ABSTRACT

Allogenic blood transfusion has long been associated with both infectious and noninfectious risks, which are discussed in this article. Although today’s blood supply is safer than ever from various pathogens, infectious risks have not been completely eliminated because of limitations in current detection methods and the potential risk of emerging pathogens. Noninfectious risks of transfusion are often underrecognized compared with infectious risks, but they are far more common, exceeding infectious risks by many. Considering the numerous complications associated with blood transfusion, it is important to develop various strategies to minimize unnecessary transfusions and to ensure the safe and appropriate use of blood and blood products when necessary. (Adv Stud Med. 2008;8(10):357-362)

n spite of being considered a routine and commonplace practice, allogenic blood transfusion is essentially a form of organ transplantation. The risks of transfusion have long been recognized, as evident by the bans on transfusion in England and France in the 17th and 18th centuries. Later on, as discovery of blood groups paved the way to successful transfusions, other complications (eg, transfusion-transmitted jaundice) began to surface. Subsequently, donor screening procedures and tests were implemented, which greatly improved the safety of blood. But because these incremental improvements in blood safety were overshadowed by newer risks and threats, providing a zero-risk blood supply became nearly impossible.

TRANSFUSION-RELATED INFECTIOUS RISKS

Transfusion risks can be categorized into infectious and noninfectious risks, with the latter further grouped into immunologic and nonimmunologic risks (Table). As a result of continuous improvements in screening and testing, today’s blood supply is safer than ever from infectious risks. But nevertheless, risk has not been eliminated completely, because many infections have window periods during which they are not detectable by assays. Moreover, there is always the potential risk of emerging new pathogens that are not recognized and cannot be formally tested for, because specific assays have not been developed for them. Currently, infectious agents for which donated blood is tested include hepatitis B (HBV) and C (HBC), HIV-1 and -2, human T-cell lymphotropic virus (HTLV)-1 and -2, West Nile virus, Treponema pallidum (syphilis), Trypanosoma cruzi (Chagas disease), and cytomegalovirus (CMV). Institutions vary, however, on which tests (eg, CMV testing) they carry out. Other infectious threats to blood
safety that are not currently tested for include Babesia, Plasmodiums (malaria), prions (variant Creutzfeldt-Jakob disease [vCJD]), hepatitis A virus, human herpes virus 8, and chikungunya virus. Various methods of pathogen inactivation (without need for specific testing) are under investigation and some have been implemented, but their efficacy and effect on the quality of blood products remains to be determined. \(^3\) 

Current estimated risks of infection per blood unit range from 1 per 100 000 to 1 per 400 000 for HBV, 1 per 1 600 000 to 1 per 3 100 000 for HCV, 1 per 1 400 000 to 1 per 4 700 000 for HIV, 1 per 500 000 to 1 per 3 000 000 for HTLV, and 1 per 4 000 000 for malaria. \(^4\) Seven reported cases of Chagas disease and 4 cases of vCJD were confirmed to be transmitted through transfusions. \(^5\) Finally, bacterial contamination is present in approximately 1 per 60 000 units of red blood cells (RBCs), but it is much more common in apheresis platelets. A mandate on bacterial surveillance strategies for platelet products has been in place since 2004, and as a result of culturing platelet products, the estimated risk of bacterial contamination of apheresis platelets has been reduced by approximately 50% (from 1:4000 to 1:8000). The most common organism in RBC units is Yersinia enterocolitica, whereas both Gram-positive and Gram-negative organisms contaminate platelet products. Other potential hazards include Epstein-Barr virus, leishmaniasis, Lyme disease, brucellosis, and parvovirus. Hepatitis G virus, SEN virus, and transfusion-transmitted virus are other infective agents commonly found in blood (1–2 in 100 donations), but their significance is presently unknown. \(^6\) Specific patient populations may be at increased risk, as exemplified by the susceptibility of immunosuppressed patients to CMV, mandating use of blood from seronegative donors for some of these patients (eg, patients with severe combined immunodeficiency or T-cell–depleted stem-cell transplant patients).

**Transfusion-Related Noninfectious Risks**

Noninfectious risks of transfusion (Table) are often underrecognized compared with infectious risks, but they are far more common, exceeding infectious risks by many factors when the total burden of disease (complications) is considered. Although the risk of transmitting major viral infections through transfusion is in the range of 1 in 1 million units, a single noninfectious complication (eg, transfusion-related acute lung injury [TRALI]) is estimated to occur in 1 case per every 5000 units of blood component transfused, and possibly even more commonly, because it is often unrecognized.

<table>
<thead>
<tr>
<th>Category</th>
<th>Risks</th>
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<tbody>
<tr>
<td>Noninfectious</td>
<td>Multiple organ failure/dysfunction syndrome attributed to cytokine release Immunomodulation, with postoperative infection—controversial Increased risk of cancer recurrence—controversial HLA alloimmunization Transfusion-associated graft versus host disease Hemolytic transfusion reactions Allergic and anaphylactic reactions Autoimmunization RBC Febrile-associated non-hemolytic transfusion reactions (HLA-related) Transfusion-associated acute lung injury Febrile non-hemolytic transfusion reactions (cytokine related) RBC storage lesions Circulatory overload Iron overload Metabolic disturbances (citrate toxicity, hypocalcemia, hyperkalemia, acidosis, and hyperammonemia)</td>
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HHV = human herpesvirus; HLA = human leukocyte antigen; HTLV = human T-cell lymphotropic virus; RBC = red blood cell.

Data from Shander and Goodnough. \(^1\)
Noninfectious risks can be grouped under immunologic and nonimmunologic complications (Table); however, this classification is somewhat arbitrary, as many “nonimmunologic” reactions also may have some immunologic components.

In general, allogenic transfusion can have both suppressive and stimulatory effects on the immune system. In the 1960s, it was noticed that blood transfusion could prolong survival of allografts in animal models, and in the 1970s, similar results were confirmed in patients receiving cadaver kidney transplantation following multiple allogeneic blood transfusions. But despite its seemingly beneficial effects in transplantation, transfusion-related immunomodulation (largely mediated by leukocytes) has been also reported to be associated with increased rate of cancer recurrence and postoperative infection in some observational studies, although cause/effect are still debated.

On the other end of the spectrum of immunologic reactions, new antigen variants introduced into the body through allogenic transfusion may stimulate the immune system to produce alloantibodies against “minor” blood cell antigens (alloimmunization). RBC alloimmunization is more common in multiply transfused patients (eg, those with sickle cell anemia). A large number of heterogeneous antigens (eg, various human leukocyte antigen [HLA] classes) can cause alloimmunization to platelets. Transfusion of RBCs to patients with preformed alloantibodies against that antigen (eg, due to sensitization in previous transfusions) can result in delayed hemolytic reactions, which may occur in approximately 1 out of 1000 to 1 out of 9000 RBC units transfused. Acute hemolytic reactions due to transfusion of ABO-incompatible blood do not require previous exposure, and result from transfusion errors in approximately 1:30 000 transfusions.

Transfusion associated graft versus host disease (TA-GVHD) is another rare immunologic complication of transfusion, in which immunocompetent, HLA-incompatible donor lymphocytes are transfused into a recipient who is immunologically incapable of eliminating them, and in whom these cells will generate an immune response against host cells. Risk factors for TA-GVHD include receipt of bone marrow transplants or transfusions from blood relatives, cell-mediated immunodeficiencies, and immunosuppressive therapy. Use of irradiated blood components eliminates the risk of TA-GVHD and therefore, should be used in these settings.

Transfusion errors are estimated to occur in 1 out of 30 000 units transfused. The transfusion of ABO-incompatible blood may result in an immediate hemolytic reaction, which remains a leading cause of fatal transfusion reactions. Issuance of donor blood to patients for whom autologous blood is available is another transfusion error.

Transfusion-related acute lung injury is characterized by acute-onset respiratory distress, bilateral pulmonary edema, fever, tachycardia, and hypotension in the presence of normal cardiac function occurring within 6 hours of transfusion. TRALI can be confused with other transfusion-related or unrelated disorders and it is believed to be frequently misdiagnosed and underreported. Its etiology is multifactorial and most commonly related to the reaction of antibodies from donor units with antigens from the recipient's neutrophils or lymphocytes, leading to increased permeability of the pulmonary vessels. Despite a clinical presentation that is similar to acute respiratory distress syndrome (ARDS), TRALI is usually transient with substantial morbidity and a mortality rate of 5% to 10%. Transfusion-associated circulatory overload (TACO) is another complication of transfusion, which presents with pulmonary edema and respiratory distress. Unlike TRALI, which is associated with increased vascular permeability, TACO-induced pulmonary edema is caused by increased central venous pressure and pulmonary blood volume, resulting in fluid extravasation into alveolar space. TACO is estimated to occur in 1 out of 3000 to as many as 1 out of 10 transfusions, depending on the patient population and definition. Distinguishing TRALI from TACO may pose a challenge, and often, varying degrees of both co-exist.

Febrile non-hemolytic transfusion reaction is the most common cause of transfusion-associated fever, occurring in 0.1% to 1% of RBC transfusions. Leukoreduction, removal of white blood cells from blood, may or may not have decreased the incidence of this complication. Other causes of transfusion-associated fever (eg, allergic reactions, hemolytic reactions, bacterial contamination, cytokine-mediated, TRALI, and HLA alloimmunization) should be considered in
febrile patients.

Upon storage, RBCs undergo changes (collectively called "storage lesion") that adversely affect their viability and function. RBCs also release bioactive by-products that accumulate in blood units, potentially causing adverse reactions in recipients. Transfusion of blood units that have been stored for prolonged periods (>14 days) has been linked to increased risk of complications and reduced survival.17

Worsening of outcomes in transfused patients is a theme repeatedly observed in studies comparing transfused with non-transfused patients in various settings and populations (ie, critically ill patients, elderly, cardiac surgery cases, trauma patients, orthopedic surgical cases, and patients with acute coronary syndrome). Compared with non-transfused patients, patients receiving allogenic transfusions have had higher mortality rates, higher risk of intensive care unit admission, longer hospital and intensive care unit stays, higher postoperative infection rates, higher risk of developing ARDS, longer time to ambulation, higher incidence of atrial fibrillation, and higher risk of ischemic outcomes.17-23 One caveat of these studies is the uncontrolled methodology. However, randomized controlled trials comparing restrictive with liberal transfusion strategies in critically ill patients have shown that, in the majority of cases, outcomes in restrictively transfused patients are at least similar to (if not better than) those found in liberally transfused counterparts.26,27

In considering the generally unfavorable outcomes associated with allogenic transfusion, it should be noted that every patient has unique oxygen delivery and consumption status and, as a result, there is patient variability in tolerance for anemia. To this point, each study may include patients with varying levels of hemoglobin (although mere hemoglobin level is not an accurate indicator of oxygen delivery and consumption), and some of these patients may indeed benefit from transfusion. For example, blood transfusion has been reported to lower the short-term mortality rate in elderly patients with myocardial infarction who had a hematocrit of 33% or lower on admission.28 Although several limitations (eg, retrospective nature, potential baseline differences between the groups, and consideration of admission hematocrit as opposed to more relevant nadir hematocrit levels) negatively affect the reliability of these observations, the data point to the fact that every transfusion decision is, in essence, a risk-benefit analysis.29 Allogenic blood transfusions are associated with many risks, but in specific (and limited) circumstances, their benefits can outweigh the risks. However, under most circumstances, the benefit-risk ratio of allogeneic blood transfusion is not favorable, and it should therefore be avoided through the use of alternative strategies and implementation of restrictive transfusion practices.30,31

**Strategies to Optimize Outcomes**

Patients with cancer are at increased risk of developing anemia due to their disease process as well as the treatment they receive (eg, chemotherapy), and anemia is one of the main risk factors for receiving transfusion therapy. For patients with chemotherapy-induced anemia (CIA), alternative options (eg, erythropoiesis-stimulating agents [ESAs] or parenteral iron) should be considered when possible as a means of preventing transfusions (discussed in article by George M. Rodgers, III, MD, PhD). The efficacy of ESAs in reducing transfusion requirements has been validated by several CIA-related studies, and just recently, a study examining transfusion trends among patients with CIA found that the transfusion experience in the Medicare CIA population treated with ESAs has consistently declined from 1992 to 2005.32 This decline has played an important role in preserving an adequate blood inventory to supply the needs of patients with acute, life-threatening anemia, for whom alternative options are less viable. On the other hand, results from recent studies have also indicated that patients with cancer who are receiving ESAs may have decreased survival and/or accelerated tumor progression. These findings have resulted in the inclusion of new warnings into the product labeling for ESAs and continuous US Food and Drug Administration review of ESA safety (see Dr Rodgers’ article).

Despite the overwhelming need to avoid or minimize the use of transfusion, it remains an essential part of medicine. In an effort to ensure the safe and appropriate use of blood and blood products when necessary, various organizations have released strategies intended to minimize transfusions and ensure safe and appropriate use of blood and blood products. The World Health Organization, for example, encourages the establishment of hospital transfusion committees with authority to determine hospital policies and resolve any transfusion-related problems.33 Some of the main functions of

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these committees include overseeing continuous availability of safe blood/blood products, monitoring transfusion reactions, performing utilization reviews, maintaining quality assurance and improvement, and meeting regulatory/accreditation requirements for transfusion services.

Incorporation of technology into transfusion practices may also improve outcomes, as evidenced by a recent study that found a computer-assisted transfusion management system (connected to a barcode identification system) to be useful in contributing to appropriate management of blood components and in preventing transfusion errors. The role(s) of the Hospital Transfusion Committee, the Transfusion Service, and the Transfusion Service Medical Director are illustrated in the Figure.

One strategy that may optimize transfusion practices involves exploring alternate surrogate biomarkers that assess adequate tissue oxygenation. The currently accepted marker, hemoglobin concentration, has been questioned in regard to its association with oxygen-carrying capacity of blood and tissue oxygen consumption, as well as its use as a trigger for transfusion. Other ways of improving transfusion practices include promoting alternatives to blood components that limit exposure to allogenic blood, better education (informed consent) of caregivers and patients regarding the risks of transfusions, and dissemination of information regarding optimum practices through practice guidelines.

Various transfusion guidelines are available from local and national organizations (e.g., American College of Physicians), as well as from individual institutions. However, because there is marked variability in transfusion practices, institution-specific protocols (discussed in the following article by Aryeh Shander, MD, FCCM, FCCP) may be preferable to more global guidelines in accomplishing changes in practice. In developing well-designed transfusion guidelines, some features that may be included are clinical and laboratory indications for the use of blood/blood products and transfusion alternatives, a standard blood request form to provide information about the patient and the need for transfusion, and a blood ordering schedule (as a guide to the number of units of blood/blood products that should normally be requested for each type of operation).

CONCLUSIONS

Given the numerous risks associated with allogenic blood transfusion, institutions can improve patient outcomes by using alternative treatments when possible and establishing protocols that aid in identification of appropriate transfusion candidates and ensure proper use of blood/blood products.

REFERENCES


