Transfusion reactions remain a common complication of transfusion therapy; reactions affecting the lungs are some of the most serious. Several different mechanisms are responsible for pulmonary transfusion reactions, and most cause adverse effects in addition to lung injury. Fluid overload can lead to pulmonary edema, antibodies reacting with plasma proteins can cause bronchospasm and anaphylaxis, and particulate matter can produce microemboli. These reactions are well understood and usually can be prevented. Transfusions are also associated with acute lung injury and acute respiratory distress syndrome (ARDS), but their etiology is poorly understood and they remain clinically problematic. Neutrophil antibodies cause some of these serious as well as mild pulmonary reactions, but the exact role of leukocyte antibodies in pulmonary reactions remains unclear. Other blood donor, blood component, and transfusion recipient factors likely play a contributing or modulating role in pulmonary transfusion reactions, but prospective studies are needed to better understand their role.

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Pulmonary Transfusion Reactions
David F. Stroncek

Blood transfusions are associated with many complications, including hemolysis, fever, infection, cutaneous eruptions, and pulmonary reactions. For many years transfusion-transmitted infections were the leading cause of morbidity and mortality associated with transfusions. The discovery of hepatitis B and hepatitis C viruses, and human immunodeficiency virus (HIV), with the understanding of the natural history and mode of transmission of these viruses, has led to the identification of risk factors for carriers of these infections. The exclusion of individuals who are members of groups or populations at risk for carrying these viruses resulted in a significant reduction in the probability of transmission of these infections by blood transfusion. Molecular characterization of these viruses led to the development of serological and molecular diagnostic tests and a further reduction in their transmission by transfusion. Assays currently used to detect viral RNA in samples from blood donors are so sensitive that the chances of any one unit of blood transmitting hepatitis B are 1 in 205,000 to 488,000, hepatitis C are 1 in 1,935,000, and HIV are 1 in 2,135,000.¹

Transfusion reactions are a more common complication of blood product administration. A multicenter clinical trial of different types of platelet transfusions in patients with leukemia found that reactions occurred in 2.2% of transfusions and 22% of patients.² These reactions included an increase in temperature of 2°C, chills with rigors, extensive urticaria, bronchospasm, cyanosis, and dyspnea.

Pulmonary complications represent some of the most serious types of transfusion reactions (Table 1). The types and frequency of pulmonary transfusion reactions have changed over time. When whole blood was the most frequent blood component transfused, pulmonary edema due to circulatory overload was more common, and when blood was stored in glass bottles, lung injury due to an air embolism or a blood transfusion contaminated with bacteria or endotoxin was more problematic. Pulmonary transfusion reactions due to allergic reactions to plasma proteins and leukoagglutinins were described many years ago and are still clinically relevant.

While tremendous progress has been made in reducing the risk of transmission of clinically relevant viruses, progress toward understanding some types of transfusion reactions has been much slower. Severe pulmonary reactions occurring within a few hours of a transfusion were first described in the mid 20th century and still remain clinically important. Severe pulmonary transfusion reactions can sometimes be fatal and are now the leading cause of transfusion-related mortality,³ but they are not completely understood. Studies in the 1950s and 1960s suggested that acute lung injury was due to the passive transfusion of antibodies reactive to peripheral blood leukocytes present in the recipients. While leukocyte antibodies likely cause some of these reactions, their transfusion cannot explain many pulmonary transfu-
sion reactions. Recent evidence suggests that bioactive factors that accumulate during the storage of blood products may contribute to lung injury. The wide variety of mechanisms that can cause pulmonary transfusion reactions will be reviewed.

**Lung Injury and Transfusion**

**Circulatory Overload**

Intravenous administration of blood, like any fluid, can cause circulatory overload, pulmonary edema, and congestive heart failure. With the advent of blood component therapy and the use of packed red blood cell (RBC) transfusions rather than whole blood, frank congestive heart failure has become less frequent. However, even though packed RBC components have replaced whole blood, circulatory overload continues to occur in one in 700 of transfusion recipients. One study found that 1% of transfusion recipients experience circulatory overload. These patients often have a significant positive fluid balance before transfusion of the component causing the reaction. Older patients and those with severe anemia, renal failure, and underlying cardiac disease are at greater risk for transfusion-associated circulatory overload. Pulmonary edema caused by fluid overload can be treated with supplementary oxygen therapy and diuretics.

Patients experiencing circulatory overload after transfusion can develop dyspnea, tachypnea, and tachycardia. Chest x-rays show cardiomegaly and pulmonary edema, but these findings are not specific for circulatory overload and can be observed with other types of transfusion reactions. Elevations in central venous pressure and pulmonary wedge pressure are more specific for circulatory overload, but invasive procedures are required to measure these parameters.

Recent studies have found that the determination of blood levels of brain natriuretic peptide (BNP) is useful in diagnosing transfusion-associated circulatory overload. BNP is secreted by cardiac ventricles when ventricular pressure or volume is increased, and elevated BNP levels are found in patients with heart failure and dyspnea. A recent study that compared BNP levels before and after transfusion found that BNP levels increased 1.5-fold in transfusion recipients with fluid overload, but the levels did not change in a control group of transfusion recipients. While increases in BNP levels can be helpful in diagnosing circulatory overload, elevated levels of BNP do not always exclude other types of transfusion reactions since BNP levels can be elevated for other reasons, including renal failure, myocardial infarction, and lung disease associated with right-sided heart failure.

**Allergic Reactions**

Transfusions can cause a wide variety of allergic reactions due to antibody–antigen complex formation. These reactions typically occur within 1 hour of a transfusion and range from mild urticaria, flushing, hives, abdominal cramping, wheezing, and hypotension, to severe anaphylactic manifestations of angioedema, bronchospasm, stridor, shock, and cardiac arrest.

Antibodies to IgA are the commonest cause of anaphylactic transfusion reactions. Selective IgA deficiency is the most prevalent type of immune deficiency. Approximately one in 400 individuals lacks IgA or a subclass or allotype of IgA, and about 30% to 40% of patients with IgA deficiency develop IgG or IgM antibodies directed to IgA. Nevertheless, many individuals with anti-IgA do not have severe transfusion reactions when transfused with products containing IgA. It is estimated that one in 50,000 transfusions is associated with an anaphylactic reaction due to anti-IgA.

If a patient who has experienced a transfusion reaction due to anti-IgA requires another transfusion, washed blood components or components from IgA-deficient donors should be used. RBC components should be washed. Patients with anti-IgA who require fresh frozen plasma (FFP) should receive plasma from a donor who is IgA-deficient, as determined by a highly sensitive IgA detection assay. Platelet components may be washed or from IgA-deficient donors. Usually, registries of rare blood donors list FFP from IgA-deficient donors and platelets can be obtained from IgA-deficient donors.

Intravenous immunoglobulin may contain IgA, and thus cause anaphylactic reactions in patients with anti-IgA. A method to prevent anti-IgA–mediated reactions to intravenous immunoglobulin has been reported. In one study, pretransfusion treatment of intravenous immunoglobulin with autologous plasma from two patients with anti-IgA prevented transfusion reactions.

Antibodies to IgA account for only 18% of all anaphylactic transfusion reactions. The cause of most other reactions is not known, but there have been reports of allergic transfusion reactions to haptoglobin, penicillin, and aspirin present in blood components. In addition, an allergic reaction has resulted from the passive transfusion of an antibody directed to cephalothin in a person taking that drug.

**Bacterial-Contaminated Blood Components**

The transfusion of blood components contaminated with bacteria can cause fevers, sepsis, septic shock, dyspnea, acute respiratory distress syndrome (ARDS), and death. The source may be a skin or environmental bacteria that contaminates the component during the collection process. In rare cases, the blood donor may be bacteremic at the time of blood
donation due to an undiagnosed colon cancer\textsuperscript{18,19} or asymptomatic bacteremia\textsuperscript{20,21}.

Bacterial contamination is most problematic for platelet components since they can be stored for up to 5 days at room temperature. Approximately one in 2,000 platelet components are contaminated with bacteria. Bacteria entering the platelet concentrate at the time of collection grows exponentially throughout the storage period.\textsuperscript{22} Platelets stored longest have the highest levels of bacteria and are most likely to cause severe reactions.

In 2003, blood centers in the United States began to assay apheresis platelets for bacterial contamination using cultures or surrogate tests. Testing is usually performed 24 hours or longer after the platelets are collected to allow bacterial growth and to increase the sensitivity of the assay. These testing strategies have reduced but have not eliminated the risk of bacterial contamination. Some blood centers in Europe are treating platelet components with agents to inactivate pathogens. While these pathogen inactivation systems were primarily designed to reduce levels of viral pathogens, they also are effective to some extent in inactivating bacteria.\textsuperscript{23}

RBC components are also subject to bacterial contamination. Because RBC components are stored at 4°C, organisms most often found in RBCs differ from those frequent in platelet components. The pathogens \textit{Yersina enterocolitica} and \textit{Pseudomonas fluorescens} are most widely present in RBC components.\textsuperscript{17} Twenty-one cases of sepsis associated with the transfusion of \textit{Y enterocolitica}–contaminated RBCs were reported in the United States between 1985 and 1996.\textsuperscript{17} Leukocyte reduction filters can remove \textit{Yersina} from RBC components.\textsuperscript{24} Since 1998 a number of countries have mandated the universal leukocyte reduction of all cellular blood components,\textsuperscript{25} which may have reduced the incidence of bacterial contamination of RBC components. A 2005 study in France estimated that one in 6.5 million RBC components was contaminated with \textit{Y enterocolitica}.\textsuperscript{26}

**Hemolytic Reactions**

Acute hemolytic reactions can be associated with pulmonary symptoms. Intravascular hemolysis due to the reaction of isohemagglutinins or alloantibodies with incompatible RBCs can cause fever, hemoglobinuria, jaundice, anemia, renal failure, and disseminated intravascular coagulation. Patients may experience back pain, restlessness, nausea, skin flushing, and dyspnea.\textsuperscript{27,28} Dyspnea is thought to be caused, at least in part, by complement activation by antibody-antigen complexes.\textsuperscript{27}

**Granulocyte Transfusions**

Granulocyte transfusions are due to the reaction of isohemagglutinins or alloantibodies with incompatible RBCs can cause fever, hemoglobinuria, jaundice, anemia, renal failure, and disseminated intravascular coagulation. Patients may experience back pain, restlessness, nausea, skin flushing, and dyspnea.\textsuperscript{27,28} Dyspnea is thought to be caused, at least in part, by complement activation by antibody-antigen complexes.\textsuperscript{27}

**Particulate Material**

During the storage of cellular blood products, aggregates up to 200 μm diameter can form; these aggregates are composed of leukocytes, platelets, and fibrin.\textsuperscript{34} RBC components are routinely transfused through standard filters with a pore size of 170 microns, which removes the largest particles. However, studies conducted in the 1970s suggested that debris in stored whole blood caused pulmonary microembolism, which resulted in pulmonary insufficiency in massively transfused trauma patients. One study found that pulmonary insufficiency in massively transfused patients could be prevented by filtering blood at the time of transfusion using filters with a pore size of 40 μm.\textsuperscript{35} However, several subsequent studies failed to find that particulate emboli contributed to respiratory failure in massively transfused trauma patients.\textsuperscript{36,37} Commercial microaggregate filters with a pore size of 40 μm have been developed but are used infrequently.

The preparation of blood components has changed dramatically since the 1970s. Many RBC components are now
filtered to remove leukocytes shortly after collection, and many of these filters also remove platelets. The use of leukocyte-reduction filters likely prevents the formation of particles during storage. Recently, particles have been noted in red cell components shortly after collection, but leukocyte-reduction filters also have been reported to remove these particles.30,31

The transfusion of large quantities of blood over a short period of time, however, remains a risk factor for ARDS.40,41 In one study, the transfusion of intensive care unit (ICU) patients with 15 or more RBC units over 24 hours was a risk factor for ARDS.40 The transfusion of more than 10 units of RBCs to patients with blunt trauma was also an independent risk factor for ARDS.42

Air Emboli
Air entering a vein during a blood transfusion rapidly travels to the pulmonary artery. Initially, an air emboli causes a rise in venous pressure and cyanosis, followed by a fall in systolic blood pressure and tachycardia. Death can occur due to respiratory failure,43,44 and the inadvertent intravenous administration of 60 to 80 mL of air can cause serious illness.45 Fortunately, conversion more than 50 years ago from glass to flexible plastic containers for blood collection, storage, and transfusion has markedly reduced the risk of air emboli.46 However, this risk has not been completely eliminated.

Leukocyte Antibodies
Case Reports
Leukocyte antibodies were first associated with transfusion reactions more than 45 years ago. In the 1950s transfusions were reported to be linked to acute pulmonary edema that was not due to circulatory overload and heart failure.47 In 1951 Barnard reported that a patient with acute leukemia experienced acute pulmonary edema as a result of a transfusion reaction rather than fluid overload.47 In the 1950s transfusions were reported to be linked to acute pulmonary edema that was not due to circulatory overload and heart failure. In 1957, Brittingham described a severe pulmonary transfusion reaction: leukoagglutinins appeared in about half of patients given 25 or more transfusions.49 As part of this series of studies, plasma known to have leukoagglutinins was transfused. The transfusion of two patients with 250 mL of plasma containing weak leukoagglutinins caused mild reactions in both recipients. However, the transfusion to a third patient of 50 mL of plasma with strong leukocyte agglutinins resulted in immediate faintness followed in about 45 minutes by vomiting, diarrhea, chills, fever, severe hypotension, severe tachypnea, dyspnea, cyanosis, and initial leukopenia succeeded by leukocytosis. The following day the transfusion recipient was comfortable, but a chest x-ray showed marked bilateral pulmonary infiltrates and a small pleural effusion; 3 days later, the x-ray abnormalities had disappeared.49

Several cases of pulmonary edema unrelated to circulatory overload following transfusion were reported in the 1960s, and they were sometimes called hypersensitivity reactions. In 1966 Philpott and Fleischner reported 3 cases,50 and in 1968 Ward et al reported one case of hypersensitivity reaction to blood transfusion. Their patient was a 19-year-old man who developed a fever, cough, and urticarial skin lesions approximately 2 hours after the initiation of a whole blood transfusion. A chest x-ray 24 hours later showed bilateral, multinodular, predominantly perihilar, pulmonary infiltrates, without evidence of heart failure; changes improved 2 days after the transfusion reaction and resolved completely 4 days after the reaction. The patient’s serum contained leukoagglutinins, and mild hypereosinophilia was noted. While the donor of the unit of blood was not tested for leukocyte antibodies, the authors speculated that the leukoagglutinin in the patient was passively transfused with the blood component. In the 1970s the concept that leukocyte antibodies cause pulmonary transfusion reactions became widely accepted. In 1970, Ward described four cases of noncardiac pulmonary edema associated with transfusion.52 These reactions were associated with chills, fever, tachycardia, nonproductive cough, and dyspnea. Four patients had chest x-rays that demonstrated bilateral, perihilar infiltrates without evidence of cardiomegaly or pulmonary vascular enlargement. Leukoagglutinins were found in the sera of individuals who donated blood administered to two of the four recipients and in one recipient. No leukoagglutinins were detected in the fourth patient or donor. The acute lung injury in these patients was attributed to “leukoagglutinin transfusion reactions.”52

In 1971, Thompson et al reported two cases of “hypersensitivity” transfusion reactions.53 Both patients became dyspneic and febrile during a whole blood transfusion, and chest x-rays showed extensive fluffy bilateral infiltrates compatible with pulmonary edema. The x-ray changes began to resolve after 24 hours in one patient and 72 hours in the second. Leukoagglutinins were detected in donors of both implicated units. The authors stated that “Although the demonstration of antirecipient leukoagglutinins in the donor serum in both our cases suggests that the acute pulmonary edema response was related to an immunologic effect on leukocytes, such a relation is not conclusively established.”53 However, they suggested that either donors be screened for leukoagglutinins or whole blood from multiparous donors not be transfused. In 1976, Andrews et al reported a patient who developed dyspnea and fever 5 hours after 3 units of whole blood were transfused.54 A chest x-ray showed bilateral pulmonary edema; dyspnea resolved within 8 hours. HLA antibodies were detected in the donor of the second unit, but not in the donors of the other two units. The antibodies in the second unit were specific for HLA-2 (HLA-A*02) and 4+ (HLA-Bw4), and the patient expressed 4+. The reaction was attributed to leukocyte antibodies: “To provide laboratory confirmation of this reaction, it is essential to search for leukocyte antibodies.”54
Series of Cases

In the 1980s, the term “transfusion-related acute lung injury” (TRALI) was first used and antibodies to HLA class I antigens were generally considered an important cause of TRALI. Pulmonary transfusion reactions were first called TRALI in 1983 by Popovsky et al in their description of of acute lung injury associated with transfusion; their five patients were given a total of 19 blood components and one component transfused to each patient contained an HLA-specific antibody.

A large series of pulmonary transfusion reactions was reported by Popovsky and Moore in 1985: 36 cases of acute lung injury following transfusion at a single institution from June 1982 through October 1984. During that time the institution transfused 194,715 blood components to 22,292 patients. The authors evaluated all patients who experienced respiratory distress within 4 hours of a transfusion, and they defined acute lung injury as x-ray evidence of pulmonary infiltrates. Seventy-two percent of the patients required mechanical ventilation. Eighty percent of patients with TRALI had a rapid resolution of pulmonary infiltrates and return of arterial blood gas values to normal within 96 hours after the initial respiratory insult. However, pulmonary infiltrates persisted for at least 7 days after the transfusion reaction in 17% of the TRALI patients. The mortality associated with TRALI in these patients was 6%. Lymphocytotoxic antibodies were found in 72% of the donors, and antibodies with specificity to HLA antigens were found in 65% of the donors.

Following the establishment of hemo-vigilance programs in the 1990s, interest in pulmonary transfusion reactions has been renewed. Several series of TRALI cases have been reported by national programs that monitor adverse events associated with transfusions. In Quebec, Canada, between 2000 and 2003, 22 cases of TRALI were reported to Hema-Quebec; implicated blood components included RBCs (eight cases), platelets (six cases), plasma (five cases), and cryoprecipitate (one case). The implicated donors tended to be older and have more prior donations than had nonimplicated donors. The proportion of female donors was the same among implicated and nonimplicated donors. Canadian hospitals, other than those in Quebec, reported 78 cases of TRALI between November 2000 and August 2003; the mortality rate was 17%. Serum was available to test for leukocyte antibodies in 316 of 414 implicated donors. Leukocyte antibodies were detected in 24% of the donors. Neutrophil antibodies were found in 9% and HLA antibodies in 18%. Only 43% of implicated donors with antibodies were female.

A summary of all TRALI cases in a single hospital in the United Kingdom over 12 years described 11 cases. The incidence of TRALI was one in 800 platelet transfusions, 1 in 7,900 FFP transfusions, and one in 17,880 RBC transfusions. Implicated donors were tested for leukocyte antibodies in 10 of 11 cases, and in all 10 leukocyte antibodies were found in at least one of the implicated donors. HLA class II antibodies were present in four cases, HLA class I antibodies in three cases, both class I and II in one case, and in two cases the antibodies were not well characterized.

A review of all serious transfusion reactions reported to the American Red Cross Blood Services between 1992 and 1998 found 46 cases of TRALI. Fifty-three percent of the cases involved females; their mean age was 54 years and ranged from 22 to 82 years. While 87% of patients recovered, of the 13% of patients who died, TRALI was felt to be a contributing factor. Implicated units included red cells, platelets, and FFP and in 50% of the cases a leukocyte antibody was found in an implicated donor.

Case-Controlled Studies

While case reports and series of cases demonstrate that transfusions can cause serious pulmonary reactions, they do not provide useful information as to the relative contribution of leukocyte antibodies. While HLA antibodies are frequently found in donors implicated in severe pulmonary transfusion reactions in individual cases, interpretation is confounded as multiple donors are usually implicated in TRALI and HLA antibodies are frequently found in multiparous female donors. Often, two to four donors and sometimes as many as nine donors are suspected. One study of apheresis donors found HLA antibodies in 17% of female donors. HLA antibodies were found in 26.3% of women with three or more pregnancies, 14.6% with one or two pregnancies, and 7.8% with no history of pregnancy. The high frequency of HLA antibodies among blood donors makes it difficult to distinguish whether HLA antibodies are common in blood components from donors implicated in pulmonary reactions because they are responsible for the reactions or because HLA antibodies are common in blood donors. Furthermore, severe pulmonary transfusion reactions may be more likely to be reported if HLA antibodies are present in an implicated donor. The question of the relative role of antibodies specific to neutrophil and HLA antigens is therefore best addressed with controlled studies.

One case-controlled study of TRALI has been reported. This study suggested that bioactive lipids that prime neutrophils play a greater role in TRALI than do leukocyte antibodies and further that some subsets of patients were more likely to experience TRALI. Silliman et al retrospectively analyzed 90 sequential TRALI cases at a single institution between 1991 and 1995. Among these 90 cases, the medical records of 46 sequential TRALI patients who received whole blood platelets were reviewed. In addition, the medical records of a control group of 225 randomly selected hospitalized subjects who also received whole blood platelet transfusions during the same period of time, but who did not experience a transfusion reaction, were assessed. The implicated blood components in the 90 TRALI cases included 72 units of whole blood derived platelets, 2 units of apheresis platelets, 15 units of RBCs, and 1 unit of FFP. TRALI was not associated with the recipients’ age, sex, number of previous transfusions, type of previous transfusion, or ABO incompatibility of the transfusion. Platelet storage time was slightly, but, significantly, longer for TRALI implicated units than for control units (4.5 ± 0.2 days vs 4.2 ± 0.1 days). Patients with hematologic malignancies and cardiac patients were at greater risk for TRALI. Leukocyte antibodies were tested in 104 donors implicated in 28 cases and in 24 donors whose platelets were transfused to five control patients. The frequency of neutro-
Neutrophil antibody reactions found that RBC transfusions were associated with an increased risk of and increased mortality from ARDS.\(^62\) While other investigations have concluded that massive transfusions are associated with ARDS, this study found that transfusions of a single red cell unit increased the risk of developing ARDS and ARDS mortality. A retrospective review of 5,260 ICU patients observed over 7 years found that any RBC transfusion given to an ICU patient 48 hours after admission was a risk factor for ARDS, ventilator-associated pneumonia, and death.\(^63\) A single-institution retrospective cohort analysis of 115 ICU patients with coagulopathy without active bleeding showed that 44 patients transfused with FFP had a greater incidence of new-onset acute lung injury than those that did not receive these transfusions.\(^64\)

**FFP and Pulmonary Transfusion Reactions**

While severe pulmonary transfusion reactions are rare, mild pulmonary transfusion reactions are much more common.\(^61\) In a prospective, randomized, double-blinded, cross-over study, cardiopulmonary reactions to FFP transfusions were determined. Among 100 ICU patients, the cardiopulmonary effects of a transfusion of a single unit of FFP from multiparous women who had three or more live births was compared with those who received a unit of control plasma from donors who were never transfused or had never been pregnant.\(^61\) The mean arterial pressure increased following the transfusion of control plasma. Further, the transfusion of multiparous donor plasma and the ratio of arterial oxygen partial pressure to inspired oxygen fraction fell following the transfusion of multiparous donor plasma but not of control plasma. Overall, five of the 200 transfusions resulted in some type of transfusion reaction: one febrile, three mild pulmonary reactions, and one TRALI. All four pulmonary reactions were associated with the transfusion of multiparous donor plasma. Neutrophil-specific, but no HLA-specific antibodies were found in the multiparous donor plasma causing the TRALI reaction and one of three of mild pulmonary reactions. Unfortunately, plasma that did not cause reactions was not tested for neutrophil or HLA antibodies. While the transfusion of FFP from multiparous women appears more likely to cause pulmonary reactions, the mechanism of these reactions is not known. Multiparous women are often alloimmunized, and neutrophil, but not HLA antibodies, are more likely responsible for some of these reactions.

**Lung Injury and Transfusions in ICU Patients**

Observations of large numbers of ICU patients have established that transfusions are associated with ARDS.\(^62\) A prospective study of acute respiratory distress in intensive care unit patients identified transfusion as a risk factor for ARDS.\(^62\) A prospective study of 688 ICU patients at risk of ARDS found that RBC transfusions were associated with an increased risk of and increased mortality from ARDS.\(^62\) While other investigations have concluded that massive transfusions are associated with ARDS, this study found that transfusions of a single red cell unit increased the risk of developing ARDS and ARDS mortality. A retrospective review of 5,260 ICU patients observed over 7 years found that any RBC transfusion given to an ICU patient 48 hours after admission was a risk factor for ARDS, ventilator-associated pneumonia, and death.\(^63\) A single-institution retrospective cohort analysis of 115 ICU patients with coagulopathy without active bleeding showed that 44 patients transfused with FFP had a greater incidence of new-onset acute lung injury than those that did not receive these transfusions.\(^64\)

While clinical observations suggest that RBC and FFP transfusions cause or contribute to lung injury, they provide no evidence as to cause of the lung injury. Lung injury due to transfusion appears to be common among ICU patients. A well-designed prospective study of transfusion reactions in these highly monitored patients would yield important information about the pathophysiology of pulmonary reactions; even a relatively small number of patients transfused with FFP could be especially useful.

### Possible Mechanisms of Lung Injury Following Transfusion

Because of the clinical importance of severe pulmonary transfusion reactions, many investigators have attempted to determine their causes (Table 2). Case reports have focused on leukocyte antibodies as responsible for severe pulmonary transfusion reactions. Animal models and laboratory studies support such a role for leukocyte antibodies. However, leukocyte antibodies are not present in many blood components that cause pulmonary transfusion reactions, and other mechanisms may be important. Because of the lack of prospective randomized studies of pulmonary transfusion reactions, it is not known how important any of the proposed mechanisms are in the pathogenesis of lung injury following transfusion. Assumptions that often are based on little evidence have likely hindered progress toward understanding pulmonary transfusion reactions. Fortunately, recent studies have investigated the role of factors other than leukocyte antibodies in these reactions.
Neutrophils in Lung Injury

Evidence for a role of neutrophils in lung injury was provided in 1977 by Craddock et al, who found that activated neutrophils can cause lung injury and respiratory distress. During hemodialysis, complement component C5a was produced, which activated neutrophils; these activated neutrophils aggregated with other neutrophils and became trapped in the pulmonary microvasculature. The dialyzed patients became transiently neutropenic and developed pulmonary vascular leukostasis, interstitial edema, and hypoxemia.

Neutrophils are important early in the development of acute lung injury and ARDS. In vitro, neutrophils can damage cultured human pulmonary microvascular endothelium. Animal models have shown that neutrophils are required for or contribute to acute lung injury.

Severe pulmonary transfusion reactions have been associated with transient leukopenia. Circulating levels of granulocytes, lymphocytes, and/or monocytes have fallen transiently during or after pulmonary transfusion reactions. This transient leukocytopenia is thought to be caused by the interaction of patient leukocytes with the transfusion of leukocyte antibodies in the implicated blood component. The leukocytes become trapped in the transfusion recipients’ lungs, resulting in pulmonary leukostasis which contributes to the pulmonary reaction. Nakagawa and Toy reported three patients with TRALI who experienced transient neutropenia; neutrophil counts fell to 80% to 90% of pretransfusion counts for several hours. One patient had antibodies specific to HLA class I antigens and two had antibodies to HLA class I and class II antigens. Marques et al reported two cases with TRALI who developed transient neutropenia and monocytopenia; in both cases antibodies specific to HLA class I and II antigens were found in the implicated blood components. Yomtovian et al described a patient with TRALI caused by the transfusion of antibodies to human neutrophil antigen-1b (HNA-1b) or NA2; the recipient also became leukopenic.

Leukocyte Antibodies and Pulmonary Reactions

Case reports have suggested a link between the transfusion of neutrophil-specific antibodies and lung injury: transfusion of neutrophil antibodies specific to HNA-1a, HNA-1b, HNA-2a, and HNA-3a antigens cause severe pulmonary reactions. Antibodies specific to HNA-3a seem to be particularly potent in causing TRALI. Three fatal cases of TRALI following the transfusion of platelet or FFP components containing HNA-3a specific antibodies have been published recently.

The role of neutrophil antibodies in severe pulmonary transfusion reactions is supported by “look-backs” that evaluated previous recipients of blood components with neutrophil antibodies. Look-back studies have been performed with two repeat donors with anti–HNA-3a who were implicated in fatal cases of TRALI. A review of the transfusion of 25 previous donations from one of the donors found no transfusion reactions. However, a review of 36 transfusions from another donor found 15 transfusion reactions, eight of which included respiratory symptoms, some of which were severe.

Neutrophil antibodies cause acute lung injury in animal models. Seeger et al used an isolated rabbit lung perfusion model to demonstrate that severe lung vascular leakage was caused by neutrophil antibodies specific to HNA-3a after a 3- to 6-hour latent period. The presence of neutrophils, complement, and anti–HNA-3a were all required to induce lung edema. Using an isolated rat lung model, Sachs et al showed that anti–HNA-2a induces pulmonary edema after a 2- to 3-hour lag period. Antibody-induced edema was dependent on leukocytes but independent of complement. The administration of the neutrophil chemoattractant and stimulant N-formyl-methiyl-leucyl-phenylalanine (fMLP) alone did not cause pulmonary edema, but when fMLP was infused with anti–HNA-2a the onset of pulmonary edema was more rapid.

HLA antibodies have been implicated in pulmonary transfusion reactions. In addition, look-back studies also have reported donors with HLA antibodies who were implicated in TRALI; however, the transfusion of HLA antibodies infrequently causes TRALI. In one review of the records of 18 patients who were transfused with a blood component from either a TRALI-implicated donor with antibodies to HLA class II antigens or a TRALI-implicated donor with antibodies to HLA class I and class II antigens, only one of the 18 experienced a transfusion reaction (the patient was on a ventilator and experienced a fall in arterial oxygen tension that was associated with the transfusion of FFP). In another investigation of the outcome of six previous transfusions from an apheresis platelet component donor with antibodies to both HLA class I and class II antigens, none of the transfusions caused reactions.

Toy et al reviewed the records of 103 patients who received a blood transfusion from a TRALI-implicated donor with an antibody broadly reactive with HLA class I and II antigens. One patient developed lung infiltrates, but it was not certain if they were due to a transfusion or hematopoietic stem cell engraftment syndrome. In a subset of 62 patients, serial chest x-rays were compared after transfusion of a TRALI-implicated unit and a control unit. A new or worsening pulmonary infiltrate was noted in four of the 62 patients after transfusion of both control and implicated units. In four other patients, a new or worsening infiltrate was noted only after transfusion of the implicated unit. However, this difference in incidence of infiltrates between control and implicated units was of borderline significance (P < .06).

Taken together, these data suggest that neutrophil antibodies likely play a role in TRALI, but there is less evidence to support a role for HLA antibodies in TRALI.

Bioactive Lipids and CD40L: Neutrophil Priming

TRALI can occur following the transfusion of blood components that do not contain leukocyte antibodies. At least some cases of TRALI are due to the transfusion of biologically active lipids, such as lysophosphatidylcholine (Lypo-
PC), that accumulate in both red cell and platelet components during storage. The bioactive lipids prime neutrophils and increase the toxic effects of activated neutrophils in the transfusion recipient. Bioactive lipids cause no direct lung damage or neutrophil activation; however, when neutrophils are exposed to them, the neutrophil response to activating factors is more intense than for neutrophils that have not been exposed to bioactive lipids. In vitro, Lyso-PC produced by stored RBC and platelet components increases activated neutrophil production of toxic oxygen species and enhances activated neutrophil-mediated damage of cultured human pulmonary microvascular endothelial cells. Animal models also show that blood cell-derived lipids contribute to acute lung injury. In a rat lung model, acute lung injury developed in lungs treated with lipopolysaccharide (LPS) followed by plasma from red cells stored 42 days or platelets stored 5 days but not in lungs treated only with LPS and plasma from fresh red cells or platelets. This effect was due to plasma lipids.

Clinical observations support a role for bioactive plasma lipids in TRALI. A retrospective study found neutrophil priming activity in patients with TRALI but not in controls with uncomplicated febrile or urticarial reactions. A prospective study of patients with TRALI found higher levels of neutrophil priming activity in units implicated in TRALI than in control (unimplicated) units.

CD40L

Another bioactive factor, CD40 ligand (CD40L), also has a role in TRALI. CD40L is released by platelets, and the levels of soluble CD40L increase in apheresis platelet components during storage. Furthermore, CD40L levels were greater in platelet components implicated in TRALI than in control platelet components. The molecule CD40 is expressed on macrophages, dendritic cells, and B cells. In animals, interactions of CD40 with CD40L are involved in acute lung injury, and the inhibition of the binding of CD40L to CD40 by anti-CD40L blocks the development of radiation-induced and ischemia-reperfusion lung injury in animal models.

Transfusion Recipient Factors

Patient factors seem to contribute to the development of pulmonary transfusion reactions (Table 3). That some but not all blood components from donors with neutrophil antibodies implicated in TRALI caused pulmonary reactions suggests that other factors are involved. In a nested case-control study of 46 consecutive patients experiencing TRALI and 235 hospitalized controls, patients being treated for hematologic malignancies and who had cardiopulmonary bypass surgery were more likely to experience pulmonary reactions.

While no other transfusion recipient factors have been identified that contribute to pulmonary transfusion reactions, patient cytokine and growth factor polymorphisms do contribute to other types of lung injury. Similar polymorphisms may also figure in the development of pulmonary transfusion reactions. Polymorphisms in the genes encoding vascular endothelial growth factor (VEGF), angiotensin-converting enzyme (ACE), and tumor necrosis factor-β (TNF-β) are associated with an increased risk of ARDS in ICU patients. A 936CT polymorphism in the gene that encodes VEGF affects plasma VEGF levels. The T allele is associated with lower levels of VEGF, and T allele homozygous and heterozygous ICU patients are at increased risk for ARDS. An insertion/deletion mutation of ACE affects its levels, with the deletion or D allele associated with higher plasma levels. ICU and coronary artery bypass graft patients who are homozygous for the D allele have an increased risk of ARDS. The 308GA polymorphism in the promoter of TNFβ influences TNF-α levels. Patients with the 308A allele have increased TNF-α levels and ICU patients with the 308A allele have a higher incidence of mortality from ARDS. These and other cytokine gene polymorphisms may affect the severity of pulmonary transfusion reactions, but they have been difficult to study in TRALI because of the low incidence of this syndrome.

Definition of Severe Pulmonary Transfusion Reactions

Some pulmonary transfusion reactions are due to well-characterized and well-defined reactions such as hemolytic reactions, allergic reactions, transfusion-associated circulatory overload, and the transfusion of products contaminated with bacteria. However, some of the most studied and most serious pulmonary transfusion reactions have been the subject of considerable confusion. Early studies of severe pulmonary transfusion reactions usually defined them as severe reactions characterized by the new onset of bilateral pulmonary edema, not resulting from heart failure or fluid overload. In 1983 Popovsky et al described TRALI as acute lung injury occurring within 4 hours of a transfusion and characterized by a chest x-ray showing new onset of florid bilateral lung infiltrates consistent with pulmonary edema without evidence of fluid overload. The term TRALI as defined by Popovsky and colleagues has gained widespread use. Major issues with the

### Table 3 Factors Contributing to Pulmonary Transfusion Reactions

<table>
<thead>
<tr>
<th>Donor</th>
<th>Product (storage)</th>
<th>Recipient</th>
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<tbody>
<tr>
<td>Neutrophil antibodies</td>
<td>Bioactive lipids</td>
<td>Anti-IgA</td>
</tr>
<tr>
<td>HLA antibodies</td>
<td>CD40L</td>
<td>Cardiac surgery</td>
</tr>
<tr>
<td>Aggregates</td>
<td>Erythrocyte antibodies</td>
<td>Cytokine polymorphisms</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Neutrophil antibodies</td>
<td>Antibody dependence</td>
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<tr>
<td></td>
<td>HLA antibodies</td>
<td>Anti-haptoglobin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cancer or blood disorder</td>
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definition of TRALI as used in most studies are that other risk factors for acute lung injury were not excluded and the results of leukocyte antibodies could and often were used to aid in the diagnosis.\(^9\)

Acute lung injury has many causes, and attributing lung injury to transfusion is often complicated by preexisting clinical conditions. Many transfused patients have medical illnesses that place them at risk for acute lung injury, such as infection, sepsis, septic shock trauma, disseminated intravascular coagulation, burns, cardiopulmonary bypass, and pneumonia. As a result, it is often difficult to distinguish acute lung injury due to transfusion or to the preexisting condition. A further complication is the bias that the transfusion of leukocyte antibodies always causes acute lung injury; this assumption has caused many transfusion services to base the diagnosis of acute lung injury due to transfusion on the presence or absence of leukocyte antibodies. Resolution of this confusion required a consensus definition of acute lung injury due to transfusion.

A National Heart, Lung and Blood Institute consensus group developed a definition of TRALI in 2005.\(^9\) TRALI was defined as acute lung injury occurring within 6 hours of a transfusion of a plasma-containing or plasma-derived blood product in a patient without preexisting acute lung injury or other acute lung injury risk factors.\(^9\) Acute lung injury is the acute onset of respiratory distress with (1) pulmonary artery occlusion pressure \(\leq 18\) mm Hg or without clinical evidence of left atrial hypertension, (2) bilateral infiltrates on chest x-ray, and (3) hypoxemia with a ratio of PaO\(_2\)/FIO\(_2\) \(\leq 300\) mm Hg or oxygen saturation of \(\leq 90\%\) on room air.\(^9\) Notably, this definition of TRALI is not dependent on leukocyte antibodies in the blood component.\(^9\)

The consensus group definition also allows for the diagnosis of TRALI when a patient has one or more acute lung injury risk factors. When acute lung injury meets all the criteria for TRALI except that another acute lung injury risk factor is present and the acute lung injury can be attributed only to transfusion, a diagnosis of TRALI can be made.

While it is important to perform all necessary laboratory tests to diagnose acute lung injury and to determine its etiology, the diagnosis of TRALI is made by excluding causes other than the transfusion. No test is available to make or confirm the diagnosis of TRALI. The detection of leukocyte antibodies or bioactive lipids in implicated blood components or donors should not be inferred to establish that the acute lung injury was due to the transfusion, and their absence should not be used to exclude TRALI.

The consensus group definition of TRALI is narrow, but if it is accepted and used appropriately, patients diagnosed with this condition will have more uniform characteristics than in the past. This narrower definition will facilitate the interpretation of clinical data on TRALI. However, this definition should not be employed to limit the study of pulmonary transfusion reactions only to TRALI. For some purposes, it may be valuable to examine less severe forms of pulmonary transfusion reactions. However, care should be taken to apply the term TRALI only to reactions meeting the new consensus definition.

### Evaluation of Donors Whose Blood Components Are Implicated in Pulmonary Reactions

Recent changes in American Association of Blood Banks standards require that donors implicated in TRALI be evaluated. The new standard states that “Donors implicated in TRALI or associated with multiple events of TRALI shall be evaluated regarding their continued eligibility to donate.”\(^9\) While this standard requires that all donors implicated in TRALI be evaluated, it also allows broad discretion in deciding if individuals can continue to donate. Since there is little consensus concerning the donor or blood component factors that are most important in causing pulmonary transfusion reactions, undoubtedly the policies and procedures used to implement this policy will vary greatly among centers.

Most centers will likely defer donors implicated in TRALI who have neutrophil-specific antibodies. The proportion of blood donors with neutrophil antibodies is very low. In one study, neutrophil antibodies were found in less than 0.1% of multiparous women,\(^9\) and in another, neutrophil antibodies were present in 1.1% of postpartum serum,\(^9\) but the antibodies were not detected after 1 year. Since the proportion of healthy blood donors with neutrophil antibodies is well below 1%, and as case reports, look-back studies, prospective studies, and animal models demonstrate that neutrophil-specific antibodies can cause pulmonary reactions, and in some cases TRALI, deferring donors with neutrophil-specific antibodies should not be controversial.

The decision to exclude implicated donors with HLA-specific antibodies is more difficult. Although many case reports suggest HLA antibodies cause pulmonary transfusion reactions, look-back studies suggest that the incidence of pulmonary reactions due to the transfusion of HLA antibodies is very low. In addition, the incidence of HLA antibodies in healthy subjects is very high relative to the number of patients that experience TRALI. Approximately 17% of female apheresis donors have HLA antibodies, and the incidence of HLA antibodies increases with parity.\(^9\) One study found HLA antibodies in 7% of female apheresis platelet donors who had never been pregnant and in 14% with one or two pregnancies;\(^9\) in another study, HLA antibodies were present in 24% of all multiparous women.\(^9\) Since the number of transfusion recipients experiencing TRALI is less than one in 1,000, the transfusion of most blood products containing HLA antibodies does not cause TRALI. Until more data are available, it is not unreasonable to decide on the deferral of donors with HLA antibodies case-by-case. When a case of TRALI involves one or two donors and one of the donors has a strong HLA antibody specific to an antigen expressed by the recipient, it would be prudent to defer the donor. However, if the cause of acute lung injury is not certain, the lung injury not severe enough to be classified as
antibodies. It would seem prudent not to exclude all donors with HLA fusion reactions is demonstrated in controlled studies, it relationship between HLA antibodies and pulmonary trans-

be performed to screen donors for HLA antibodies, but until a for neutrophil antibodies are not available. Such testing can have circulating neutrophil antibodies, yet solid-phase assays that lend themselves to high-throughput screening of donors would also be helpful. While two thirds of platelet products prepared from buffy coats are suspended primarily in a storage solution, apheresis platelets and platelets prepared from platelet-rich plasma are stored primarily in plasma. Testing of apheresis platelets by culture 24 hours after collection has reduced the risk of reactions due to bacterial contamination. Replacing plasma in platelet components with a storage solution would likely decrease reactions due to leukocyte antibodies and antibodies to plasma proteins such as IgA and haptoglobin. The use of pathogen inactivation with platelets and RBC components and/or point-of-transfusion bacteria testing would further reduce reactions due to bacterial contamination.

It has been proposed for several years that multiparous women be prevented from donating plasma-containing blood components, since their plasma is more likely to contain leukocyte antibodies than is that of nulliparous women and men. In 1971, Thompson et al suggested that individuals with leukoagglutinins and multiparous women be excluded from donating whole blood. While the exclusion of multiparous blood donors would likely prevent an unknown proportion of TRALI, such a policy would not prevent all cases and its impact might be slight. Furthermore, since most multiparous women lack neutrophil or HLA antibodies, many blood donors would be needlessly excluded.

Data currently available support excluding donors who have circulating neutrophil antibodies, yet solid-phase assays that lend themselves to high-throughput screening of donors for neutrophil antibodies are not available. Such testing can be performed to screen donors for HLA antibodies, but until a relationship between HLA antibodies and pulmonary transfusion reactions is demonstrated in controlled studies, it would seem prudent not to exclude all donors with HLA antibodies.

**Prevention of Pulmonary Transfusion Reactions**

Improvements in technology have reduced the incidence of pulmonary reactions. The reduction or elimination of plasma from cellular blood components could further reduce pulmonary reactions. Little plasma is now present in most RBC components. RBC components are almost universally prepared with additive solutions to extend their shelf-life to 42 days. A reduction of plasma volume in platelet components would also be helpful. While two thirds of platelet products prepared from buffy coats are suspended primarily in a storage solution, apheresis platelets and platelets prepared from platelet-rich plasma are stored primarily in plasma. Testing of apheresis platelets by culture 24 hours after collection has reduced the risk of reactions due to bacterial contamination. Replacing plasma in platelet components with a storage solution would likely decrease reactions due to leukocyte antibodies and antibodies to plasma proteins such as IgA and haptoglobin. The use of pathogen inactivation with platelets and RBC components and/or point-of-transfusion bacteria testing would further reduce reactions due to bacterial contamination.

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**Models of Pulmonary Transfusion Reactions**

Most clinical and laboratory studies have focused on TRALI, a very severe form of nonallergic immune-mediated pulmonary transfusion reactions. While it is helpful for clinical and regulatory purposes to document that a case of acute lung injury was the result of a transfusion, studying TRALI to understand the pathophysiology of pulmonary transfusion reactions has been difficult and not very productive. Despite many advances in the understanding and elimination of adverse effects of transfusions, much remains unknown about pulmonary transfusion reactions in general and TRALI in particular.

The TRALI model of pulmonary transfusion reactions has several deficiencies. TRALI represents only the most clinically severe subset of reactions (Fig 1). While TRALI is now more precisely defined, the distinction between TRALI and less severe types of pulmonary transfusion reactions is arbitrary. The incidence of TRALI is highly variable among institutions, but it is always rare and, as a result, not readily amenable to study. Perhaps the most problematic aspect of TRALI is its close link to HLA antibodies. Case reports in the 1970s and 1980s closely tied TRALI and HLA antibodies. Despite that recent data have not supported a close association between TRALI and the transfusion of HLA antibodies, and that the new definition of TRALI is independent of antibody test results, it will likely remain difficult, if not impossible, to avoid an “HLA antibody basis” in any investigations of TRALI.

An alternative view of nonallergic immune-mediated pulmonary transfusion reactions could advance this field (Fig 2). Such a model could be helpful in the interpretation of new data and in designing new studies. Based on current data, a general view of pulmonary transfusion reactions other than those due to fluid overload, anaphylaxis, hemolysis, and bacterial contamination can be constructed. This model should encompass both serious and mild reactions and the following clinical observations: (1) pulmonary reactions are due to the transfusion of soluble plasma factors that likely include, but are not limited to, leukocyte antibodies, bioactive lipids and CD40L; (2) neutrophil antibodies are more likely to cause lung injury than are HLA antibodies, but factors in addition to or other than leukocyte antibodies cause most reactions; (3) the degree of lung dysfunction associated with transfu-
sions varies markedly; (4) most reactions are mild and may not be attributed to a transfusion by the clinical care team; and (5) TRALI represents only the most severe form of pulmonary transfusion reaction and only a small fraction of all pulmonary transfusion reactions.

These concepts have several implications. Nonallergic immune-mediated pulmonary transfusion reactions represent a syndrome rather than a single entity, with a broad spectrum of severity and causes. Prospective studies of all pulmonary reactions caused by a single mechanism such as leukocyte antibodies may be more manageable and fruitful than are studies that focus only on TRALI. Pulmonary transfusion reactions including TRALI are likely caused by several different mechanisms, and some of these mechanisms may cause a wide spectrum of severity of lung injury, with TRALI the worst. Since TRALI occurs infrequently, it will be difficult and expensive to determine its pathogenesis. If the full spectrum of pulmonary transfusion reactions is systematically examined, both mild and severe, it may be possible to characterize mechanisms, variables, co-modifying factors, and patient/donor/blood component factors that contribute to lung injury.

Prospective controlled studies are important to address basic questions such as: (1) How many apheresis platelet donors have neutrophil-specific or HLA-specific antibodies? (2) Which bioactive factor levels increase in stored blood components and do these factors contribute to transfusion reactions? (3) How often does the transfusion of HLA antibodies, neutrophil-specific antibodies, and bioactive materials cause pulmonary transfusion reactions? (4) What proportion of subjects experience serious reactions and mild pulmonary transfusion reactions? (5) Why do patients transfused with the same antibody or cytokine have different reactions? (6) What patient factors affect the incidence and severity of pulmonary transfusion reactions?

Conclusions
Transfusion reactions are common, and pulmonary reactions represent one of the more serious types of transfusion reaction. Understanding of transfusion reactions has improved, but the mechanisms responsible for many of them remain unclear. Some of these reactions would likely be avoided by suspending cellular components in additive/storage solutions rather than in plasma. However, since factors produced by blood cells during storage are responsible for some reactions, replacing plasma with storage solution would not completely eliminate all transfusion events. Further study is necessary to understand the causes of these reactions and develop better strategies to prevent them.

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