Transfusion-related lung injury

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Respiratory compromise related to transfusion may be divided broadly into cardiogenic and noncardiogenic. Acute noncardiogenic pulmonary edema occurring immediately after transfusion of donor plasma known to contain leukoagglutinins was first clearly described by Brittingham in 1957. Scattered case reports of allergic pulmonary edema or anaphylactic pulmonary edema followed. In 1985, Popovsky and Moore published the first prospective study of this complication that they termed transfusion-related acute lung injury (TRALI). They reported a much higher incidence of the complication than had previously been considered likely, and following their report, increasing numbers of individual cases and small case series were published. With the development of hemovigilance schemes in the late 1990s, it became apparent that TRALI was not only an important cause of transfusion-related morbidity but also, with the reduction in infective complications of transfusion, a leading cause of transfusion-related mortality. In the first decade of this century, a better understanding of the pathophysiology led to successful preventative strategies. The increased understanding and interest in TRALI led also, via active hemovigilance schemes, to improved recognition of cardiogenic dyspnea due to volume overload, now generally termed transfusion-associated circulatory overload (TACO).

TRALI: clinical features
Clinical reports of TRALI describe a sudden deterioration in lung function closely related to blood transfusion. The changes occur rapidly and generally begin within two hours and nearly always within six hours of the subsequently implicated transfusion. A small number of reports suggest that the onset may rarely be delayed until 12 hours or more after transfusion. The conscious patient describes a tightness in the chest, feels short of breath, develops a dry cough, and may also experience nausea, dizziness, and rigors. On examination, the patient is hypoxic, is often hypotensive, and has tachypnea and tachycardia. Widespread crepitations are heard on auscultation of the chest. Rigors and fever are commonly reported but are not always present, and fever may develop only some hours after the transfusion.

On intubation, or on suction of the already ventilated patient, a typical finding is of a copious frothy tracheal exudate, much like lightly whipped egg white. The nature and quantity of this exudate are often remarked on by attending anesthetists, and it may be considered one of the hallmarks of severe TRALI. Arterial blood gases show hypoxia and hypercapnia that are often severe. Chest X-rays show nodular shadowing typically in the “bat’s wing” pattern of acute respiratory distress syndrome (ARDS) (Figure 59.1). Physiologic measurements such as pulmonary artery wedge pressure or esophageal Doppler study of the left atrium show systemic hypovolemia that may be marked. Further diagnostic tests of value are described in this chapter.

These cases represent the severe end of the spectrum of the disorder. Most early published reports describe severe cases such as these, but with more knowledge of the condition many milder cases are being recognized. Milder cases are proportionately less dramatic.

Recovery of respiratory function starts as early as six hours after the onset in milder cases, but in some cases deterioration may continue until 24 hours or beyond.

Some authors have reported a slightly different clinical picture in which the chief signs are rigors and fever with transient respiratory dysfunction, hypertension rather than hypotension, and occurrence usually within 30 minutes of transfusion. Pulmonary edema is not always demonstrated radiologically, and recovery is within 1 or 2 hours. These reactions have typically been associated with cellular blood components. It has been suggested that these cases may represent a different and non-antibody-related etiology (discussed further in this chapter) from the “classical” severe cases. However, a similar spectrum of mild to moderate reactions of this nature has also been documented with transfusion of plasma containing antibody to a neutrophil antigen, anti-HNA-2.5

Acute lung injury with noncardiogenic pulmonary edema is common among critically ill patients and is generally considered to have a multifactorial pathogenesis. Many sick patients receive transfusion, especially after multiple trauma. There is evidence that TRALI is a significant contributor to acute lung injury (ALI) and that plasma-rich components from female donors are particularly implicated. The relationship between ALI and TRALI is further discussed in this section.

Pathophysiology
It is now understood that many cases of TRALI, including the most severe cases, are due to an antibody–antigen interaction between donor and donation. Other mechanisms have been postulated and may be contributory to antibody-related cases or to other causes of
lung damage. It has been suggested, and is a helpful distinction, that TRALI should be clearly divided into antibody-related and non-antibody-related lung damage.

**Acute lung injury**

ALI is the result of a capillary endothelial leak that allows fluid to pass from the pulmonary vessels, initially into the interstitial space and subsequently into the alveolar space. Because this edema is distinct from hydrostatic edema caused by cardiac failure or volume overload, it is sometimes known as nonhydrostatic edema. Numerous stimuli have been suggested to contribute to the likelihood of developing nonhydrostatic pulmonary edema, including sepsis, trauma, aspiration of gastric contents, disseminated intravascular coagulation, and high tidal volume ventilation. In some cases of TRALI, the transfusion appears to be the only probable cause of the lung injury, whereas in other cases it may be only one of several possible factors present. Histopathology, clinical findings, and experimental work have helped elucidate the nature of the stimulus from the transfused blood and the mechanism of the lung damage.

**Histopathology**

Histopathologic findings from fatal TRALI cases are consistent with those for early ARDS, showing interstitial and intra-alveolar edema\(^3,6-10\) and extravasation of neutrophils into the interstitial and air spaces (Figure 59.2).\(^3,6,7,10\) Hyaline membranes and destruction of the pulmonary architecture have been reported.\(^6,7\) A consistent finding in TRALI is the presence of increased numbers of neutrophils within the pulmonary capillary vasculature and small pulmonary vessels.\(^9,10\) On electron microscopic pictures, neutrophils were degranulated and focally in direct contact with denuded stretches of the capillary wall. A positive correlation has been reported between capillary leukostasis and desquamated epithelial cells, and between the degree of capillary leukostasis and the amount of proteinaceous fluid within the alveolar air spaces.\(^10\)

From these observations, it appears that the neutrophil is central to the occurrence of lung damage. After sequestration in the early stages of TRALI, neutrophils and endothelial cells of the pulmonary microvasculature establish close contact. Activation of the neutrophils leads to endothelial damage and capillary leakage. The transit of proteinaceous fluid from the vessels into the air spaces results in acute pulmonary edema. In the later stage, especially of severe...
TRALI, neutrophils extravasate from the capillary into the alveoli and induce further pulmonary injury.

Evidence for an antibody-related etiology

The relationship between TRALI and leukocyte antibodies in donor plasma was first noted by Brittingham, who reported that leukoagglutinins present in the plasma of a multitransfused patient induced an acute pulmonary reaction when transfused to a volunteer. Severe pulmonary edema was similarly induced in a healthy volunteer who received an experimental gamma globulin concentrate. It is likely that the preparation contained high levels of HLA class II antibodies. In addition to these cases of TRALI resulting from experimental transfusion of plasma containing leukocyte antibodies, there are numerous case reports of TRALI in which a transfused unit has been found to contain antibodies reactive with recipient leukocytes. In two large series of TRALI, where pulmonary infiltrates were apparent in chest X-rays, leukocyte antibodies in the donor of a transfused blood component were detected in 61% to 89% of cases.

Animal models have provided confirmation of this antibody-mediated mechanism of TRALI. Severe vascular leakage was reproduced in isolated rabbit lungs by application of HNA-3a antibodies in an ex vivo rabbit lung model. From this experiment, it was concluded that leukoagglutinating antibodies and concomitant complement activation are capable of causing TRALI. Other animal experiments have confirmed that antibodies are capable of causing TRALI but suggest that complement is not a prerequisite for TRALI induced by antibodies to CD177 (HNA-2), because the induction of TRALI was found to be dependent on the density of the cognate antigen and occurred in a complement-free environment. Alternative mechanisms leading to TRALI have been proposed and are discussed in this chapter, but the available evidence demonstrates that donor leukocyte antibodies reacting with recipient antigens are the predominant mechanism. Large clinical studies were able to corroborate these experimental findings, as were hemovigilance data obtained in countries in which plasma from female donors (or female donors with a history of pregnancy) was no longer used for clinical transfusion.

Specificities of antibodies identified as causing TRALI

Antibodies to HLA class I and II antigens and to neutrophil antigens have all been clearly implicated as causing TRALI. Evidence from hemovigilance schemes and laboratories specializing in TRALI investigation has shown that the majority of cases (75–90%) are associated with HLA antibodies, and that with improved detection techniques about 50% of these are directed against HLA class II antigens. Antibodies to neutrophil antigens are found in about 10–25% of cases. Interestingly, in three large clinical studies that investigated donor-related risk factors for TRALI patients, HLA class I antibodies were not identified as risk factors. In contrast, two of the three studies calculated an odds ratio of 3.08–3.2 for HLA class II positive units and of 1.71–4.85 for units from donors who produced a positive test with granulocytes in the laboratory.

Mechanisms of lung damage in TRALI

Priming and activation of neutrophils

The dogma that TRALI is mediated by activated neutrophils has lost some of its cogency during recent years, mainly because TRALI could still be precipitated in animals depleted of neutrophils. It appears reasonable to consider neutrophils as major, but not sole, mediators in a process that also includes monocytes and the endothelium. Neutrophils activated by injurious agents will respond by de novo synthesis of a range of highly toxic reactive oxygen species (ROS) and the release of preformed granular enzymes, proteins, and neutrophil extracellular traps (NETs). Neutrophils may be activated directly by one sufficiently strong stimulus, but the process often requires two or more stimuli. The first or “priming” stimulus will potentiate the response to a second or “activating” stimulus. A large percentage of patients who develop TRALI are sick, and there is in vivo evidence that surgical procedures and active infections induce neutrophil priming. In response to priming agents, neutrophils undergo polarization, a process that leads to "stiffening" of the cell. This "stiffening" augments mechanical retention of neutrophils within the pulmonary capillary bed and prolongs their passage through the lungs (discussed further in this chapter). Prolonged, close contact between neutrophils and the endothelium provides a microenvironment in which transmembrane receptors and released mediators of each cell type can interact closely. Sequestered neutrophils, having been primed in the circulation, and endothelial cells can be activated by exogenous stimuli present in the blood bag. These transfused stimuli include antibodies, cytokines, and bioactive lipids (also discussed further here).

Antibodies to neutrophil antigens involved in TRALI cases are able to prime and activate neutrophils in some cases without additional stimuli, explaining why even completely healthy individuals can develop TRALI if the antibody stimulus is sufficient.

Aspects of neutrophil passage through the pulmonary microvasculature

The alveolar capillary bed is a complex interconnecting network of short capillary segments. The path of a neutrophil from arteriole to venule crosses up to eight or more alveolar walls and encounters more than 50 capillary segments. Approximately half of these pulmonary capillaries are narrower than the diameter of a spherically shaped neutrophil. The pulmonary circulation normally contains about 30%, the “margination pool,” of the total blood neutrophil pool. The stimulus-induced decrease in deformability appears to be more important than selectin-mediated rolling, a key mechanism of neutrophil adhesion within other capillary beds, but changes in surface receptors in primed neutrophils will also lead to molecular adhesion to endothelial cells. Under physiologic conditions, primed and locally trapped neutrophils migrate from the capillaries into the alveoli as part of a local inflammatory reaction. In TRALI, the primed and trapped neutrophil encounters a further activation signal in the form of transfused antibody or other transfusion stimulus, activates its microbicidal arsenal, and induces endothelial damage.

Activation of pulmonary endothelial cells

TRALI can also be triggered by activated pulmonary endothelium. In addition to constitutively expressed surface receptors, activated endothelial cells upregulate surface membrane receptors that
facilitate neutrophil adhesion and priming. Primary activation of endothelial cells has been suggested as the mechanism responsible for TRALI induction after infusion of bioactive lipids. More recently, antibodies recognizing proteins present on the endothelial surface (i.e., HNA-3a) were shown to directly interfere with endothelial function, indicating that barrier breakdown leading to lung edema does not necessarily involve the activation of neutrophils. These experimental data are in line with a clinical observation in which a HLA-B44-negative patient transfused with blood containing anti-HLA-B44 antibodies developed a “half-sided” TRALI in his recently transplanted, HLA-B44-positive lung only. These antibodies must have either reacted with transplant endothelium or, possibly, donor-type (alveolar) macrophages.

Activation of monocytes

The question of whether white blood cells other than neutrophils might contribute to TRALI was raised when investigators tried to unravel the mechanism behind HLA class II–induced TRALI. In contrast to HNA and HLA class I, HLA class II antigens are usually not present on neutrophils (or endothelial cells), but are present on monocytes. Kopko et al. suggested a monocyte-dependent mechanism, where HLA class II antibodies bind to monocytes, induce the release of neutrophil-activating mediators, and finally induce neutrophil activation and TRALI. Using human plasma with anti-HLA-DR7 and -DR52 specificity and human neutrophils and monocytes in an ex vivo rat lung model, Sachs et al. showed that HLA class II antibodies can induce TRALI via such a multistep pathway, including the initial activation of monocytes and the release of interleukin-8 (IL8). Subsequently, experiments in mice delineated that monocytes may also be involved in HLA class I–mediated TRALI, because depletion of these cells suppressed HLA class I antibody–mediated TRALI, as did the blockade of MIP2 receptors, the murine analog of IL8.

Platelets and TRALI

The extent to which platelets participate in TRALI is still unresolved. Both blockage of platelet function by aspirin and immune-mediated platelet depletion were recorded to suppress TRALI in a murine model, but other experiments using different methods of platelet depletion have failed to confirm this, indicating that the process of elimination itself rather than the absence of platelets could mediate protection. There are also conflicting data on the involvement of platelets in neutrophil extracellular trap formation. Whether platelets are present in alveolar capillary wall lesions (e.g., as neutrophil–platelet aggregates) is also unresolved.

Neutrophil, monocyte, and endothelial cell interplay

The interplay between neutrophils, monocytes, endothelial cells, and possibly platelets—regardless of whether it has primarily been started by neutrophil, monocyte, or endothelial cell activation—contributes largely to lung damage. Neutrophils respond to monocyte- and/or endothelial cell–derived mediators by activating and expressing integrins and by releasing pro-inflammatory mediators and granule contents. Released mediators activate endothelial cells, which, in turn, mobilize selectins, upregulate adhesion proteins, and produce inflammatory mediators; thereby, they enhance neutrophil and platelet adhesion and neutrophil, platelet, and monocyte activation. It is within this interplay that the lung barrier breaks down and allows transit of proteinaceous fluid and, later, of neutrophils into the alveolar space. At least in the experimental setting, other blood cells seem to act as attenuators in this complex process.

Mechanisms of lung injury by different mediators in transfused blood components

The exact pathway leading to lung damage associated with transfusion depends on the nature of the antibody or other stimulus and the interplay between it and the cellular components.

Antibodies to human neutrophil antigens

Serologic workup of TRALI patients identified antibodies to human neutrophil antigens in a number of cases. In hemovigilance schemes, they were detected in approximately 10% of cases before preventive measures were installed. As discussed above, the ability of these antibodies to induce TRALI has been shown in ex vivo models of lung injury. HNA antibodies, particularly those of HNA-2 and HNA-4a specificity, are capable of directly activating neutrophils, which appears to be the mechanism by which they induce TRALI (Figure 59.4A). Of note, antibodies against HNA-3a can interact directly with endothelial cells, because their cognate antigen CTL-2 is expressed not only on neutrophils but also on endothelial cells of the lungs. Binding of anti-HNA-3a to endothelial cells leads to the production of ROS within the endothelium, as a consequence of which endothelial cells loosen their contacts and allow fluid to shift to the alveolar spaces (Figure 59.4E). It is suggested that this direct mechanism of TRALI induction accounts for the high rate of fatal cases of TRALI associated with HNA-3a antibodies. The activation of endothelial cells by direct binding of HNA-3a antibodies leads also to cellular activation and neutrophil recruitment, indicated by the fact that these antibodies can induce (milder) TRALI in a murine model in the absence of neutrophils, but induce more severe TRALI when neutrophils are present, corroborating the idea that once the process is started, multiple players become involved.
Antibodies to HLA class I antigens

HLA class I antibodies are frequent in the donor population, and the presence of such antibodies in transfused plasma can be anticipated to be a common cause of TRALI. The cognate antigens are expressed on all cell types that are discussed to play a role in TRALI. It is well documented that HLA class I antibodies can directly bind to neutrophils and prime oxidases in both humans and rats. In line with this, there are numerous anecdotal reports of TRALI associated with HLA class I antibodies, especially of anti-HLA-A2 specificity, which is directed against a frequent HLA antigen. However, HLA class I antibodies were not associated with increased risk of TRALI in several observational studies.

Most TRALI experiments in animals were performed with anti-MHC (major histocompatibility complex) class I antibodies. Of note, only one out of several tested monoclonal MHC class I antibodies induces TRALI in mice when infused (anti-H2K<sup>b</sup>, clone 34.1.2s), and results obtained with these experiments, albeit highly informative, should be interpreted carefully, especially when it comes to their impact on transfusion medicine. An elegant study performed in mice by Looney and coworkers presented in vivo data on the mechanism of endothelial cell–dependent TRALI (Figure 59.4D). Transfusion of an MHC class I monoclonal antibody to mice expressing the cognate antigen induced TRALI and acute peripheral blood neutropenia. Mice lacking neutrophils and mice lacking the Fcy-receptor were resistant to MHC class I antibody–induced TRALI. Transfer of wild-type neutrophils into FcγR<sup>−/−</sup> mice restored TRALI following antibody infusion. This model is consistent with binding of the antibody directly to endothelial cells, in the first vascular bed encountered after infusion, and recruitment of neutrophils through binding of the immunoglobulin Fc portion to the neutrophil Fcy receptor. The protection observed in FcγR<sup>−/−</sup> mice argues against direct neutrophil activation by the antibody. The idea of Fc-receptor-dependent trapping has been challenged by numerous findings from other investigators, all performed with the same monoclonal antibody as inducer of TRALI. A major aspect is that depletion of monocytes abrogates TRALI in this model, indicating that monocyte activation needs to be considered as a crucial step in anti-MHC class I–induced murine TRALI.

As outlined above, direct neutrophil binding of HLA class I antibodies was demonstrated for humans and rats, and evidence that HLA class I antibodies can also cause TRALI by direct binding to neutrophil antigens comes from case reports of “inverse TRALI.” In one well-documented case, infusion of human granulocytes caused severe lung injury in a patient who had class I antibodies. The antibodies cannot have reacted with the native endothelial cells but did react in vivo with the donor granulocytes, in keeping with a mechanism of TRALI by direct activation of neutrophils (Figure 59.4A and 59.4B). In summary, different experimental findings reported for HLA class I antibodies make it very likely that numerous activation steps must generally come together before the reaction commences in a patient. This may involve antibody binding to neutrophils, endothelial cells, and monocytes. The fact that human antibodies—in contrast to the monoclonals used in animal studies—are polyclonal and differ in their binding characteristics and avidity may explain the lack of a clear association of HLA class I antibodies and TRALI in studies of donor risk factors.

Antibodies to HLA class II antigens

In contrast to HNA and HLA class I, HLA class II antigens are usually not present on neutrophils (or endothelial cells), but on monocytes. Neutrophils and endothelial cells may express HLA class II upon stimulation, but HLA class II antigen expression was not found on vascular endothelium of pulmonary capillaries or...
intravascular neutrophils in a patient who experienced fatal TRALI caused by an HLA class II antibody. Although a direct mechanism between HLA class II antibodies and the other two cell types cannot formally be excluded, monocytes appear currently as major target cells for these type of antibodies (Figure 59.4C). It is unlikely that transfused antibodies have direct access to the alveolar space through an intact endothelium in sufficient concentration to induce release of cytokines and subsequent activation of neutrophils and/or endothelial cells, but where there is already some damage to the pulmonary endothelium, such a reaction may exacerbate ALI.

It remains possible that detection of antibodies to HNA and HLA could be surrogates for antibodies to as-yet-unknown antigens on other cell types (e.g., on monocytes). Alloantibodies to these or other cells might explain some apparently antibody-negative cases.

Inverse TRALI: transfusion of neutrophils

In most cases of TRALI, antibodies or neutrophil-priming agents present in the blood component are causative for the pulmonary reaction. However, TRALI, as described above, has also been reported in alloimmunized patients receiving blood components that contain neutrophils. Viable neutrophils may still be present in other blood components, and Popovsky and Moore estimated that 6% of observed TRALI cases were caused by antibodies present in the recipient. As universal leukocyte reduction has been introduced in many countries, inverse TRALI caused by leukocytes in platelet concentrates (PCs) and red blood cells (RBCs) must nowadays be considered as a rare constellation; it will remain of particular relevance to patients receiving granulocyte transfusions.

Non-antibody mediators of TRALI

Bioactive lipids

Blood components may accumulate intermediate metabolic products, such as bioactive lipids, during storage. These substances are breakdown products of membrane lipids, including lysophosphatidylcholines (lysoPCs), which can prime respiratory burst reactions of the neutrophil. Because these neutrophil-priming agents do not develop in stored acellular plasma, their generation is dependent on the presence of blood cells. RBCs are known to alter significantly during their shelf life (see also Chapter 9), and this blood component is a candidate mediator of antibody-negative TRALI. Indeed, administration of supernatant from stored (but not from fresh) human RBCs caused TRALI in an ex vivo and later also in an in vivo animal model of TRALI (Figure 59.4F and 59.4G). However, in a syngeneic rat model of RBC transfusions by Vlaar et al., these findings could not be reproduced: RBCs were prepared from donor rats and transfused after storage. When rats were pretreated with LPS, there was no difference in the histopathology score or cytokine levels after the transfusion of fresh (day 0) and old (day 14) rat RBCs. When red cells and supernatant were transfused separately, the supernatant induced lung inflammation but no lung edema, and lysoPCs were not involved in the inflammatory reaction.

Biologically active breakdown products were also investigated in the setting of platelet transfusions. In a cross-species study, supernatant of aged human platelets, but not of fresh platelets, caused ALI in an ex vivo rat lung model. In a syngeneic rat model, whole aged platelet suspensions, but not fresh ones, led to neutrophil adherence and some edema in lung. However, when LPS was used to mimic patient-related risk factors, stored platelets no longer induced TRALI despite an increased lysoPC content.

In summary, there is currently no clear evidence on whether lysoPCs (or other bioactive lipids) are involved in TRALI or not. It should be noted that cumulative data from three large clinical trials are not supportive for a role of RBC storage time and/or lysoPC content as relevant risk factors for TRALI.

CD40 ligand (CD40L)

CD40L is another neutrophil-priming breakdown product. It is a platelet-derived pro-inflammatory mediator found in cell-associated and soluble (sCD40L) forms. It may be found in PCs and accumulates during storage. sCD40L binds to CD40, which is present on the surface of monocytes, macrophages, and neutrophils. This CD40L–CD40 interaction induces neutrophil priming, which was suspected to be associated with TRALI after platelet transfusions because its concentration in transfused PCs that were involved in TRALI cases was found to be significantly higher than in control units. In vitro, human microvascular endothelial cells pre-incubated with LPS experienced severe damage when sCD40L-primed neutrophils were added, whereas unprimed neutrophils did not induce such damage. In a rather complicated murine experiment, others have questioned the role of CD40L in TRALI. In line with these animal experiments and in contrast to other case reports, patients with TRALI after cardiac surgery did not differ in their sCD40L levels from controls. In summary, the contribution of CD40L to TRALI is still incompletely defined.

Immunoglobulins

Normal IgG has been postulated to activate neutrophils in a patient with osteopetrosis being treated with gamma interferon and granulocyte and monocyte colony-stimulating factor. The patient had very low levels of endogenous IgG1 and IgG2 and developed severe lung injury shortly after transfusion of platelets from an untransfused male donor. No leukocyte antibodies could be found in either donor or recipient. It is suggested that transfused IgG binding to the neutrophils, which were already primed by interferon and stimulating factor, was sufficient to cause neutrophil activation and lung injury. This case may be considered a good example of “multiple-hit” TRALI.

Reports of lung injury following intravenous IgG infusion are rare and seem to be associated with high doses or concentrates prepared intentionally with a high level of leukocyte antibodies. It is possible that antibodies are both diluted and neutralized during the preparation of the pooled product, as suggested for pooled viricidally treated plasma.

Multiple-hit/threshold theory of TRALI causation

Where the stimulus to endothelial and neutrophil activation is sufficient, lung damage can occur in an otherwise healthy individual with no other likely cause of lung injury. Evidence for this comes from reports of TRALI in transfused volunteers as described here and also from reports where plasma has been used for clinical reasons in otherwise healthy individuals. These cases are a minority, and most patients receiving transfusion and especially transfusion of plasma have significant comorbidities, some or many of which may also result in priming or activation of neutrophils or damage to pulmonary endothelial cells. It has been suggested that TRALI will be more common in such patients. Early reports noted that most patients with TRALI had recently undergone surgery and suggested that this in itself was a sufficient second stimulus in many cases. Some experimental evidence for the “two-hit” or “multiple-hit” theory has been provided by studies on bioactive lipids described...
The multiple-hit theory has been further developed by Bux and Sachs, who suggest that neutrophil and endothelial cells are central to the pathogenesis of TRALI and that activation of these cells requires sufficient stimuli from one or more sources to reach a certain threshold, at which point full activation and lung damage will ensue (Figure 59.5). Depending on the magnitude of the neutrophil or endothelial cell response, the lung damage can be mild or severe with corresponding clinical effects.

**Transfusion-associated circulatory overload**

TACO has become increasingly recognized through hemovigilance schemes. In contrast to TRALI, the essential pathogenesis is of increased pulmonary capillary pressure leading to hydrostatic pulmonary edema. Patients particularly at risk are the small and elderly, those with preexisting cardiac disease, and those with relative fluid overload such as some patients with dialysis-dependent renal failure. Obstetric cases are also reported and may be related in part to the raised circulating volume during pregnancy and the cardiac effects seen in preclampsia. Transfusion of any fluid, crystalloid, or colloid can lead to cardiac overload. Where blood transfusion is involved, all components have been implicated, and unlike TRALI there is no overrepresentation of high-volume plasma component transfusion. There is no clear evidence that red cells themselves are implicated by pathophysiological mechanisms other than intravascular volume. It remains possible that stored red cells with relatively poor oxygen delivery characteristics may contribute to cardiac ischemia and thus cardiogenic edema, but there is no clear evidence in favor of this hypothesis.

**TACO: definition**

The hemovigilance working party of the International Society of Blood Transfusion revised their definition of TACO in 2014 to better capture the range of cases whereby there is volume overload usually with radiographic pulmonary edema resulting from transfusion of blood components (Table 59.1).

**TACO: epidemiology**

Heart failure and pulmonary edema brought on or worsened by transfusion have been recognized for many years. Patients with severe anemia due to vitamin B₁₂ deficiency were particularly

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**Table 59.1** International Society of Blood Transfusion definition of TACO (2014)

| Case 
| --- |
| Cases of TACO are characterized by acute or worsening respiratory distress within 6 hours of transfusion (some cases may occur up to 12 hours), with the following features: 

**Primary Features**

- Evidence of acute or worsening pulmonary edema with bilateral infiltrates
- An enlarged cardiac silhouette on chest imaging
- Enlarged heart contour should always be present if looked for.

- Evidence of fluid overload

Evidence of fluid overload could be: a positive fluid balance; a response to diuretic therapy combined with clinical improvement.

**Features to Support Diagnosis Are**

- Elevated BNP or NT-pro BNP to more than 1.5 times pretransfusion value (if available)
- Increase in mean arterial pressure or increased pulmonary wedge pressure; typically the mean arterial pressure is raised, often with widened pulse pressure; however, hypotension may occur (in cases of acute cardiac collapse).

Confirmed cases (definite imputability) should show at least two primary features or one in combination with two supportive features. Cases with only one primary feature (e.g., without chest imaging) may be reported as possible or probable TACO depending on supporting features.

In ICU, patients who may be receiving positive pressure ventilation with varying degrees of PEEP (positive end expiratory pressure) pulmonary edema may be difficult to diagnose at higher levels of PEEP or indeed become apparent if PEEP is reduced or removed.

known to be susceptible to sudden cardiac decompensation after transfusion. The rising incidence of cardiac overload due to transfusion was first highlighted by hemovigilance data from Quebec in 2010. Subsequently, with increased recognition and reporting, it has emerged as a major cause of transfusion-related morbidity and mortality in many countries, including Ireland and the United Kingdom. Reports from the UK hemovigilance system (SHOT UK) show an increase in reports from three in 2007 to 96 in 2013, the latter being an incidence of one in 10,000 blood components transfused. In Ireland, over 10 years the reported rate was seen to increase from one in 42,000 to one in 6268 units of red cells transfused. Prospective surveys suggest a higher rate still, perhaps as much as 1%. The incidence per unit is higher after red cell transfusion than with plasma or platelets alone, although this may be due to the patient’s underlying illness and indication for transfusion rather than a specific effect of component type. Morbidity and mortality may be difficult to ascribe only to blood transfusion in a vulnerable patient who may also receive other fluids, but there is no doubt that transfusion appears to be a key factor in many cases. The majority of patients developing TACO are elderly with a history of cardiac disease, respiratory disease, renal failure, or a combination of these conditions. A small number have no known cardiorespiratory comorbidities. Patients are typically elderly with known cardiac failure, but younger previously fit patients may also be affected. Others have identified an unexpectedly high incidence in obstetric patients, perhaps related to the expanded blood volume seen in pregnancy. Cases have also been reported in children.

**TACO: diagnosis**

Diagnosis is by identification of hydrostatic pulmonary edema as in Figure 59.6 and accompanying text on the differential diagnosis of TRALI/ALI and TACO/cardiac failure. Hypertension is characteristic of TACO, whereas hypotension is characteristic of TRALI. It is not impossible for a patient to have both volume overload due to incautious fluid management and a capillary leak whether due to TRALI or to ALI from other causes.

**TACO: treatment**

Treatment is that of cardiac failure or volume overload, putting the patient in an upright position, and giving oxygen and diuretics, fluid restriction, and even phlebotomy. Continuous positive airway pressure or even mechanical ventilation may be necessary, and in patients with marked renal failure dialysis with removal of fluid may be used.

**TACO: prevention**

Avoidance of unnecessary transfusion is the best preventive measure for TACO. Although the risks of transfusion are well known in anemia due to vitamin B₁₂ deficiency, a more common cause of

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**Figure 59.6** Flow chart for diagnosis of TRALI.

Dyspnea/Hypoxia within 6 hours of transfusion

- Transcutaneous O₂ sat <90% or PaO₂/FiO₂ <300 mm Hg
- No
  - Observe for further deterioration

  - Transfusion-related cause
    - eg, bronchospasm, anaphylaxis,
      Shock secondary to infected unit or
      ABO incompatibility
  - Non-transfusion related
    - eg, Infection
    - Pulmonary embolus
    - Myocardial infarct
- Yes

  - Transfusion-related cardiac overload
    - Prior cardiac failure
    - Overhydration in renal failure
  - O₂ therapy and diuretics are indicated
  - Cardiac failure plus TRALI not excluded

- Yes

  - ALI due to shock, sepsis, aspiration, etc + possible TRALI
  - Treat underlying condition and
    Support respiration
  - Investigate donors if TRALI considered likely
  - Factors increasing likelihood of TRALI:
    - New neutropenia or monocytopenia
    - Transfusion of plasma-rich components
    - Copious frothy yellow or pink tracheal exudate

- No

  - Probable TRALI
  - Support respiration
  - Investigate donors

- Yes

  - TRALI or ALI
  - Other likely cause of ALI present?
  - Yes
  - Investigate donors if TRALI considered likely
  - Factors increasing likelihood of TRALI:
    - New neutropenia or monocytopenia
    - Transfusion of plasma-rich components
    - Copious frothy yellow or pink tracheal exudate
  - No
  - Cardiac failure plus TRALI not excluded

- No

  - ?evidence of pulmonary edema
    - clinical or radiological
    - No
    - Transfusion-related cause
      - eg, bronchospasm, anaphylaxis,
        Shock secondary to infected unit or
        ABO incompatibility
    - Non-transfusion related
      - eg, Infection
      - Pulmonary embolus
      - Myocardial infarct
    - Yes
  
- No

- Is the edema cardigenic/hydrostatic?
  - Yes
    - Transfusion-related cardiac overload
      - Prior cardiac failure
      - Overhydration in renal failure
    - O₂ therapy and diuretics are indicated
    - Cardiac failure plus TRALI not excluded
  
- No

- Observed for further deterioration

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anemia is iron deficiency. TACO has been reported following transfusion of such patients. Transfusion is rarely necessary in the absence of active bleeding and should be avoided in patients with easily correctable chronic anemia. Pretransfusion assessment for risk factors for TACO such as low body weight and the comorbidities mentioned, especially fluid overload and poorly controlled heart failure, may allow a careful transfusion protocol with diuretic cover and close observation. In “at-risk” patients, top-up transfusions should be restricted to no more than one unit of red cells at a time, or in small patients of no more than 4 mls/kg body weight of plasma reduced or optimal additive red cells, in order to achieve a rise in hemoglobin of 1 g/dL. There is no prospective or retrospective evidence for or against the use of fresher red cells in this circumstance.

Hypertension, tachypnea, tachycardia, and reduced oxygen saturation are all signs of cardiac overload. Early recognition may allow reduction in transfusion rate, discontinuation of transfusion, or use of oxygen and diuretics to halt or reverse the developing volume overload.

**Transfusion-associated dyspnea (TAD)**

TAD is defined by increased breathlessness not meeting the criteria for TRALI or TACO or an allergic reaction and occurring within 24 hours of transfusion. Respiratory distress should be the most prominent clinical feature and should not be explained by the patient’s underlying condition or any other known cause. It is important to record and classify such reactions, but given the uncertainty as to whether there is a specific pathophysiology, their clinical usefulness in managing transfusion is uncertain.

**ALI and transfusion in critically ill patients**

Clinical evidence for the theory that “multiple hits” may result in TRALI has been provided by studies involving critically ill patients who are known to be susceptible to ALI. Numerous retrospective studies have suggested a relationship between the amount of blood transfused and morbidity and mortality. All these studies are beset by the difficulty in allowing for the confounding factor of how much blood the patient required also being a marker for the severity of the illness. The Transfusion Requirements in Critical Care (TRICC) trial of transfusion triggers was both prospective and randomized, and it found a significantly higher incidence of pulmonary edema and a higher incidence of ALI in patients receiving more transfusion where the standard component was relatively plasma rich. Gajic et al. studied the clinical associations with ALI developing in patients during mechanical ventilation that was required for management of critical illness. They found a strong association with transfusion of plasma, but not with red cell transfusion, the age of transfused red cells, the leukocyte content of transfused red cells, or platelet transfusion. Further studies identified transfusion of female plasma as being particularly associated with development of ALI in keeping with an antibody type of mechanism. A prospective study in intensive care patients comparing male donor and parous female plasma found similar results. The incidence of ALI associated with transfusion in these studies was of the order of 1 in 50 to 200 units of female plasma transfused, a far higher incidence than the reported incidence of TRALI in other circumstances. These findings are in keeping with the Bux–Sachs threshold model of TRALI in which highly susceptible patients subject to multiple toxic insults to neutrophils and endothelial cells develop lung damage after a relatively mild additional stimulus from transfusion.

**Diagnosis and differential diagnosis**

**Respiratory dysfunction**

The development of new respiratory dysfunction caused by pulmonary edema in association with recent transfusion should be considered as evidence of possible TRALI. Significant respiratory dysfunction consistent with ALI can be defined as a decrease in transcutaneous oxygen saturation to less than 90% or an arterial PO2 of less than 60 mm Hg while breathing room air, or a PaO2–FiO2 ratio of less than 300 mm Hg.

Pulmonary edema can be demonstrated by clinical examination and chest X-ray. Alternative causes of sudden respiratory dysfunction, without edema, include transfusion-related problems such as allergic reactions with bronchospasm, shock associated with a bacterially infected unit or with ABO incompatibility, and causes unrelated to the transfusion such as cardiac arrhythmias, infection, and pulmonary embolus (Figure 59.6).

**Distinguishing between hydrostatic and nonhydrostatic pulmonary edema**

Once pulmonary edema is demonstrated, it is necessary to determine whether it is cardiogenic (hydrostatic) or caused by increased capillary permeability as in TRALI and other forms of ALI (nonhydrostatic). Cardiogenic pulmonary edema may be caused by TACO or by factors unrelated to transfusion, such as simple overhydration, especially in renal failure.

**Radiology**

Radiographic appearances of edema from increased pulmonary capillary permeability are often characteristic with patchy or nodular shadowing; they are mainly peripheral but spare both the apices and the costophrenic angles, and have the appearance of air bronchograms. This pattern is sometimes likened to a bat’s wing. In contrast, cardiogenic edema typically shows upper lobe venous distension and edema in the perihilar and basal areas. Edema in overhydration or renal failure is typically perihilar, and shows no air bronchograms. In severe TRALI or in later stages, the radiologic appearances may progress to a complete white-out of the lung fields.

**Physiologic measurements**

Physiologic measurements are aimed primarily at assessing the cardiac status. Measurement of the left atrial pressure or volume may be by pulmonary artery wedge pressure through a Swan–Ganz catheter, via esophageal Doppler ultrasound, or by transthoracic echocardiography. High left atrial filling pressure or volume suggests cardiogenic pulmonary edema or fluid overload. Normal or low pressure or volume is in keeping with noncardiogenic pulmonary edema. Low levels indicate hypovolemia, a common finding in TRALI. Electrocardiography may also be helpful in detecting cardiac strain patterns or evidence of infarction.

Prior or new cardiac failure does not exclude the possibility of TRALI, because both may be present in the same patient. However, cardiac failure does indicate that the use of diuretics, which are otherwise contraindicated in TRALI, may be beneficial.

**Laboratory tests**

A serum level of B-type natriuretic peptide (BNP) of <250 pg/mL is consistent with ALI rather than cardiac failure, whereas a level of >250 pg/mL or a twofold increase from a previous level is consistent with cardiac failure. A low level is not completely specific for ALI
nor very sensitive, as many patients with ALI also have cardiac dysfunction. A high level may also be seen in renal failure.

A protein concentration in the pulmonary edema of greater than 70% of the serum protein is strong evidence in favor of a capillary-to-alveolar leak as seen in ALI from any cause.

Implicating transfusion as a cause of nonhydrostatic edema

Consensus definition of TRALI

A consensus definition of TRALI was agreed upon in 2004. A clinical diagnosis of TRALI is considered when a new episode of ALI has occurred within six hours of a blood component or derivative transfusion. Where no other cause of ALI is found, the diagnosis of TRALI is considered probable whatever further tests show. Where another possible cause of ALI is present, the diagnosis of TRALI can only be considered possible (Table 59.2). These criteria are useful but do not include laboratory tests. Many cases of TRALI will be in patients with competing etiologies for ALI. Further recipient and donor investigation can help determine, often in retrospect, the probability that the lung injury was wholly or partly due to transfusion.

Laboratory tests

Changes in circulating leukocytes

Leukopenia, in particular neutropenia and monocytopenia occurring within the first hour after the transfusion and possibly present before the development of clinical lung injury, is supportive of transfusion as opposed to other causes of ALI. The neutropenia is often followed by neutrophilia 5–6 hours later. Monocytopenia is common, may be absolute, and may be more persistent than the neutropenia. Neither change is completely specific or sensitive. The degree of neutropenia is likely to be greater with neutrophil-specific antibodies such as anti-HNA-3a and anti-HLA-A2, whereas monocytopenia alone is most likely to be seen with HLA class II antibodies. Neutropenia is seen without evidence of lung damage with some neutrophil-specific antibodies.

<table>
<thead>
<tr>
<th>Table 59.2 2004 Consensus conference definition of TRALI</th>
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<tbody>
<tr>
<td><strong>I. TRALI criteria</strong></td>
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<tr>
<td>A. ALI</td>
</tr>
<tr>
<td>1. Acute onset</td>
</tr>
<tr>
<td>2. Hypoxemia</td>
</tr>
<tr>
<td>a. Research setting:</td>
</tr>
<tr>
<td>i. PaO2/FiO2 &lt;300, or</td>
</tr>
<tr>
<td>ii. SpO2 &lt;90% on room air</td>
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<tr>
<td>b. Nonresearch setting:</td>
</tr>
<tr>
<td>i. PaO2/FiO2 &lt;300, or</td>
</tr>
<tr>
<td>ii. SpO2 &lt;90% on room air</td>
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<tr>
<td>iii. other clinical evidence of hypoxemia</td>
</tr>
<tr>
<td>3. Bilateral infiltrates on frontal chest radiograph</td>
</tr>
<tr>
<td>4. No evidence of left atrial hypertension (i.e., circulatory overload)</td>
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<tr>
<td>B. No preexisting ALI before transfusion</td>
</tr>
<tr>
<td>C. During or within 6 hours of transfusion</td>
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<tr>
<td>D. No temporal relationship to an alternative risk factor for ALI</td>
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</table>

| **II. Possible TRALI**                                   |
| A. ALI                                                    |
| B. No preexisting ALI before transfusion                  |
| C. During or within 6 hours of transfusion                |
| D. A clear temporal relationship to an alternative risk factor for ALI |

Source: Kleinman et al. (2004). Reproduced with permission of Wiley.

Donor tests

To implicate a particular donation as a cause of antibody-related TRALI requires leukocyte typing of the recipient and antibody testing of the donors (discussed in this chapter). Samples for neutrophil and HLA typing should be taken early from the patient in case death ensues. The finding of a donor–recipient antibody–antigen match is of value in donor management and will make the diagnosis of TRALI more likely than a negative investigation, especially where only a small number of units have been transfused. Such matches also occur in patients without TRALI, and are of increasing statistical likelihood where a large number of units have been transfused. A positive match does not prove that TRALI has occurred.

Management and outcome

Management of the patient

The mainstay of treatment is respiratory support, either with oxygen alone or with oxygen and continuous positive airway pressure by mask or mechanical ventilation. In severe cases with systemic hypovolemia, there must be adequate fluid replacement in addition to positive pressure ventilation. This will often require central venous pressure or left atrial volume monitoring. Additional strategies such as high-frequency ventilation and prone ventilation can be of value. Diuretics are contraindicated, because they have been clearly reported to worsen the hypovolemia and hypotension in several cases. Only where there is concomitant fluid overload from cardiac failure or other causes are diuretics indicated. The use of corticosteroids after the insult is of uncertain value. When the diagnosis is made within six hours and the lung damage is severe, use of high-dose steroids might in theory limit further damage by inhibition of neutrophil activation. Prednisolone, methylprednisolone, and dexamethasone have all been used, but there is no useful clinical evidence regarding efficacy. When the diagnosis is made later, they are unlikely to be of value. In intractable cases for which maximal ventilation is insufficient, extracorporeal membrane oxygenation has been used to support the patient until recovery. The use of plasmapheresis with the intent of removing the causative antibody has been reported. Further transfusions should be given if clinically indicated, but plasma-rich products from female donors should be avoided.

Clinical course and outcome

Most patients begin to improve by 24 hours after the initial injury. Milder cases improve as early as six hours. Chest X-rays usually show clearing of edema by 48–96 hours. Nearly all patients who recover do so without any long-term lung damage. Other organ damage such as acute renal failure is seen in more severe cases, although it is not clear whether this is all due to hypoxia and hypovolemia or whether there is damage to capillary beds in organs other than the lungs. Mortality in different published series varies between 5% and 30%. This depends in part on how cases are ascertained. Where patients receiving transfusion were assessed prospectively for the complication, the incidence was higher, presumably because of recognition of milder cases, but the mortality was low (6%). Where reports depend on a physician recognizing and reporting the condition, the incidence is lower but mortality higher. As an example, the hemovigilance scheme in the United Kingdom reported seven deaths out of 28 possible, probable, or likely cases reported in 2002, a mortality of 25%. Mortality is more
likely in patients receiving larger volumes of single-donor plasma (including fresh frozen plasma [FFP]) rather than RBCs and more likely in patients with more comorbidities.

**TRALI in neonates and children**
TRALI has been reported in children with the same features as noted in adults, including leukopenia, nonhydrostatic pulmonary edema, and hypovolemia. Some of the published reports ascribed death of the child partly or wholly due to the transfusion reaction.\(^{65,86,87}\) Age range of cases is from 0 months to 16 years, but only a few neonatal cases have been reported.\(^{57,88}\) and no neonatal cases have been reported to the UK hemovigilance scheme over 10 years. Use of blood components is more common in neonates than older children, and neonates also receive larger volumes of single-donor plasma relative to their weight. It is possible that neonates are in some way less susceptible to TRALI.

**Directed donations and TRALI**
A particular feature of pediatric TRALI is its occurrence after the use of directed donations from the mother. This practice has been documented to cause TRALI and can be expected to be high risk by virtue of the high probability of the mother having leukocyte antibodies that will match her child’s antigen specificity.\(^9\) By the same rationale, directed donations from a wife to a husband, or of a leukocyte-containing component from a child to a mother or a husband to a wife, will be particularly likely to cause TRALI.

**Donor investigation**
Strategies of donor investigation vary among blood centers. The dual aim of investigation is to help establish the diagnosis and to allow appropriate management of implicated donors. A typical scheme adapted from Su and Kamel\(^9\) is shown in Figure 59.7. Investigation of donors is undertaken only when a diagnosis of TRALI is considered probable or possible. Donations transfused within the six hours before the development of lung injury are considered to be under suspicion. Where the number of possibly implicated donors is small (four or fewer), all donors should be investigated. Where the number of possibly implicated donors is greater, the high-risk donors with a history of pregnancy or transfusion are initially investigated. If a donor or donors are found with an antibody that matches a cognate antigen, investigations of the lower risk donors are not undertaken. If no donor is implicated in the initial investigation, further lower risk donors can be tested in those cases that are considered to be probable TRALI. A further selection policy is to initially investigate only those donors of plasma-rich components. Investigations are undertaken at a qualified laboratory with adequate sensitivity for HLA class I and II antibodies, and HNA antibodies. Recipient HLA and HNA typing may be performed prospectively or only when a donor antibody is found. Tests for recipient antibodies may be undertaken when the lung injury followed transfusion of granulocyte concentrate, or following non-leukocyte-reduced component transfusion in which no donor–recipient antibody–antigen match can be identified. When a non-antibody mechanism is suspected, or if an antibody-related etiology has been largely excluded, tests on the residual donation for abnormal lipids or other bioactive substances may be carried out at a research or reference center.

**Management of implicated donors**
Management of implicated donors varies among countries and centers. It is possible to permanently defer all donors who are implicated in a case of TRALI by virtue of having leukocyte antibodies of any specificity. This would undoubtedly exclude many donors unnecessarily, and the logical extension of such a policy is that all donors with leukocyte antibodies should be deferred whether or not they have been possibly implicated in a case of TRALI. Alternatively, only those donors with antibody matching a recipient antigen are excluded from future donation. This policy assumes that some feature of the antibody in that donor makes them more likely to have caused TRALI in the index case, and thus to cause TRALI with further donations. Finally, it is possible to defer donors who are either possibly or definitely implicated only from donation of plasma-rich components. In addition, some centers automatically defer permanently any donor found to have anti-HNA-3a because of the high frequency of the antigen in the recipient pool (95%) and the common association with severe TRALI. As more countries restrict the manufacture of plasma-rich components to male or nulliparous untransfused female donors, the policy of donor management will become less contentious.

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**Figure 59.7** Flow chart for investigation and management of donors.
Variables affecting the incidence of TRALI

The frequency of reported TRALI depends upon variables affecting the donors, the recipients, and the physicians. Antibody-associated TRALI, which is the common and severe form, is nearly always associated with blood donations from female donors with a history of pregnancy and is both more common and more severe with transfusion of plasma-rich products, such as FFP or apheresis platelets. HLA antibodies have been found in approximately 15% of all female donors but are more common in those who have had more pregnancies and more recent pregnancies, and they are even more common with more sensitive tests. Human neutrophil antibodies are less common. Therefore, incidence of TRALI will depend in part on the donors used by the local blood center. Policies to reduce the number of components containing antibodies are discussed further in this chapter.

Lookback studies for regular donors of blood whose antibody-containing plasma has been implicated in a case of TRALI show that many cases of TRALI are either overlooked or unreported. In addition, infusion of an antibody to a recipient with a matching antigen does not necessarily result in TRALI. Both inherited and acquired recipient variables and details of the transfusion will affect the likelihood of developing clinically apparent TRALI. Inherited variables have not been defined but will almost certainly include polymorphisms in the immune response pathways. The presence of high levels of soluble HLA antigens in the recipient’s plasma may be protective. Acquired recipient variables include the presence of other lung insults and other forms of comorbidity, as discussed. Transfusion variables include the titer and specificity of antibody, the volume of plasma infused, and the speed of infusion. Plasma-reduced RBCs transfused over 90 minutes rarely cause antibody-associated TRALI, whereas FFP given over 15 minutes—a more than 50-fold higher rate of plasma transfusion—is not uncommonly implicated.

Finally, the likelihood of diagnosing and reporting TRALI depends heavily on the physician’s knowledge of the condition.

Reported frequency of TRALI

One single-hospital prospective study estimated frequency for all blood components transfused without any donor selection as 1 in 5000 units. A retrospective single-hospital study estimated the incidence as 1 in 7900 units of FFP only. Hemovigilance data from voluntary reports in the United Kingdom found a reported incidence of approximately 1 in 30,000 units of FFP transfused. Retrospective studies of ALI/TRALI in critically ill patients and a single prospective trial of TRALI after FFP infusion found that as many as 1 in 50 to 200 units of plasma from parous female donors could cause some respiratory dysfunction when compared to plasma from male donors.

It is not possible to give a single figure for incidence, but the chance of female donor plasma containing an antibody matching a recipient antigen is greater than 1 in 50. Severe and clinically distinct TRALI probably occurs about 1 in 2500 to 4000 units of female donor plasma transfused. ALI in which transfusion is a contributory factor in a critically ill patient may be much more common.

Prevention

The majority of severe TRALI cases have an antibody-related etiology. Therefore, prevention is largely aimed at reducing the likelihood of transfusion of the causative antibodies. There are several strategies to be considered.

Avoidance of unnecessary transfusion of plasma

This includes unjustified transfusion of plasma components such as FFP and unnecessary transfusion of plasma associated with RBCs. Use of FFP varies considerably among countries, and it has been demonstrated that use to correct minor coagulopathies is both ineffective and unnecessary. Avoidance of unnecessary transfusion of FFP will reduce the potential for transfusion of units containing antibody. RBCs in additive solution containing less than 20 mL residual plasma are uncommon causes of TRALI, and in those recorded cases there have usually been multiple antibodies in the donor plasma matching cognate antigens in the recipient. Whole blood donations, particularly from high-risk donors (parous female or previously transfused donors), can be processed into RBCs in additive solution with minimal remaining plasma. Similarly, use of platelet additive solutions will reduce the volume of plasma with platelets.

High-risk donor exclusion

The most straightforward form of this policy is to exclude donations from all female donors from production of plasma-rich components. Some individual blood centers have followed such policies locally for some years. The effectiveness of this intervention was demonstrated in the United Kingdom, where such a policy was instituted nationally in 2003. An active hemovigilance scheme clearly showed a 66% decrease both in the incidence of probable TRALI and in associated deaths over the next three years (Figure 59.8). Further developments of this policy include excluding only females with a history of pregnancy and excluding any donor with a history of transfusion or organ grafting. Evidence of the efficacy of excluding female donor plasma comes from many countries, including those of North America and the Netherlands, Germany, and Australia.

Antibody testing

By testing donors for HLA and HNA antibodies, it is possible to exclude all donors with detectable antibodies, or those with antibodies of certain specificities or titer, either from all blood donation or just from donation of apheresis plasma-rich components. This strategy is attractive in that unnecessary exclusion of valuable donors is avoided but it also depends on the sensitivity and specificity of the antibody tests. It has been used with apparent success in some centers.

Use of pooled plasma

Pooled solvent/detergent-treated plasma does not appear to cause TRALI. It is hypothesized that this is because of dilution of antibodies, neutralization of HLA antibodies by soluble HLA antigens in the plasma of other donors, and subsequent removal of the immune complexes in the processing. Extensive use of solvent/detergent-treated plasma in Europe has not been associated with TRALI.

Nonantibody TRALI and inverse TRALI

Leukocyte reduction reduces the production of cellular activation or breakdown products that have been implicated in TRALI. It also will prevent the rare but distinct cases of inverse TRALI related to bystander granulocyte transfusion.
Conclusion
It has taken over 50 years for the full extent of TRALI to be appreciated. It is now recognized as one of the major but preventable adverse outcomes of transfusion. Preventive strategies through female donor exclusion have proved highly effective. Concerns about loss of donor plasma for transfusion have not proved a major problem partly because more rational and evidence-based use of plasma is reducing demand. TACO typically occurs in patients with cardiac failure, expanded blood volume due to pregnancy, renal failure, or other causes. With the reduction in TRALI-related deaths and introduction of hemovigilance schemes, it has emerged as an important cause of transfusion-related morbidity and mortality.

Disclaimer
The authors have disclosed no conflicts of interest.

Key references
A full reference list for this chapter is available at: http://www.wiley.com/go/simon/transfusion


