumstances. The ASH 2014 Choosing Wisely(®) recommendations include: **(1) do not anticoagulate for more than 3 months in patients experiencing a first venous thromboembolic event in the setting of major, transient risk factors for venous thromboembolism; (2) do not routinely transfuse for chronic anemia or uncomplicated pain crises in patients with sickle cell disease; (3) do not perform baseline or surveillance computed tomography scans in patients with asymptomatic, early-stage chronic lymphocytic leukemia; (4) do not test or treat for heparin-induced thrombocytopenia if the clinical pretest probability of heparin-induced thrombocytopenia is low; and (5) do not treat patients**

with immune thrombocytopenia unless they are bleeding or have very low platelet counts.

Weiskopf RB, Viele MK, Feiner J, Kelley S, Lieberman J, Noorani M, Leung JM, Fisher DM, Murray WR, Toy P, Moore MA: Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA* 1998, 279:217-221.

This is an interventional study done to determine whether acute, severe, isovolemic reduction in hemoglobin to 5g/dl in healthy, resting individuals would result in inadequate cardiac compensation mechanism and, therefore, compromise oxygen delivery to tissues. No evidence of inadequate oxygenation as assumed by lack of change in oxygen consumption and plasma lactate concentrations. These observations were noted in 11 preoperative volunteer patients and 21 non-surgical volunteer patients with hemoglobins of 5 g/dl or less.

Viele MK, Weiskopf RB: What can we learn about the need for transfusion from patients who refuse blood? The experience with Jehovah's Witnesses. *Transfusion* 1994, 34:396-401.

A transfusion threshold of 7 g per dL (70 g/L) of hemoglobin has been proposed for patients, although scant human data are available to support this recommendation. The medical community's experience with Jehovah's Witnesses was examined, in order to assess the lowest tolerable hemoglobin concentration and the lower transfusion threshold of 7 g per dL (70 g/L) of hemoglobin. A MEDLINE search was conducted to capture medical and surgical reports involving Jehovah's Witnesses from 1970 through early 1993. Sixty-one reports of untransfused Jehovah's Witnesses with hemoglobin concentrations \leq 8 g per dL (80 g/L) or hematocrits \leq 24 percent (0.24) were identified. Of 50 reported deaths, 23, as stated in the original reports, were primarily due to anemia. Except for three patients who died after cardiac surgery, all patients whose deaths were attributed to anemia died with hemoglobin concentrations \leq 5 g per dL (50 g/L). Twenty-five survivors were reported with hemoglobin \leq 5 g per dL (50 g/L). These data have significant limitations but suggest that survival, without transfusion, is possible at low hemoglobin concentrations, while mortality with an unknown incidence is encountered at hemoglobin concentrations below 5 g per dL (50 g/L).

Samir M Fakhry¹ and Paola Fata How low is too low? Cardiac risks with anemia. *Critical Care* 2004, 8(Suppl 2):S11-S14 (DOI 10.1186/cc2845)

Despite the increasing availability of data supporting more restrictive transfusion practices, the risks and benefits of transfusing critically ill patients continue to evoke controversy. Past retrospective and observational

studies suggested that liberal transfusion strategies were more beneficial in patients whose hematocrit levels fell below 30%. An expanding body of literature suggests that an arbitrary trigger for transfusion (the '10/30 rule') is ill advised. A recent randomized controlled trial provided compelling evidence that similar, and in some cases better, outcomes result if a restrictive transfusion strategy is maintained. The impact of this accumulating evidence on clinical practice is evident in large reports, which show that the average transfusion trigger in critically ill patients was a hemoglobin level in the range 8–8.5 g/dl. Based on the available evidence, transfusion in the critically ill patient without active ischemic heart disease should generally be withheld until the hemoglobin level falls to 7 g/dl. Transfusions should be administered as clinically indicated for patients with acute, ongoing blood loss and those who have objective signs and symptoms of anemia despite maintenance of euvolemia. The hemoglobin level at which serious morbidity or mortality occurs in critically ill patients with active ischemic heart disease is a subject of continued debate but it is likely that a set transfusion trigger will not provide an optimal risk–benefit profile in this population.

Murphy GJ et al. *Liberal or Restrictive Transfusion after Cardiac Surgery*. NEJM. 2015; 372: 997-1008.

Whether a restrictive threshold for hemoglobin level in red-cell transfusions, as compared with a liberal threshold, reduces postoperative morbidity and health care costs after cardiac surgery is uncertain.

METHODS Multicenter, parallel-group trial patient older than 16 years who were undergoing nonemergency cardiac surgery were recruited from 17 centers in the United Kingdom. Patients with a postoperative hemoglobin level of less than 9 g per deciliter were randomly assigned to a restrictive transfusion threshold (hemoglobin level <7.5 g per deciliter) or a liberal transfusion threshold (hemoglobin level <9 g per deciliter). The primary outcome was a serious infection (sepsis or wound infection) or an ischemic event (permanent stroke [confirmation on brain imaging and deficit in motor, sensory, or coordination functions], myocardial infarction, infarction of the gut, or acute kidney injury) within 3 months after randomization. Health care costs, excluding the index surgery, were estimated from the day of surgery to 3 months after surgery.

RESULTS :2007 patients underwent randomization; 4 participants withdrew, leaving 1000 in the restrictive-threshold group and 1003 in the liberal-threshold group. Transfusion rates after randomization were 53.4% and 92.2% in the two groups, respectively. The primary outcome occurred in 35.1% of the patients in the restrictive-threshold group and 33.0% of the patients in the liberal-threshold group (odds ratio, 1.11; 95% confidence interval [CI], 0.91 to 1.34; P=0.30); there was no indication of heterogeneity according to subgroup. There were more deaths in the restrictive-threshold group than in the liberal-threshold group (4.2% vs. 2.6%; hazard ratio, 1.64;

95% CI, 1.00 to 2.67; P=0.045). Serious postoperative complications, excluding primary-outcome events, occurred in 35.7% of participants in the restrictive-threshold group and 34.2% of participants in the liberal-threshold group. Total costs did not differ significantly between the groups. **CONCLUSIONS** A restrictive transfusion threshold after cardiac surgery was not superior to a liberal threshold with respect to morbidity or health care costs.

Other observations about this study:

1. The study is British, and it is very well established that the use of blood in the UK and the EU is significantly lower than US usage at baseline.
2. The "liberal" group still has a trigger Hb of 9g/dl, lower than the more traditional 10 g/dl.
3. The number of patients whose treatment was defined as "severe non-adherence" to the protocols in both groups was high (9.7% in Restrictive group and 6.2% in Liberal group) and even higher in the "non-adherence" groups (R was 30% and L was 45.2%)---so total percentages of patients in both study groups where the protocols of the study were not maintained--(patients either over or undertransfused by physicians deciding not to follow the study protocols)--was 39.1% for the Restrictive group and 51.4% for the Liberal group. These patients were NOT excluded from the data. The conclusion has a nearly non-significant P-value at 0.045.
4. Even with the dubious inclusion of these "non-adherent" patients, the conclusions of this study are not really negative to our push to have careful consideration of each transfusion event decision.
5. The use of other types of blood products did not vary between the groups of patients

Dzik W and Rao A. Why do physicians request fresh frozen plasma? *Transfusion*. 2004; 44: 1393.

The authors note that FFP transfusion is the most common intervention before image-guided procedures in the US, the most common reason given is elevated INR *, amounting to about 3 million units transfused a year.

Segel JB and Dzik WH. Transfusion medicine/hemostasis clinical trials network. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence based review. *Transfusion*. 2005; 45: 1413-1425.

Authors report an analysis of 25 studies evaluating the ability of abnormal coagulation parameters to predict bleeding associated with

invasive bedside or image-guided procedures. Of the 25 studies reviewed, one was a clinical trial (transjugular liver biopsy to percutaneous biopsy with tract plugging). The remaining were case series which included patients undergoing bronchoscopy with biopsy, central vein cannulation, femoral angiography, liver biopsy, kidney biopsy, paracentesis, thoracentesis, and lumbar puncture. Overall the authors concluded that elevated coagulation parameters provide little or no predictive value for bleeding complications from image-guided interventions. They assert that in the absence of randomized controlled studies, mild to moderate elevation of coagulation times, should neither be assumed to represent an increased risk for periprocedural bleeding nor to be used as an indication for FFP or clotting factor concentrates.

Kelley TC et al. Use of tranexamic acid results in decreased blood loss and decreased transfusions in patients undergoing staged bilateral total knee arthroplasty. *Transfusion*. 2014. 54(1): 26-30.

TA is an antifibrinolytic that reduces blood loss and transfusion rates in TJA. The authors compared 51 patients undergoing bilateral TKA who received TXA with 70 who did not (control group). No significant differences between demographics or preoperative Hb were found. TA subjects had a significantly lower ($p < 0.001$) mean blood loss (373.8 +/- 264.6 ml versus 871.6 +/- 457.7 ml), significantly higher ($p < 0.005$) Hb levels on Post op day 1 and 2, and significantly lower ($p < 0.001$) mean number of transfused allogenic units (0.60 +/- 0.84 units vs. 1.53 +/- 1.30 units).

Karaaslan F et al. Reducing blood loss in simultaneous bilateral total knee arthroplasty: Combined intravenous-intra-articular tranexamic acid administration. A prospective randomized controlled trial. *Knee*. 2014 Dec 13. pii: S0968-0160(14)00285-3. doi: 10.1016/j.knee.2014.12.002. [Epub ahead of print]

Reducing blood loss in simultaneous bilateral total knee arthroplasty: Combined intravenous-intra-articular tranexamic acid administration. A prospective randomized controlled trial. **BACKGROUND:** We asked whether tranexamic acid (TXA) administration could reduce blood loss and blood transfusion requirements after simultaneous bilateral total knee arthroplasty (TKA). This study examined the role of a novel method of TXA administration in TKA. **METHODS:** TXA was administered as a bolus dose of 15mg/kg 10min before the inflation of the tourniquet on the first side. This was followed by intraarticular administration of 3grams at 10min before the deflation of the tourniquet. IV infusion of 10mg/kg/h was continued for 3h following completion on the second side. We measured volume of drained blood 48h postoperatively, decrease in hemoglobin levels 12h postoperatively, amount of blood transfused (BT), and number of patients requiring allogenic BT. **RESULTS:** Median postoperative volume of drained blood was lower in the group receiving TXA (500.00mL) than in control subjects (900.00mL)

Lacroix, J et al. *Age of Transfused Blood in Critically Ill Adults*. NEJM. 2015; Online <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1500704>

Fresh red cells may improve outcomes in critically ill patients by enhancing oxygen delivery while minimizing the risks of toxic effects from cellular changes and the accumulation of bioactive materials in blood components during prolonged storage.

Methods Multicenter, randomized, blinded trial, we assigned critically ill adults to receive either red cells that had been stored for less than 8 days or standard-issue red cells (the oldest compatible units available in the blood bank). The primary outcome measure was 90-day mortality. **Results** Between March 2009 and May 2014, at 64 centers in Canada and Europe, 1211 patients assigned to receive fresh red cells (fresh-blood group) and 1219 patients were assigned to receive standard-issue red cells (standard-blood group). Red cells were stored a mean (\pm SD) of 6.1 ± 4.9 days in the fresh-blood group as compared with 22.0 ± 8.4 days in the standard-blood group ($P < 0.001$). At 90 days, 448 patients (37.0%) in the fresh-blood group and 430 patients (35.3%) in the standard-blood group had died (absolute risk difference, 1.7 percentage points; 95% confidence interval [CI], -2.1 to 5.5). In the survival analysis, the hazard ratio for death in the fresh-blood group, as compared with the standard-blood group, was 1.1 (95% CI, 0.9 to 1.2; $P = 0.38$). There were no significant between-group differences in any of the secondary outcomes (major illnesses; duration of respiratory, hemodynamic, or renal support; length of stay in the hospital; and transfusion reactions) or in the subgroup analyses. **Conclusions** Transfusion of fresh red cells, as compared with standard-issue red cells, did not decrease the 90-day mortality among critically ill adults.

Anker SD, et al. *Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency* NEJM, 2009; 361: 2436-48.

Iron deficiency may impair aerobic performance. This study aimed to determine whether treatment with intravenous iron (ferric carboxymaltose) would improve symptoms in patients who had heart failure, reduced left ventricular ejection fraction, and iron deficiency, either with or without anemia.

METHODS

Enrolled 459 patients with chronic heart failure of New York Heart Association (NYHA) functional class II or III, a left ventricular ejection fraction of 40% or less (for patients with NYHA class II) or 45% or less (for NYHA class III), iron deficiency (ferritin level < 100 μ g per liter or between 100 and 299 μ g per liter, if the transferrin saturation was $< 20\%$), and a hemoglobin level of 95 to 135 g per liter. Patients were randomly assigned, in a 2:1 ratio, to receive 200 mg of intravenous iron (ferric carboxymaltose) or saline (placebo). The primary end points were the self-reported Patient

Global Assessment and NYHA functional class, both at week 24. Secondary end points included the distance walked in 6 minutes and the health-related quality of life.

RESULTS Among the patients receiving ferric carboxymaltose, 50% reported being much or moderately improved, as compared with 28% of patients receiving placebo, according to the Patient Global Assessment (odds ratio for improvement, 2.51; 95% confidence interval [CI], 1.75 to 3.61). Among the patients assigned to ferric carboxymaltose, 47% had an NYHA functional class I or II at week 24, as compared with 30% of patients assigned to placebo (odds ratio for improvement by one class, 2.40; 95% CI, 1.55 to 3.71). Results were similar in patients with anemia and those without anemia. Significant improvements were seen with ferric carboxymaltose in the distance on the 6-minute walk test and quality-of-life assessments. The rates of death, adverse events, and serious adverse events were similar in the two study groups.

CONCLUSIONS Treatment with intravenous ferric carboxymaltose in patients with chronic heart failure and iron deficiency, with or without anemia, improves symptoms, functional capacity, and quality of life; the side-effect profile is acceptable.

Slichter SJ. Evidence Based Platelet Transfusion Guidelines. *Hematology*. 2007; 1: 172-178.

Slichter SJ. New Thoughts on the Correct Dosing of Prophylactic Platelet Transfusions to Prevent Bleeding. *Curr Opin Hematol* 2011; 18: 427-435.

Estcourt LJ et al. Platelet transfusions in haematology patients: are we using them appropriately? *Vox Sanguinis*. 2012;. 1-10.

Sparrow RL. Red blood cell storage and transfusion-related immunomodulation. *Blood Transfus*. 2010; 8 Suppl 3: s26-s30.