Rethinking Blood Transfusions: Risks, Benefits and Cost Considerations

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Introduction

Blood transfusion has been part of medical practice for hundreds of years, first pioneered in 1628.[1] Blood has been used in various clinical settings with the intended benefit of increasing oxygen delivery capacity and increasing intra-vascular blood volume. During World War II, blood donation became a national priority as American soldiers were transfused with blood products in resuscitation efforts in the field after trauma. However, a few decades later, with the new knowledge of transmission of infectious diseases, there was greater caution with blood transfusion. In the 1970's and 1980's, the emergence of human immunodeficiency viruses (HIV) and viral hepatitis led to greater public awareness about the risks of receiving a blood transfusion. Even more recently, blood transfusion has come to be viewed as an organ transplant equivalent and multiple clinical studies have indicated that greater caution and care with transfusion should be taken. While blood transfusion remains a key intervention in medical practice, its risks and benefits must be weighed carefully by the provider and patient.

The following are six clinical vignettes that highlight key concepts that are important in medical decision making regarding blood transfusions.

Blood is Safer, But Still Has Risks

Tom Jones (all patient names used in this report are fictitious) is a 55-year-old man admitted for melena and fatigue. His vital signs are stable and he reports no cardiac or pulmonary symptoms. On endoscopy, he has a gastric ulcer, which is treated appropriately and his melena ceases. On admission, the patient is found to have a hemoglobin of 8.0 g/dL and he is transfused with 1 unit of packed red blood cells. After discharge, his internist is notified by the blood bank that Mr. Jones was transfused with blood contaminated with hepatitis C that had not been detected on routine screening. The recipient was previously hepatitis negative. Whose responsibility is it to contact the patient and notify him of the contaminated transfusion? Was transfusion even indicated?

The incidence of hepatitis B, hepatitis C, and HIV have decreased in the pool of donated blood with improved screening and testing.[2] The current risk of transmission of hepatitis B infections through blood transfusion is 1 in 200,000 to 500,000; hepatitis C is 1 in 1,390,000; and HIV is 1 in 2,000,000.[3] Patients must be counseled about the infectious risks of blood prior to transfusion. If contaminated blood is transfused, then it is the responsibility of the ordering provider and the blood bank to notify the patient of this complication.

Potential non-infectious risks exist as well for the recipient of blood donation. Immunomodulation (transient adverse changes in the immune response) is a potential complication from blood transfusion.[4] The hypothesized mechanism is that transfusion of allogeneic blood may upregulate humoral immunity, down-regulate cellular immunity, and induce a proinflammatory state. This is an area of medicine under investigation, but it is

important to recognize its potential clinical effect. The increased incidence of post-operative infection after blood transfusion and possible effect on increased tumor progression in cancer patients may be due to the immunomodulatory effects of allogeneic blood transfusion.[5]

Comment. The transfusion of red blood cells was likely not indicated for Mr. Jones as he had no significant symptoms. Fatigue is not considered a serious symptom that requires transfusion for treatment. Evaluation of anemia likely would have shown iron deficiency and appropriate treatment with oral or parenteral iron would have improved the patient's symptoms without blood transfusion. In this case of possible contamination of viral hepatitis in the transfused blood, it would be the responsibility of the attending physician and the blood bank to notify the patient. It is not within the scope of this article to review appropriate transfusion thresholds for various clinical conditions. Although the topic is highly nuanced, there are multiple studies that indicate most patients can reach a hemoglobin of 7 to 8 g/dL without adverse effects.[6-8]

Inappropriate Transfusion May Lead to Adverse Outcomes

Maria Garcia is a 39-year-old woman admitted to the ICU with severe sepsis secondary to bacterial pneumonia. She is treated with appropriate antibiotics and supportive care. On admission, her hemoglobin is 11.0 g/dL, but after multiple lab draws, blood loss with central venous catheter placement, and arterial catheter placement, her hemoglobin drifts down to 7.5 g/dL by day 5 of hospitalization. At this time, she is improving from the pneumonia, sepsis is resolved, and she likely will be transferred to the floor soon. The physician caring for her is considering a blood transfusion. What potential adverse outcomes should the physician anticipate?

Blood transfusion can have potential negative clinical outcomes in a variety of clinical settings. These include increased mortality, risk for infection, and transfusion-related complications. Hébert et al.[6] published the seminal study, Transfusion Requirements in Critical Care trial (TRICC) in 1999, which called into question long-standing transfusion practices. In critically ill patients, there was no statistically significant difference in mortality between patients in the "liberal group" transfused at a trigger hemoglobin of less than 10 g/dL versus patients in the "restrictive group" transfused at a trigger of less than 7 g/dL. The liberally transfused group had significantly higher in-hospital mortality (28.1% versus 22.2%). This landmark study reframed the standard transfusion trigger to 7 g/dL for most critically ill patients, which may be lower than what many physicians used in practice.

In a large outcomes study of 1,915 patients, Engoren et al.[7] showed that in patients who underwent first time isolated coronary artery bypass surgery, mortality was higher for those who received blood transfusion. After adjustment for co-morbidities, transfusion was associated with a 70% increase in mortality (risk ratio = 1.7, CI = 1.4-2.0, $p = 0.001$). A prospective study of 15,534 patients admitted to a Level I trauma center showed that blood transfusion was a strong independent predictor of mortality ($p < 0.001$), ICU admission ($p < 0.001$), ICU length of stay (LOS; $p < 0.001$) and hospital LOS ($p < 0.001$) after controlling for severity of shock based on lactate, base deficit, shock index, and admission anemia.[9]

In a meta-analysis of 20 peer-reviewed articles, allogeneic blood transfusion had an

increased risk of post-operative bacterial infection.[10] The common odds ratio for the incidence of post-operative bacterial infection after transfusion was 3.45 (range 1.43-15.15) with 17 of 20 articles demonstrating p values less than or equal to 0.05. The odds ratio was greater in a sub-analysis of trauma patients at 5.263 (range 5.03-5.43, p = 0.005-0.0001).

Patients should be informed about the risks of non-infectious related complications as part of the consent process. Transfusion Related Acute Lung Injury (TRALI) and hemolytic transfusion reactions are major contributors to transfusion related complications.[11] TRALI is a process that mirrors Acute Respiratory Distress Syndrome, occurring after allogeneic blood transfusion. TRALI has gained recognition as a clinical phenomenon, however, it may be under-recognized and under-reported.[12] Hemolytic transfusion reactions can be due to incompatible ABO match or from minor antibodies not tested routinely. Hemolytic reactions may result in febrile illness, shock, and death.

The US Food and Drug Administration requires reporting of suspected transfusion reactions if there is an associated fatality.[10] The additional impact on patient outcomes must be considered with blood transfusion. Furthermore, the costs associated with adverse outcomes from blood transfusion add to the expenditure for each unit given.

Comment. Based on evidence from the TRICC trial,[6] blood transfusion will not improve Ms. Garcia's mortality risk at this time.

Use of Blood is Under Increasing Scrutiny

You are an involved member of the medical staff at your local hospital. The Chief of Staff approaches you one day and states that she is concerned about the high use of blood products in your institution and wants to know more about the regulatory developments in this area. She asks you to investigate and report back to the Quality Committee for the hospital. What are the latest regulatory developments? What guidelines are medical societies developing regarding blood transfusion?

In 2007, The Joint Commission (TJC) convened a stakeholders meeting to examine the evidence regarding patient blood management. A Technical Advisory Panel was convened in 2008 and drafted measures for testing. The measures were pilot tested in multiple hospitals across the country. The Technical Advisory Panel recommended the final measures with modification and these were submitted to the National Quality Forum (NQF) in November 2010.[13] Although the Patient Blood Management Performance Measures Project has not been endorsed for national use, it serves as a tool for healthcare organizations to evaluate blood utilization and the transfusion process.

As TJC examines and codifies practices in transfusion medicine, so are other medical organizations. The Society of Thoracic Surgeons (STS) and Society of Cardiovascular Anesthesiologists jointly have developed recommendations regarding blood transfusion, blood conservation, and anemia management.[14] In its outcomes research, STS measures blood use by participating hospitals and physicians. These data are provided to participating physicians with comparative analysis to their counterparts at other institutions. The AABB (formerly the American Association of Blood Banks) has published practice guidelines on red cell transfusion to guide clinicians further in the appropriate indications for transfusion.[15] The Eastern Association for Surgery of Trauma (EAST) and the American College of Critical Care Medicine (ACCM) have divided guidelines into seven categories for appropriate blood

Table 1. The Joint Commission Patient Blood Management (PBM) Performance Measures Project.[11]

PBM-01: Transfusion Consent	Patients of all ages with a signed consent who received information about the risks, benefits, and alternatives of transfusion prior to the initial transfusion of red blood cells, plasma, or platelets or the initial transfusion were deemed a medical emergency.
PBM-02: RBC Transfusion Indication	The number of transfused red blood cell (RBC) units with a pre-transfusion hemoglobin or hematocrit result and clinical indication documented from patients of all ages who received RBCs.
PBM-03: Plasma Transfusion Indication	The number of transfused plasma units (bags) with a pre-transfusion laboratory testing result and clinical indication documented from patients of all ages who received plasma.
PBM-04: Platelet Transfusion Indication	The number of transfused platelet doses with pre-transfusion platelet testing completed and clinical indication documented from patients of all ages who received platelets.
PBM-05: Blood Administration Documentation	The number of red blood cells, plasma, or platelet transfusion units/doses (bags) transfused to patients of all ages that had documentation of the following: patient identification and an order to transfuse (or Blood ID Number) confirmed prior to the initiation of transfusion, transfusion start date and time, and blood pressure, pulse, and temperature recorded at specific intervals.
PBM-06: Preoperative Anemia Screening	Select elective surgery, orthopedic, and hysterectomy patients 18 years and older with documentation of preoperative anemia screening 14-45 days before anesthesia start date.
PBM-07: Preoperative Blood Type Testing and Antibody Screening	Select elective orthopedic, cardiac, and hysterectomy surgical patients 18 years and older who had a type and screen or type and crossmatch ordered preoperatively and completed prior to anesthesia start time.

Table 2. EAST and ACCM clinical practice guideline: Red blood cell transfusion in adult trauma and critical care.[12]

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. (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 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. (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 7 g/dL in critically ill patients requiring mechanical ventilation (MV). There is no benefit of a "liberal" transfusion strategy (transfusion when Hb 10 g/dL) in critically ill patients requiring MV. (Level 2) 7. Consider transfusion if Hb 7 g/dL in resuscitated critically ill trauma patients. There is no benefit of a "liberal" transfusion strategy (transfusion when Hb 10 g/dL) in resuscitated critically ill trauma patients. (Level 2) 8. Consider transfusion if Hb 7 g/dL in critically ill patients with stable cardiac disease. There is no benefit of a "liberal" transfusion strategy (transfusion when Hb 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 8 g/dL) on hospital admission. (Level 3)
B. Recommendations Regarding RBC Transfusion in Sepsis	1. There are insufficient data to support Level 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 (Acute Respiratory Distress Syndrome) are common clinical sequelae of massive transfusion. Prior studies have suggested that RBC	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 is associated with respiratory complications, including ALI and ARDS that remains even after adjusting for potential confounders.	transfusion-associated morbidity and mortality, despite under-diagnosis and under-reporting. (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 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 multiple organ failure and systemic inflammatory response syndrome. *(*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)

transfusion in surgical and critical care settings.[16] These are a few examples of the efforts of American medical societies to define when blood transfusions may be appropriate.

Blood is Costly

The Chief of Staff thanks you at the next Quality Committee meeting for your excellent report. During the meeting, she mentions that the expenditures for blood bank seem to be increasing each year and with cutbacks in funding the hospital needs to "reign in budgets". What are the costs associated with blood transfusion? What impact does this have on the health system in the United States?

Recent studies demonstrated that the total cost of administration of red blood cells is higher than the acquisition costs. Shander et al. showed that acquisition cost alone of RBCs ranged from $150-$248 per unit.[17] After accounting for direct and indirect costs of administration, total costs per unit of blood ranged from $522-$1183. Costs for the two US hospitals were $726-$1183 per unit of blood given. Using these results and Department of Health and Human Services statistics for blood transfusion, the estimated acquisition costs for hospitals per year is more than $3 billion.[14] Total transfusion costs are between $10.2 and $15.4 billion. These studies do not take into account other potential costs such as lost productivity of healthcare workers (as they provide additional care to patients receiving a blood transfusion) and management of adverse transfusion outcomes.

Perioperative Anemia is Best Treated Proactively, Not Reactively

Raj Sharma is a 69-year-old man from your community who is to undergo coronary artery bypass surgery in four weeks. On pre-operative screening, he has a hemoglobin of 8.5 g/dL. He has iron deficiency anemia. He is referred to a gastroenterologist for evaluation and colonoscopy. What interventions would be indicated to treat his anemia? Will treating his anemia change his risk for transfusion peri-operatively?

The prevalence of anemia in the pre-operative surgical patient may be up to 76%, depending on the type of surgery and other medical comorbidities.[18] This patient population may benefit significantly from intervention to correct anemia before further blood loss is incurred. A British medical society has adopted guidelines that evaluation and treatment of anemia before surgery should be requisite.[19]

In non-cardiac surgery, pre-operative anemia is an independent predictor of post-operative mortality.[20,21] The lower the pre-operative hemoglobin is, the higher the mortality risk. In orthopedic surgery, pre-operative anemia confers increased risk for peri-operative blood transfusion.[22,23]

Treatment with preoperative intravenous iron is effective in increasing hemoglobin in orthopedic patients.[24,25] Patients who received pre-operative epoetin alfa then underwent large joint arthroplasty (hip or knee) showed improvement in perioperative hemoglobin and decreased risk for blood transfusion.[26-28] Erythropoietin use decreased exposure to perioperative allogeneic transfusion in orthopedic and cardiac surgery.[29] Oral iron supplementation for at least two weeks prior to colorectal cancer surgery increases hemoglobin values in anemic patients and reduces the need for intraoperative transfusion.[30]

Pre-operative anemia is a significant risk factor for worsened outcomes in the peri-operative setting. There may be several reasons that it is not treated more aggressively: (1) Medical providers have become "immune" to the presence of anemia in patients. Anemia is seen so commonly that many providers may ignore a low hemoglobin of 8 g/dL and explain that "it could be worse". However, the converse argument should be made that "it could be better". (2) Providers may not want to take time to address the problem proactively and instead take the reactive approach of giving a blood transfusion if the hemoglobin declines sharply after surgery. (3) Many providers may be unaware of alternative approaches that exist and the evidence for using them.

Comment. In the case of Mr. Sharma, administration of parenteral iron 4-6 weeks prior to surgery to correct his iron deficiency is indicated. Oral iron may be insufficient to correct his iron deficiency and consequent anemia in time for surgery. Intravenous iron is much safer in its current preparations than compared to previous preparations. It can be given on an outpatient basis in an infusion center. Intravenous iron, when prescribed for the indication of iron deficiency anemia, often does not require insurance pre-authorization.

Patient Blood Management (PBM): Applying it to your Practice

Janet Smith is a 55-year-old woman who is a nurse in your practice. She needs to have a total hip arthroplasty for a long-standing arthritis and related debility. She is well-read and knows that there are risks with blood transfusion and she would like to avoid this if at all possible. She does not want to risk being exposed to hepatitis C like Mr. Jones. What interventions can be offered to her to reduce her risk for peri-operative transfusion?

Blood transfusion has significant risks associated with its use. Clearly, there are appropriate circumstances where it is indicated. However, medical providers need to be more judicious in deciding when to transfuse. In a 2011 systematic review, Wilkinson found that gaps in the medical evidence and poor methodology of trials, particularly in the past, did not provide a strong evidence base for the use of red blood cell transfusions.[31]

PBM is the application of evidence-based concepts designed to maintain hemoglobin concentration, minimize blood loss, and optimize hematopoiesis. Pragmatically this means: (1) treating anemia proactively, (2) delaying surgical or invasive interventions until anemia can be corrected, (3) utilizing mechanical and medical interventions to minimize bleeding and blood loss at the time of surgery, (4) using blood products with an evidence-

based approach, (5) optimizing physiologic tolerance of anemia.[32] This requires a shift in mindset of the provider from the old approach of "give blood when the patient needs it" to the new approach of "optimize the patient and then only give blood once other measures have been taken".

PBM programs are being formalized in many hospitals across the country. The individual components have been shown to be effective in multiple clinical settings. A comprehensive PBM program in cardiac surgery was effective at reducing blood transfusion rates compared to hospitals without such a program.[33] Furthermore, safety was demonstrated in the PBM approach with comparatively fewer deaths and reduced complications.

Comment**.** Screening for anemia prior to surgery is indicated. Timely treatment of anemia is key to reducing Ms. Smith's risk for transfusion. Some patients may ask about pre-operative autologous donation (PAD), which has been shown to have mixed outcomes. Discussion of PAD is not within the scope of this article and should only be considered in the peri-operative setting if other blood management strategies have failed.

Conclusions

While the safety of blood products has improved in regards to quality of the product, there are significant clinical concerns regarding transfusion of allogeneic blood. Providers need to understand the risks and benefits of transfusion and counsel patients accordingly. When possible, a proactive approach to evaluating and treating anemia should be taken. Patient Blood Management is a comprehensive approach to treating anemia and reducing unnecessary blood transfusions.

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