Transfusions confer such risks as acute TRALI, alloimmunization, and iron overload, so they must be used only when benefits outweigh the risks.

Adverse Effects of Transfusion
Radhika Dasararaju, MD, and Marisa B. Marques, MD

Background: Patients with malignancy comprise a unique group for whom transfusions play an important role. Because the need for transfusions may span a long period of time, these patients may be at risk for more adverse events due to transfusion than other patient groups.

Methods: A literature search on PubMed that included original studies and reviews was performed. The results were summarized and complemented by our clinical experience. Long-term complications of transfusions, such as transfusion-associated graft-vs-host disease, alloimmunization, transfusion-related immunomodulation, and iron overload, are discussed.

Results: Transfusion-related acute lung injury, transfusion-associated circulatory overload, and hemolytic transfusion reaction are deadly complications from transfusion. These adverse events have nonspecific presentations and may be missed or confused with a patient's underlying condition. Thus, a high level of suspicion and close monitoring of the patient during and following the transfusion is imperative. Common reactions (e.g., febrile nonhemolytic transfusion reaction, allergic reaction) are not life threatening, but they may cause discomfort and blood product wastage.

Conclusions: Every transfusion carries risks of immediate and delayed adverse events. Therefore, oncologists should prescribe transfusion for patients with cancer only when absolutely necessary.

Introduction
Patients with malignancy comprise a unique group for whom transfusions play an important — and sometimes lifesaving — role. Typically, patients with cancer are pancytopenic, immunosuppressed, or both, and these conditions affect their transfusion needs as well as the interpretation of signs and symptoms of possible reactions. Because their need for transfusions may span a long period of time, this patient population may be at risk of experiencing more adverse events due to transfusion than any other patient group. That being said, a 4-year study by Huh and Lichtiger1 revealed that reactions occurred less frequently in patients with cancer and that febrile nonhemolytic transfusion reactions (FNHTRs) and allergic reactions were the most common (51.3% and 36.7%, respectively). FNHTRs are particularly difficult to differentiate from the patient’s underlying illness, considering that many are already febrile before the transfusion. A thorough review of vital signs before and after the transfusion, associated signs and symptoms, and timing of the increased temperature are essential to make the correct diagnosis. To prevent FNHTRs, transfusion services strive to offer leukoreduced

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products alone to patients with cancer. Leukoreduced red blood cells (RBCs) and platelets have the added advantage of mitigating the risk of cytomegalovirus (CMV) transmission because they are CMV safe.2

**Premedication Prior to Transfusion**

In 2007, according to Geiger and Howard,3 physicians at a research hospital prescribed an antipyretic and an antihistamine (usually acetaminophen and diphenhydramine) prior to almost 70% of transfusions. This figure is higher than the rest of the United States at about 50%. Although the practice of premedication to prevent FNHTRs and allergic reactions is likely to continue, several published reports have questioned its validity. A prospective study of hematology/oncology patients suggested that premedication use can be decreased without increasing reaction rates and that prestorage leukoreduction, reduced plasma from platelet units, or both diminish but do not eliminate FNHTRs.4 Another study concluded that, although routine pretransfusion antipyretics reduce patient inconvenience and morbidity rates associated with FNHTRs, as well as decrease product wastage, the process is not cost effective.5 A randomized controlled trial of 315 patients with leukemia or post–stem cell transplantation without a history of transfusion reactions showed that premedication and bedside leukoreduction significantly decreased the risk of FNHTRs.6 And, more recently, a systematic review found no evidence to justify premedication to prevent FNHTRs and allergic reactions regardless of patient history.7

**Acute Transfusion Reactions**

Although FNHTRs and allergic reactions are common and familiar to most health care professionals, these reactions are not as life threatening as acute hemolytic transfusion reactions (AHRs), transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI). According to the US Food and Drug Administration (FDA), 30 to 44 patients died due to transfusion reactions per year in the United States between 2009 and 2013.8 The top 3 causes of transfusion-related fatalities for the combined 5 years were TRALI at 38%, TACO at 24%, and AHRTRs at 22%.8 The remaining deaths were caused by microbial contamination at 10%, anaphylaxis at 5%, and other causes, such as transfusion-associated graft-versus-host disease (TA-GVHD) and hypotension, at 1%.8 The dilemma for the health care team caring for patients with cancer who develop a reaction is to determine: (1) If the signs and symptoms represent a true reaction or a coincidence (ie, fever), and (2) how serious a reaction is if it has occurred. The differentiation between the patient's underlying status and a reaction to explain new signs and symptoms, as well as the type of reaction, is difficult to ascertain because of the nonspecific manifestations of transfusion-related adverse events (Table 1).9–15 Fever, chills, nausea, vomiting, pain, itching at the intravenous (IV) insertion site, variations in blood pressure, tachycardia, dyspnea, and restlessness are among the most common reasons a reaction is suspected. Although fever may indicate an FNHTR, it may also be a sign of a potentially fatal complication such as AHRTR or sepsis. For this reason, transfusion administration guidelines must be strictly followed to avoid a reaction, such as an AHRTR, caused by the infusion of the incorrect unit to the patient and to detect one as soon as it occurs.9,16 Because the severity of the reaction and its consequences are directly proportional to the volume of incompatible product transfused, early recognition and rapid intervention are essential to minimize harm. After stopping the transfusion at the earliest sign of reaction, the IV access line should be kept open with normal saline. The next critical step is to check that the blood product was intended for that recipient.9 Immediately thereafter, the remainder of the unit with the attached tubing and compatibility label or “bag tag” must be sent to the transfusion service (ie, blood bank) accompanied by a description of the clinical picture, vital signs before and during the transfusion, and a sample of the patient's blood. Fresh

![Table 1. — Signs and Symptoms of Acute Transfusion Reactions](https://example.com/table1.png)

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Possible Transfusion Reaction</th>
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<tbody>
<tr>
<td>Fever</td>
<td>FNHTR+</td>
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<tr>
<td></td>
<td>AHRTR</td>
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<tr>
<td></td>
<td>TRALI</td>
</tr>
<tr>
<td></td>
<td>Microbial contamination</td>
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<tr>
<td>Itching</td>
<td>Allergic reaction</td>
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<tr>
<td>Rash</td>
<td></td>
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<tr>
<td>Urticaria</td>
<td></td>
</tr>
<tr>
<td>Wheezing</td>
<td></td>
</tr>
<tr>
<td>Facial edema</td>
<td></td>
</tr>
<tr>
<td>Decrease oxygen saturation to &lt;90% on room air</td>
<td>TACO</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>AHRTR</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>Microbial contamination</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>TACO</td>
</tr>
<tr>
<td>Hypertension</td>
<td>AHRTR</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Microbial contamination</td>
</tr>
<tr>
<td></td>
<td>TRALI</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Pain at IV infusion site</td>
<td>AHRTR</td>
</tr>
<tr>
<td>Abdominal/chest/flank pain</td>
<td>Allergic reaction</td>
</tr>
</tbody>
</table>

AHTR = acute hemolytic transfusion reaction, FNHTR = febrile nonhemolytic transfusion reaction, IV = intravenous, TACO = transfusion-associated circulatory overload, TRALI = transfusion-related acute lung injury. +Fever is most often due to underlying infection among patients with cancer, especially if the blood product (red blood cells or platelets) is leukoreduced. From references 9 to 15.
urine should also be sent if hemolysis is suspected. In the blood bank, a clerical check is repeated and pre-transfusion data, such as ABO type, antibody screen, crossmatch result if packed RBCs were implicated, and any other pertinent history are reviewed. Because the laboratory workup is aimed at detecting or excluding hemolysis, such workup starts with the inspection of the plasma color followed by a direct antiglobulin test (DAT) and screening for free hemoglobin in plasma and urine. A newly positive post-transfusion DAT result compared with a negative DAT pretransfusion result suggests an AHTR. In such cases, the patient’s clinical team must be notified as soon as possible so aggressive hydration can be initiated to limit the deleterious effects of free plasma hemoglobin. A negative laboratory workup is expected for all other types of adverse effects of transfusions (Table 2). 

**Acute Hemolytic Transfusion Reaction**

Most often, AHTRs are caused by immune incompatibility between the donor and the recipient (typically, antigen-positive RBCs are transfused to a patient with the corresponding antibodies). The most severe AHTR is due to immunoglobulin (Ig) M anti-A, usually from a processing error in which the wrong blood was sent to the transfusion service with the patient’s name, or from failing to perform a patient identification check at the bedside and transfusing a unit of RBCs intended for someone else. In the last 5 years, 13 patients died from an ABO-mediated AHTR. In addition, non-ABO antibodies caused more than twice as many fatal AHTRs in the same time-period (29 deaths). As seen in Table 2, a variety of symptoms may denote an AHTR. Because the volume of incompatible blood transfused correlates with the severity of the reaction, it is important for transfusionists to stay with the patient for the first few minutes of every transfusion and then advise the patient to immediately notify the nursing staff if any new symptoms occur. Other variables that affect the severity of an AHTR include the recipient antibody type and titer. Because AHTRs may also be delayed, patients should be instructed on how to report any symptoms that develop within 24 hours, especially if they were transfused as outpatients.

Hemolysis due to anti-A and anti-B is mainly intravascular because IgM readily activates complement, inducing the formation of a membrane attack complex. In turn, complement activation leads to the release of vasoactive amines, histamine, and other inflammatory cytokines such as interleukins and tumor necrosis factor α, which activate coagulation and fibrinolysis. In addition, complement-activation products and cytokines cause hypotension. Free plasma hemoglobin is both damaging to the endothelium and a nitric oxide scavenger, causing vasoconstriction and hypoxia. Hemolysis mediated by IgG antibodies (non-ABO) is mainly extravascular through phagocytosis of the transfused RBCs by splenic macrophages via their Fc receptors. However, in patients with high-titer IgG antibodies to RBC antigens, combined extravascular and intravascular hemolyses may occur.

Patients with cancer are also at risk of an AHTR when receiving ABO-incompatible platelets with anti-A, anti-B, or both in the plasma. To minimize this risk, transfusion services are expected to avoid units with high-titer ABO antibodies, if known, because testing is not routine at all institutions. In the event that hemolysis is suspected following incompatible platelets, a post-transfusion DAT would provide useful information. Hemolysis can also occur from improper storage of RBCs, leading to thermal, mechanical, or osmolar injury and, rarely, bacterial contamination. The concomitant infusion of hypotonic solutions or medications with RBCs also results in hemolysis and is not recommended. Rh immunoglobulin (passively acquired IgG anti-D) or intravenous immunoglobulin (IVIG; which contains anti-A and anti-B) can also cause hemolysis, and this complication should be promptly recognized.

A suspected AHTR is confirmed by a change in plasma color and a positive result on DAT for IgG, complement, or both. In such patients, an extended workup may include haptoglobin, lactate dehydrogenase, bilirubin, plasma-free hemoglobin, creatinine, and a disseminated intravascular coagulation profile. Management is mainly supportive with IV fluids, diuretics, vasopressors, and blood products if bleeding induced by disseminated intravascular coagulation ensues. Strict adherence to patient identification procedures, and proper specimen collection practices help prevent AHTRs and improve transfusion safety.

**Transfusion-Related Acute Lung Injury**

Twenty years ago, the American-European Consensus Conference published a definition of acute lung injury. Ten years later, TRALI was defined as new-onset acute lung injury within 6 hours of transfusion with a PaO₂/FIO₂ ratio of no more than 300 mm Hg or oxygen saturation of at least 90% on room air and bilateral infiltrates on chest radiography in the absence of left atrial hypertension. TRALI is most often caused by antibodies to human leukocyte antigens (HLAs) or human neutrophil antigens (HNAs) in the transfused blood product given to a patient whose leukocytes express the cognate antigen.

It is believed that TRALI follows a 2-hit model: (1) Neutrophils are primed and sequestered in the lungs due to an underlying clinical condition, and (2) they become activated by the infusion of antibodies or biological response modifiers (ie, cytokines and lipids accumulated in the blood product).
In addition to the lungs, neutrophils accumulate in other organs (e.g., liver, central nervous system), likely contributing to the morbidity and mortality of TRALI. A case-nested study reported that patients with hematological malignancies undergoing induction chemotherapy were at increased risk for TRALI. In addition, TRALI may occur in patients with neutropenia, presumably by the infusion of vascular endothelial growth factor or antibodies to HLA class II that bind to pulmonary endothelium and cause pulmonary leak. Because plasma from females was implicated in most initial cases of TRALI, almost all units of plasma currently manufactured in the United States are from male donors. Since this change, the risk of TRALI from plasma is comparable with that from RBC and platelet products.

TRALI is a diagnosis of exclusion because it is clinically indistinguishable from other causes of respiratory distress (see Table 2). Thus, when patients develop sudden dyspnea, hypoxia, and hypotension during or within 6 hours of transfusion, the possibility of TRALI must be considered. Although fever is also

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Diagnosis</th>
<th>Symptoms</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>AHTR</td>
<td>DAT positive (may be negative if all incompatible red cells destroyed) Hemolized plasma, hemoglobinuria Antibody screen positive; negative if due to ABO incompatibility Eluate with alloantibody or anti-A or anti-B Falling hematocrit level Haptoglobin decreased, LDH increased If DAT negative, consider thermal, osmotic, mechanical, or chemical cause</td>
<td>Fever</td>
<td>Negative for AHTR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gram stain and culture positive of implicated unit (usually platelets)</td>
</tr>
<tr>
<td>TRALI</td>
<td>Negative for AHTR Transient leukopenia Chest radiography with bilateral pulmonary infiltrates</td>
<td>Urticaria</td>
<td>Negative for AHTR</td>
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<tr>
<td></td>
<td></td>
<td>Itching</td>
<td>Mainly clinical diagnosis</td>
</tr>
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<td></td>
<td></td>
<td>Rash</td>
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<tr>
<td></td>
<td></td>
<td>Wheezing</td>
<td></td>
</tr>
<tr>
<td>TACO</td>
<td>Negative for AHTR</td>
<td>Respiratory distress</td>
<td>Negative for AHTR</td>
</tr>
<tr>
<td></td>
<td>High brain natriuretic peptide</td>
<td>Dyspnea</td>
<td>IgA deficiency with class-specific or subclass-specific anti-IgA (later determination)</td>
</tr>
<tr>
<td></td>
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<td>Bronchospasm</td>
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<td>Sweating</td>
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<td></td>
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<td>Flushing</td>
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<td></td>
<td></td>
<td>Nausea, vomiting, abdominal cramps</td>
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<tr>
<td></td>
<td></td>
<td>Substernal pain</td>
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<td></td>
<td></td>
<td>Hypotension</td>
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<td></td>
<td></td>
<td>Shock</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Localized angioedema</td>
<td></td>
</tr>
<tr>
<td>Transfusion-Associated Dyspnea</td>
<td>Negative for AHTR, TACO, TRALI, and allergic reactions</td>
<td>Temperature rise within 4 hours of transfusion, not caused by underlying condition, with or without chills or rigors</td>
<td>Negative for AHTR</td>
</tr>
<tr>
<td>FNHTR</td>
<td></td>
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</tr>
</tbody>
</table>

AHTR = acute hemolytic transfusion reaction, DAT = direct antiglobulin test, DIC = disseminated intravascular coagulation, FNHTR = febrile nonhemolytic transfusion reaction, Ig = immunoglobulin, IV = intravenous, LDH = lactate dehydrogenase, TACO = transfusion-associated circulatory overload, TRALI = transfusion-related acute lung injury. From references 9 to 15 and 17 to 21.
common, it may not initially occur. In addition to the laboratory workup to exclude hemolysis, a complete blood count may show acute neutropenia, which is a useful marker of TRALI.\textsuperscript{18,19} Chest radiography supports the diagnosis of TRALI with newly developed bilateral pulmonary infiltrates, but the infiltrates can also be seen in cases of TACO and other causes of acute lung injury.

Treatment for TRALI consists of respiratory support and pressors. Although some patients receive corticosteroids, steroids have not been proven to be beneficial and diuretics are not indicated.\textsuperscript{31} Mortality rates range from 5% to 25%, and, with vigorous respiratory support, 80% of patients recover within 48 to 96 hours.\textsuperscript{36} Confirmation of TRALI occurs when anti-HLA or anti-HNA in the serum of the donor matches the phenotype of the patient.\textsuperscript{36} Any donor implicated in a case of TRALI should be indefinitely deferred from donating blood in the future.

**Transfusion-Associated Circulatory Overload**

The true morbidity and mortality rates of TACO are unknown due to the uncertain prevalence of TACO. Because TACO is now the second leading cause of transfusion-associated mortality in the United States, it is likely that awareness of its life-threatening potential has increased.\textsuperscript{8} By contrast to TRALI, which is difficult to prevent except by minimizing transfusions and avoiding donors with HLA and HNA antibodies, TACO is conceivably preventable.\textsuperscript{13,37,38} Health care professionals should identify transfusion recipients unable to effectively process the volume challenge and either avoid transfusions altogether, prescribe the smallest possible number of units, and/or ensure a slow infusion rate. The risk of TACO increases with age and the number of units transfused, especially in patients with congestive heart failure, chronic pulmonary disease, anemia, or those receiving plasma products.\textsuperscript{57,38} TACO should be suspected when the patient develops new or exacerbated respiratory distress, pulmonary edema, or evidence exists of left or right heart failure or elevated central venous pressure (see Table 2). These signs and symptoms usually present within 2 hours of the transfusion onset but may take up to 6 hours to manifest.\textsuperscript{13} It is often difficult to distinguish TACO from TRALI, although hypertension (not hypotension) is expected. If available, a high brain natriuretic peptide level or pro–brain natriuretic peptide may help diagnose TACO.\textsuperscript{20} In addition to slow infusion rates and close monitoring for the development of symptoms, concurrent infusion of other fluids should be avoided. Furthermore, pretransfusion diuretics can considerably decrease the risk of TACO.\textsuperscript{38}

**Transfusion-Associated Dyspnea**

Transfusion-associated dyspnea is defined as acute respiratory distress occurring within 24 hours of transfusion that is not explained by the patient's underlying medical condition and does not meet the criteria for TRALI, TACO, or an allergic reaction.\textsuperscript{21,39}

**Microbial Contamination**

Although bacterial contamination of RBCs is extremely rare, bacterial overgrowth in platelet units continues to be possible despite the implementation of various detection methods in the last 10 years.\textsuperscript{40} Bacterially contaminated platelets are the most common transfusion-transmitted disease and present a particular risk to patients with cancer due to their considerable exposure to platelets and their frequent immunocompromised state. Introduction of skin flora into the collected unit during phlebotomy, storage of the unit at room temperature or, rarely, asymptomatic donor bacteremia, all contribute to the risk. Although the presence of bacteria is often unsuspected, Fig 1 shows a unit in which the growth of methicillin-resistant *Staphylococcus aureus* caused fibrin clots and helped to prevent the unit from being issued from our transfusion service. Subsequent culture confirmed the clinical suspicion of bacterial contamination. In the last 5 years, *S aureus* infections have accounted for the majority of deaths due to infected platelet units, although other gram-positive and gram-negative organisms have also been implicated.\textsuperscript{8}

Parasites that infect RBCs, such as *Babesia microti* or various malarial species, are the most likely etiology of infection from RBCs.\textsuperscript{31} Awareness of these transfusion-transmitted infections is of particular importance for oncologists. Babesiosis or malaria would not be suspected as the cause of unexplained fever in patients who lack the usual risk factors (eg, travel to an endemic area). Furthermore, the diagnosis requires a high level of suspicion and expert review of the patient’s peripheral blood (Fig 2). Thus, it is imperative that transfusion-transmitted infections be included in the differential diagnosis of fever in patients with cancer and should be followed by the specific diagnostic laboratory evaluation as soon as symptoms develop. Splenectomized patients are at significantly increased risk of developing severe babesiosis, which carries a grave prognosis. In such circumstances, RBC exchange may be indicated to decrease the parasite burden in critically ill patients.\textsuperscript{42} Because donor testing does not include assays for babesiosis and malaria, prevention is based on history of exposure, which can be ineffective. Polymerase chain reaction and indirect immunofluorescence are being investigated to screen donors but are not yet in use.\textsuperscript{41,45}

Due to their immunocompromised state, patients with cancer are also at risk for other infections, including those due to CMV, parvovirus B19, and West Nile virus. Because leukoreduction nearly eliminates the risk of CMV infection and polymerase chain reaction
for West Nile virus infection is routinely performed in donors, these infections are no longer significant concerns. However, parvovirus B19 remains a threat.

Transfusion through indwelling central venous catheters with subclinical microbial colonization may lead to a septic reaction.

**Allergic Transfusion Reactions**

Minor allergic reactions manifested as pruritus and rash are common transfusion reactions, but they are benign and usually easily treated. However, allergic reactions can also represent life-threatening systemic anaphylaxis with hypotension and respiratory distress. Typically, they are IgE-mediated type 1 hypersensitivity reactions, leading to mast cell activation and the release of inflammatory mediators. Complement fixation and macrophage-derived cytokines may also contribute to allergic symptoms. Although the exact offending agent is typically unknown, these reactions occur when the patient has been presensitized to an immunologically active compound in the plasma of the donor. Examples of allergens include foods, medications, and polymorphic forms of serum proteins other than IgA, like haptoglobin, C3, C4, transferrin, and albumin. The passive transfer of IgE antibodies to common environmental allergens and anaphylatoxins or platelet biological response mediators (eg, cytokines, chemokines) generated during storage also plays a role.

For patients with mild symptoms such as pruritus or rash, transfusion may be restarted under close supervision and at a slower rate following treatment with an antihistaminic and if symptomatic improvement is seen; however, this practice is controversial.

Severe allergic reactions are caused by antibodies to plasma proteins (eg, IgA, haptoglobin). IgA-related anaphylactic reactions occur in IgA-deficient patients with serum IgA levels below 0.05 mg/dL who have developed class-specific IgA antibodies, even without any previous pregnancy or transfusion (“naturally occurring”). Anaphylaxis causes bronchoconstriction that results in respiratory distress, wheezing, stridor, angioedema, and hypotension (see Tables 1 and 2). Prompt action should be taken to maintain oxygenation and improve blood pressure. Epinephrine may be intravenously or intramuscularly administered in addition to corticosteroids and antihistaminics. If bronchospasm is present, then respiratory symptoms may not respond to epinephrine; adding a β2 agonist or aminophylline may be required.

Severe reactions should be further investigated to determine their etiology and to prevent their occurrence in future transfusions. Patients with an IgA deficiency and anti-IgA should be transfused products from IgA-deficient donors alone or given RBC washed units. For platelets, plasma reduction decreases the incidence of allergic reactions. In emergent situations, regular products may be given after premedication with antihistamines and steroids if the risk of withdrawing the transfusion is higher than the risk of anaphylaxis. The newly approved platelet additive solution, PAS C, replaces most of the plasma in the unit, decreasing the risk of allergic reactions and FNHTRs.

**Febrile Nonhemolytic Transfusion Reaction**

FNHTRs are the most common immediate adverse event of transfusion in patients with cancer. They are characterized by a temperature of 100.4°F (38°C) or an increase of 1.8°F or 1°C from the pretransfusion value, with or without chills, during or within 4 hours following the completion of the transfusion, occurring more often with platelets than RBCs (see Tables 1 and 2). FNHTRs are a consequence of the passive transfer of stored cytokines or due to recipient antibodies against HLAs, HNAs, or platelet antigens that stimulate the release of cytokines.

When receiving leukoreduced products, FNHTR is a diagnosis of exclusion and other possibilities like...
AHTR, microbial contamination, TRALI, medication adverse events, or an underlying infection should be considered first, because prestorage leukoreduction makes FNHTRs unlikely. For patients experiencing recurrent FNHTRs despite leukoreduction, washed RBCs in 2 L saline and premedication with an antipyretic may be useful. In addition, these patients could be given a narcotic analgesic for chills, rigor, or both.

**Delayed Adverse Events of Transfusions**

**Delayed Hemolytic Transfusion Reaction**

Delayed hemolytic transfusion reactions (DHTRs) can be expected between 3 and 10 days following a transfusion of apparently compatible RBCs in patients with RBC antibodies with a low titer and which went undetectable during pretransfusion testing. Following the transfusion of RBCs containing the antigen the patient had been presensitized against, an anamnestic response occurs with a rapid increase in the antibody titer between 1 and 2 weeks. Because these antibodies are IgG and recognize antigens of the Kidd, Duffy, Kell, Rh, and MNS systems, extravascular hemolysis is expected. Patients may complain of weakness and jaundice, and the laboratory workup will show a drop in hematocrit level, circulating microspherocytes, increased levels of lactate dehydrogenase and bilirubin, and a positive result on DAT. Using a type and screen procedure, a new RBC alloantibody can be identified unless the antibody has bound to the transfused RBCs. In those cases, an elution is essential to determine the antibody specificity. A positive DAT result following the transfusion due to a new alloantibody but without signs of hemolysis occurs more often than a DHTR and is termed a delayed serological transfusion reaction.

**Transfusion-Associated Graft-vs-Host Disease**

Recipients of transfusion who are immunocompromised are at risk for developing TA-GVHD, a potentially fatal complication. The transfusion of viable T lymphocytes and the patient’s inability to mount an immune response, either due to immunosuppression or due to similarity in HLA (such as when a donor is a first-degree relative), allows the lymphocytes to survive and proliferate in the recipient. Patients with lymphoid malignancies (particularly Hodgkin lymphoma), those undergoing chemotherapy with purine analogs or fludarabine, or those with cellular immunodeficiency, as well as neonates, are at risk for developing TA-GVHD. Clinically, TA-GVHD is similar to GVHD post–stem cell transplantation, but it occurs earlier (≤ 2 weeks of the transfusion) and suppresses bone marrow. TA-GVHD presents as a rash with fever, diarrhea, cholestasis, nausea, vomiting, and pancytopenia. Diagnosis is usually clinical, supported by biopsies from the skin, liver, or gastrointestinal tract, and sometimes with molecular techniques to determine genetic chimerism. The mortality rate is high because no effective treatment has been ascertained and the neutropenia caused by TA-GVHD is profound. The best strategy for health care professionals is to prevent the occurrence of TA-GVHD by irradiating the cellular blood components.

**Post-Transfusion Purpura**

Post-transfusion purpura is a rare immunological phenomenon characterized by sudden thrombocytopenia that takes place 2 to 14 days following a blood transfusion. It is caused by platelet alloantibodies (mostly anti-HPA-1a) in a patient previously sensitized from pregnancy or transfusion. Because the thrombocytopenia is typically severe (< 10 × 10^9/L), patients complain of petechial, purpura, or mucosal bleeds. The diagnosis of post-transfusion purpura is confirmed by the detection of platelet-specific alloantibodies in the serum. Most cases are self-limited and the platelet count recovers within 5 weeks. IVIG alone or in combination with corticosteroids is the mainstay of treatment. Patients with severe bleeding may benefit from platelet transfusions, preferably with units lacking the offending antigen.

**Red Blood Cell Alloimmunization**

The transfusion of RBCs may induce alloantibodies, potentially causing major problems in chronically transfused patients such as those with myelodysplastic syndromes. Chronically transfused patients who are also minorities may be at greater risk when receiving RBCs from a primarily Caucasian donor population, as is typically seen in patients with sickle cell disease. Although clinical factors that affect the rate of alloimmunization have been suggested, predicting which patients will form 1 or more alloantibodies after each RBC transfusion is not possible. Sanz et al reported that alloimmunization occurred in 15% of transfusion-dependent patients with myelodysplastic syndromes or chronic myelomonocytic leukemia and that the incidence of alloimmunization increased with the number of donor units.

**Platelet Alloimmunization**

Because platelets express HLA- and platelet-specific antigens, they may also induce alloantibodies. Sensitization may occur from pregnancy, transfusion, or transplantation and lead to platelet refractoriness (lack of appropriate response from transfusion). Although clinical factors, such as fever, sepsis, disseminated intravascular coagulation, splenomegaly, and active bleeding, as well as drug use, are more likely to cause decreased response from platelet transfusions than alloantibodies, the latter may be difficult.
to overcome. Because ABO incompatibility may compromise post-transfusion platelet count increments, patients may benefit from a trial of ABO-compatible platelets before the initiation of HLA-matched platelet transfusions. The best strategy to prevent platelet refractoriness is to avoid allogeneic transfusion by using exclusively leukoreduced RBCs and platelets. Alloimmunization to the D antigen (Rh) may be another concern if Rh-negative patients receive Rh-positive platelet transfusions. Rh antigens are not expressed on platelets, but they are present in the few RBCs in each unit of platelets. Although one study has concluded that the risk of developing anti-D is negligible and does not warrant the use of Rh immunoglobulin to prevent it, health care professionals should make a decision on a case-by-case basis when treating a patient who may become pregnant in the future.

Transfusion-Related Immunomodulation

Several lines of evidence, both in vitro and in vivo, have suggested that allogeneic transfusions alter the recipient's immune system and his or her ability to respond to infections and tumor antigens. However, transfusion-related immunomodulation (TRIM) continues to be a debatable complication of transfusion. TRIM may be multifactorial and possibly mediated by allogeneic mononuclear cells, leukocyte-derived soluble mediators, or soluble HLA peptides, among others. A review by Refaai and Blumberg of TRIM summarizes the effects of transfusion in the immune system as the following:

- Decreased Th1 and increased Th2 cytokine production in vitro
- Reduced responses in mixed lymphocyte culture
- Decreased proliferative response to mitogens or soluble antigens in vitro, thus causing impaired delayed-type hypersensitivity skin responses
- Increased CD8 T cells or suppressor function in vitro
- Decreased natural killer cells and activity in vitro
- Decreased CD4 helper T cells
- Decreased monocyte/macrophage function in vitro and in vivo
- Enhanced production of anti-idiotypic antibodies suppressive of mixed lymphocyte response in vitro
- Decreased cell-mediated cytotoxicity against target cells in vitro
- Humoral alloimmunization to cell-associated and soluble antigens
- Increased T-regulatory cells and function

Iron Overload

In addition to patients with hemoglobinopathies (e.g., thalassemia, sickle cell disease), those with myelodysplastic syndromes and aplastic anemia often require chronic transfusion support. Transfusion dependency in myelodysplastic syndromes has been associated with worse outcomes, including decreased rates of survival. Chronic transfusions cause significant iron overload because iron absorption is tightly regulated and the body has limited ability to excrete excess iron. Considering that 1 unit of RBCs has 200 to 250 mg of iron, most patients will develop iron overload after transfusion of 10 to 20 units. Deposition of iron in the parenchymal tissues and reticuloendothelial cells causes progressive end-organ damage such as hepatomegaly and liver dysfunction, heart failure, hypogonadism, diabetes mellitus, skin pigmentation, and arthropathy. For this reason, the debate regarding iron chelation therapy in myelodysplastic syndromes is currently ongoing despite the lack of data from randomized controlled trials.

Conclusions

Transfusion safety encompasses the continuum from donor qualification and screening to the appropriate choice of blood components and the monitoring of patients for adverse events. Patients with malignancy constitute a unique group, especially when disease- or treatment-induced bone marrow failure causes severe pancytopenia and demands transfusions. Furthermore, their clinical condition may contribute to transfusion reactions while making their recognition more challenging. Although extensive and strong evidence supports a restrictive transfusion approach, the data are limited to patients without malignancies; therefore, extrapolation is not possible. Nonetheless, a judicious approach to transfusion, as well as the administration of single units followed by patient assessment, will help to decrease the likelihood of adverse events in patients with cancer undergoing transfusion.

References


