

# Trauma Surgery and Transfusion Options

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**Learning Objectives:** 1) To understand the nature of complications associated with allogeneic transfusion. 2) To describe the role that cell salvage plays in allogeneic avoidance.

**Abstract**

Allogeneic transfusion carries many risks. These risks include infectious disease transmission, transfusion-related immunosuppression, and transfusion-related acute lung injury. In addition, the cost of providing blood products for patient care is rapidly escalating. For these reasons, blood management is advocated. Blood management is defined as the appropriate provision and use of blood and blood products while using strategies to reduce or avoid the need for blood transfusion. By doing so, patient outcomes are improved. This article details some of the risks associated with allogeneic transfusion and outlines some ways of avoiding this transfusion.

## Overview

Severe anemia has long been recognized to be life-threatening. Studies in Jehovah’s Witness patients have shown that a hemoglobin level below 2 g/dL is universally fatal.<sup>1</sup> Thus, the risk of anemia is significant. Traditionally, the primary strategy for treating anemia has been to give the patient an allogeneic transfusion. While under many circumstances this may be a life-saving treatment, like any medical treatment, the risks of transfusion need to be weighed against the benefits of the transfusion. Beyond the hemolytic transfusion reaction caused by clerical error and the risk of contracting viral disease, most health care practitioners do not fully understand the broad range of complications that can result from allogeneic transfusion. Allogeneic transfusion is associated with risks that need to be understood and should be balanced in light of the complications of not administering the unit. Table 1 is a summary of the various risks associated with allogeneic transfusion. The following discussion highlights the complications that appear to be influencing a change in transfusion practice away from use of allogeneic transfusion. For trauma surgery, the alternative to allogeneic transfusion, which offers the best opportunity for allogeneic avoidance, is cell salvage. This alternative will also be discussed.

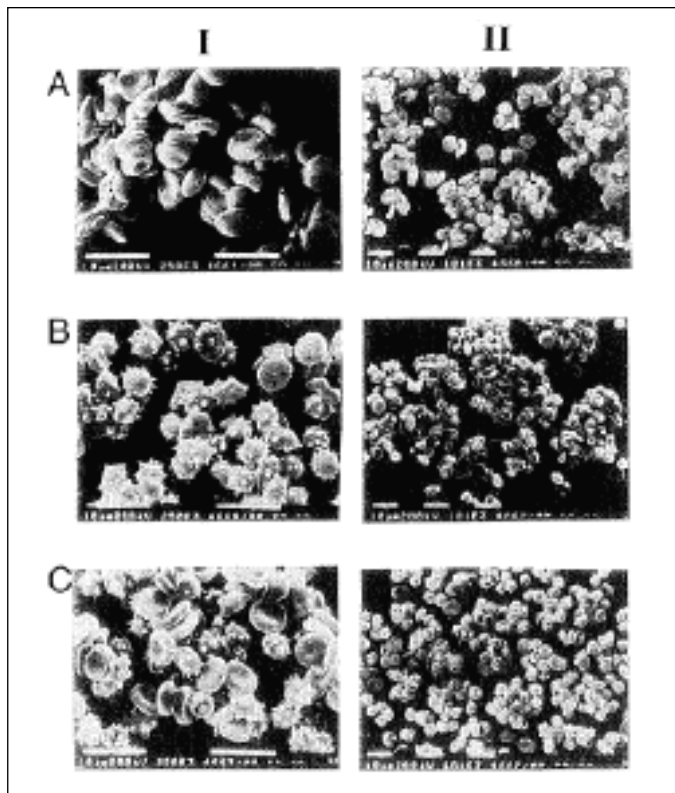
## Infectious Disease Transmission

The risks of allogeneic transfusion are numerous. The general perception of both the medical community and the lay public is that the greatest risk associated with allogeneic blood transfusion is that of contracting viral disease. Rates of viral transmission vary, depending on the virus, ranging from 1 in 2.4 million units for human immunodeficiency virus, 1 in 872,000 units for hepatitis C, and 1 in 1.4 million for West Nile virus.<sup>2,3</sup> Interestingly, complications from clerical error, bacterial contamination,<sup>4</sup> and transfusion-related acute lung injury (TRALI)<sup>5</sup> present far greater risks than does the risk of viral disease transmission. What is more common is the risk of bacterial contamination. The incidence of fatal septic complications following platelet transfusions due to bacterial contamination is estimated to be as high as 1 in 25,000 units.<sup>6</sup> This risk results because platelets are kept at room temperature to maintain platelet viability. If the blood is contaminated during the blood donation, or the patient is bacteremic during the donation, the unrefrigerated platelet concentrate makes an ideal culture medium. Fortunately, the current risk of bacterial contamination may be far less than the 1 in 25,000 figure noted here. Recently, a requirement for some form of bacterial testing has been imposed on the blood banking industry. The type of testing is not agreed on but usually takes the form of pH measurement with a contaminated platelet product demonstrating an acidic environment from continued aerobic metabolism.

## Storage Defect-Associated Injury

Recently, interest has focused on the effect of storage on the functionality of the red blood cell. Classically, studies on blood storage have focused on maintaining the normal life span of the red cell during storage. More recently, a shift toward evaluating the functionality of the red cell has been undertaken. During the storage of a red cell, red cell shape change occurs due to a reduction in intracellular adenosine triphosphate, sialic acid, and nitric oxide.<sup>7-9</sup> After approximately 14 days of storage, dependent on the storage solution, the red cells lose their biconcave disc shape and become echinocytes<sup>7</sup> (Fig. 1). Echinocytes are globular structures with spikes.

Onset Time	Mechanism	Complication
Acute	Immunologic	Acute hemolytic
		Allergic/anaphylactoid
	Infectious	Transfusion-related acute lung injury (TRALI)
		Metabolic
Delayed	Infectious	Bacterial contamination
		Volume overload
	Immunologic	Storage defect-associated injury
		Delayed hemolytic
	Infectious	Posttransfusion purpura
		Graft-versus-host disease
	Metabolic	Transfusion-related immunomodulation (TRIM)
		Viruses, parasites, prions
	Oncogene	
	Iron overload	



**Figure 1.** Scanning electron micrographs of stored blood on day 1 (A), day 21 (B), and day 35 (C). Note the shape change from the biconcave disk to the echinocyte as storage time increases. This shape change is attributed to changes in intracellular 2,3-diphosphoglycerate (DPG) and adenosine triphosphate. Columns I and II are different powers of magnification. (Reprinted from Hovav T, Yedgar S, Manny N, et al. *Alteration of red cell aggregability and shape during blood storage. Transfusion* 1999;39(3):277-81, with permission.)

Animal models have demonstrated that these echinocytes do not pass through capillaries in the same fashion as do normal, unstored cells.<sup>8</sup> In these models, the number of functional capillaries decreases following the infusion of a stored blood product. The decrease in functional capillaries is associated with a decrease in tissue oxygenation.<sup>9,10</sup> This work suggests that our attempts to increase tissue oxygen delivery through blood transfusion may, in fact, be doing the opposite.

This storage injury may have a direct relationship to morbidity and mortality in patients undergoing major surgery. Stored blood transfusions are associated with a higher incidence of postoperative infection, fever, and poor wound healing.<sup>11,12</sup> Basran et al,<sup>13</sup> in a retrospective review of patients undergoing repeat cardiac surgery, showed a linear effect of the storage age of blood on mortality, intensive care unit length of stay, and renal failure with older blood leading to worse outcomes. This may be due to the red cell shape change or the accumulation of proinflammatory mediators during the storage period.<sup>14</sup> Although this storage effect is controversial, it is frightening to contemplate the impact that this might have on the blood banking system.

### Transfusion-Related Immunomodulation

The complication following transfusion, which may be of greatest importance to a surgical patient, is that of immunosuppression. The notion that the transfusion of allogeneic

blood might have an immunosuppressive effect was first noticed in kidney transplant patients more than 30 years ago; those recipients who received allogeneic transfusions had a better allograft outcome when they were transfused.<sup>15</sup> The apparent immunosuppression induced by blood transfusion is known as transfusion-related immunomodulation (TRIM) and is thought to be caused by the passager lymphocytes in the blood products.

Although TRIM may be beneficial for the transplant recipient, TRIM might worsen the condition of other patients. It has been suggested that TRIM might result in higher cancer recurrence rates in patients undergoing cancer surgery. This same effect is suggested to cause increases in the rate of postoperative infections (i.e., infections not borne in the blood product itself). A recent review has highlighted the controversies in these areas.<sup>16</sup> By combining the results of 87 observational and 3 randomized control trials of patients with various types of cancer, Blajchman<sup>19</sup> demonstrated that the majority of these studies indicate that allogeneic transfusion has a "significant adverse effect" on the survival of cancer patients. However, this trend toward causing an adverse effect was not absolute; in most of the cancer types reviewed there was at least one study showing that allogeneic transfusion did not have an adverse effect on outcome.

TRIM appears to increase postoperative infection rates. A recent meta-analysis of 20 studies evaluating transfusion and postoperative infection indicated that patients were almost 4 times more likely to have a postoperative infection if they had received a blood transfusion.<sup>17</sup> This effect on postoperative infection appears to be dose-related. For every unit that is administered, there is a linear increase in postoperative infection.<sup>18,19</sup> This dose-related effect highlights a critical issue, which is that transfusion therapy may be necessary, but minimizing it as much as possible should be attempted.

Some controversy clearly exists regarding the extent of these immunosuppressive effects; nevertheless, there seems to be a sizeable body of literature supporting the TRIM effect of allogeneic blood transfusion. Given that the mechanism of TRIM is currently thought to be related to the white blood cells (or their breakdown products) that are present in blood products, a number of investigators have suggested that leukoreduction may ameliorate the risk of immunomodulation.<sup>12-14</sup> Currently most of the industrialized world, with the exception of the United States and South Africa, use prestorage leukoreduced blood products.<sup>15</sup> Mixed results on whether this manipulation removes all of the TRIM effect have been published.<sup>16,17</sup> A recently published Canadian study highlighted the uncertainty of TRIM-amelioration by leukoreduction.<sup>18</sup> The charts of several thousand transfused cardiac surgery, hip fracture repair, and intensive care unit patients were divided into two periods: those transfused prior to the nationwide implementation of universal leukoreduction (mid-1999) and those transfused afterward. The primary outcomes included suspected or confirmed infection and in-hospital mortality, and the secondary outcomes included various organ failures, antibiotic use, transfusion reactions, and fever. The group that was transfused with leukoreduced blood suffered significantly less in-hospital mortality, less antibiotic use, and fewer fevers. The rates of infection were not significantly different between the two groups.<sup>18</sup>

### Transfusion-Related Acute Lung Injury

TRALI is now considered the most common cause of transfusion-related death. The incidence has been estimated to be as high as 1 case for every 79 recipients of allogeneic blood.<sup>21</sup> Death from TRALI is estimated to range from 5% to 25%.<sup>22</sup> It is characterized by noncardiogenic pulmonary edema, most frequently

as a result of passively transferred donor antibodies against recipient leukocyte antigens. The diagnosis is one of exclusion of other causes of acute lung injury. Table 2 highlights the diagnostic criteria for TRALI, which were developed from a consensus conference held in 2004. TRALI has been associated with all plasma-containing blood and blood components, including intravenous immunoglobulin.<sup>23</sup> Some investigators have suggested that plasma from multiparous females may be a major factor in the etiology of this syndrome. Currently, the blood banking community is contemplating the elimination of multiparous women from the donor supply in an attempt to eliminate this complication. Once again, this reduction in possible blood donors would have significant consequences in the provision of blood products for needy patients.

### Transfusion Cost

The factor that is causing the greatest shift in transfusion practice relates to the cost of blood. Many think that blood is donated by patients without cost and is provided to patients without cost. However, the cost of processing and testing the donated unit entails sizeable cost, generally without reimbursement to the hospital. In 2000, the average cost per adult red blood cell unit in the United States was \$469.<sup>12</sup> The cost of transfusion therapy has been increasing because blood product shortages, enhanced viral and bacterial testing, and, in some circumstances, leukocyte-depletion filtering.

The cost of acquiring blood from a donor center such as the Red Cross or an independent center such as the Central Blood Bank of Pittsburgh does not take into account the complications associated with these transfusions.<sup>24</sup> According to a study by Vamvakas and Caven,<sup>25</sup> length of stay is increased by 1.3% per unit of red blood cells transfused and hospital charges increase by 2.0%. Blumberg et al<sup>26</sup> have estimated that the true cost of a unit of packed red blood cells to be somewhere between \$1,000 and \$1,300 per unit.

Growing costs have made transfusion therapy of increasing importance to maintaining hospital profitability. Because most patients who receive blood transfusions are insured by Medicare, the method by which Medicare uses to reimburse a hospital is of critical importance. Medicare reimburses hospitals under a diagnosis-related group, which is a fixed payment per diagnosis. If a patient receives blood transfusions during the hospital stay, no additional reimbursement is gained other than that which comes from the diagnosis-related group-based payment. So, the more blood that a patient receives during an inpatient visit, the less likely the hospital is to profit on a patient's care.

**Table 2. Diagnosis of Transfusion-Related Acute Lung Injury<sup>40</sup>**

1. No acute lung injury prior to transfusion
2. Acute lung injury occurs during or within 6 hours of transfusion
3. Acute onset of respiratory distress
4. Hypoxemia
5. Bilateral lung infiltrates on chest radiograph
6. No evidence of circulatory overload
7. No other acute lung injury risk factors (septic shock, sepsis, aspiration, lung contusion, pneumonia, multiple trauma, drug overdose, burn injury, cardiopulmonary bypass, inhalation injury, acute pancreatitis) overload

Recently, there has been a growing recognition on the part of hospital administrators that the cost of providing blood transfusions is a significant component of an institution's operating costs. These blood-associated costs are frequently one of the largest budget items that a hospital faces. The rate of growth of this cost is increasing rapidly, thus interfering with the profitability of many surgical procedures.

### Transfusion Alternatives

In the United States, 46 units of allogeneic blood are used for every 1,000 people. This rate is significantly less in Canada, where the rate is 32 units per 1,000 people. Some of this differential can be explained by more aggressive attempts to avoid allogeneic transfusion. Some of this may relate to the Transfusion Requirements in Critical Care (TRICC) trial wherein a prospective, randomized control trial was conducted in 11 intensive care units across Canada.<sup>27</sup> In these critically ill patients, two different transfusion strategies were taken. In the restrictive transfusion group, blood was transfused at a hemoglobin of 7 g/dL; whereas in the liberal group, blood was transfused at a trigger of 10 g/dL. As would be easily guessed, the liberal group received more allogeneic blood. What was surprising was that these patients had outcomes that were no different than the restrictive group. In fact, when subgroups of this study were analyzed based on the age of the patient and the severity of the illness, the young patients who were less critically ill had higher survival rates than did the more aggressively transfused patients. What this study suggests is that a reduction in transfusion trigger should be undertaken from the classic trigger of 10 g/dL to 7 g/dL, even in our most critically ill or injured patients.

For the trauma patient, the options for allogeneic blood avoidance are limited by the acuity of the patient's presentation. Cell salvage is worth considering in this patient population. Classically, cell salvage has been considered to be contraindicated in surgery in which bacterial contamination of the salvaged blood might be likely. Rather than being based on adverse patient outcome, the contraindication arises from a failure of the manufacturers of these devices to obtain Food and Drug Administration approval for use of these devices in surgical procedures that might contain bacterial contamination. Despite this contraindication, the evidence to use this technology in off-label procedures appears to be compelling. Red cells processed through a typical cell salvage washing system will be more reflective of a normal circulating cell than will allogeneic stored red cells (Table 3). The remaining discussion will focus on the information that is available supporting use in trauma surgery.

First, bacterial contamination of cell salvage blood appears to be routine, regardless of whether it comes from a bowel operation or other location. Bland et al<sup>31</sup> found that bacterial contamination of cell

**Table 3. A Comparison of Cell Salvage Red Blood Cells (RBCs) Versus Stored RBCs**

Cell Salvage RBCs	Stored RBCs	
Osmotic fragility	Normal	Decreased
2,3-diphosphoglycerate (DPG)	Normal	Decreased
Long-term survival	Normal	Decreased
Potassium content	Low to normal	Elevated
Coagulation factors	None	None

**Table 4. Summary of Studies Wherein Bacterial Contamination Is Noted During Cell Salvage**

Lead Researcher	Surgery Type
Bland LA	Cardiac operations
Kang Y	Liver transplantation
Ozman V	Abdominal trauma
Schwieger IM	Cardiopulmonary bypass
Timberlake GA	Hemorrhaging trauma
Bowley DM	Penetrating abdominal trauma

salvage blood in cardiac surgery approaches 30% of the units processed and readministered. Kang et al<sup>32</sup> reported that 9% of the blood returned to liver transplant patients had bacterial contaminants, usually of skin origin. In these circumstances of bacterial contamination, no clinical sequelae were noted. Contamination from skin flora has been assumed to be inconsequential but the contaminants of frank stool have been thought to be different. This area has also been investigated primarily in trauma, where several authors have reported on frank stool contamination of reinfused, salvaged blood, yet no increased sepsis rates were noted.<sup>33-36</sup> These studies would suggest that cell salvage in the face of bacterial contamination can be done safely (Table 4).

The next question that might arise when pondering the use of cell salvage in trauma surgery is what impact does the processing have on the presence of bacteria? Because the red cells are concentrated during processing, one might postulate that bacteria might also be concentrated. The impact of cell salvage processing on blood that has been bacterially contaminated was first investigated by Boudreaux et al,<sup>37</sup> who inoculated expired units of blood with bacteria and found that washing was capable of reducing contamination to 5% to 23% of the starting contamination. In a similar study, Waters et al<sup>38</sup> found an approximately 99% reduction in bacterial contamination when the combination of cell washing and a leukocyte-depletion filtration was performed. In the same article, a dose-response curve was generated that showed that a 99% reduction of a starting load of bacteria of  $10^7$  still left  $10^5$  bacteria. This level of contamination was identified to occur in surgical procedures in which gross fecal contamination of the blood was observed. Thus, differentiating between gross contamination and possible or unobserved contamination is important. In the circumstance of gross contamination, prudence would suggest that the blood be discarded; whereas in procedures in which no contamination is visible, it would appear that washing and filtering provides a safe blood product.

It is important to keep in mind that during the course of most operations, a bacteremia is present related to the surgical trauma. Broad-spectrum antibiotics are routinely used to manage this routine bacteremia. In one study performed on hypovolemic dogs, survival rates went from 30% to 90% when bacterially contaminated blood was administered in conjunction with antibiotics.<sup>39</sup> This study suggests that antibiotic administration should be combined with cell salvaging in a contaminated environment.

In summary, known risk exists with allogeneic blood, yet only theoretical risk is associated with cell salvage blood. Until data are generated supporting the theoretical risk of cell salvage in these circumstances, it seems reasonable to avoid the known risk of allogeneic blood through the use of cell salvage.

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