Among the risks associated with blood transfusion, the possible transmission of an infectious disease is uppermost in the minds of patients and physicians alike. Yet, because of the diagnostic testing now routinely performed in Germany and elsewhere, blood transfusions only very rarely transmit infection with viruses such as HIV and HCV (1). Other well-known adverse effects include those that are due to antibodies not normally present in the patient’s bloodstream, e.g., transfusion-related hemolysis. In contrast, transfusion-related acute lung injury (TRALI), a problem usually caused by irregular leukocyte antibodies in the donor’s blood, is little known not only among patients, but even among physicians, despite its being the leading cause of transfusion-related death in the United States and the United Kingdom, and even though deaths from TRALI have been reported here in Germany as well (2).

The British organization SHOT (“Serious Hazards of Transfusion”), which monitors transfusion-related complications, reports that TRALI is now the most common cause of severe transfusion reactions in the United Kingdom (3). 2,628 severe transfusion reactions were reported in the U.K. from 1996 to 2004, of which 162 were cases of TRALI; 36 of the latter were fatal. Reliable statistics on the incidence and lethality of TRALI in Germany are not yet available. An extrapolation from the British data, on the assumption that they apply to the situation in Germany as well, would suggest that TRALI occurs here with an incidence of 1 per 55,000 transfusions of blood products, and that 10% of all TRALI reactions in Germany are lethal (3, 4). These values lie within the range of current figures for TRALI in other countries as well.

Because the quantity of blood products consumed annually in Germany is about three times as great as that consumed in the United Kingdom, and the quantity of blood products containing plasma is four times as great (5), one might expect that about 90 TRALI reactions would occur in this country each year. From 1995 to 2002, however, a total of only 101 cases of TRALI were reported to the Paul Ehrlich Institute (though the annual number has increased in recent years) (6). Apparently, TRALI was hitherto little known in Germany,

**SUMMARY**

**Introduction:** Haemovigilance surveys reveal that transfusion-related acute lung injury (TRALI) is a rare, but often life-threatening and fatal complication of blood transfusion. TRALI is the leading cause of transfusion-associated death in the USA and Great Britain. Therefore, reporting of TRALI to the responsible authorities in Germany is compulsory. **Methods:** Review of the literature on transfusion-related acute lung injury. **Results and discussion:** Since TRALI is barely known among clinicians and no unitary definition of TRALI exists, there are no valid data referring to incidence of TRALI in Germany. However, in 2004 an internationally agreed TRALI definition was established. TRALI typically occurs within 6 hours after transfusion with acute respiratory distress, hypoxemia and new bilateral pulmonary infiltration on chest X-ray. This characterization based on clinical criteria will facilitate the diagnosis of TRALI so that patients will get appropriate therapy at an early stage. Since granulocyte-reactive antibodies of donor origin are frequently associated with the syndrome (immune TRALI), reporting of TRALI to blood services is important to avoid further transfusion reactions caused by blood products of implicated immunized donors.

**Key words:** TRALI, transfusion, lung injury, neutrophil, leukocyte
and thus rarely reported. On the other hand, Section 16 of the German Federal Blood Transfusion Law (Transfusionsgesetz) requires all severe undesired effects of blood products to be reported to the blood transfusion service, to the Paul Ehrlich Institute (6), and to the Drug Commission of the German Medical Association, or to the German Medical Association. One reason why this law is so often not complied with is perhaps that, until 2004, it was not clear what sort of reaction should be considered a typical manifestation of TRALI. Dyspnea due to transfusion-associated pulmonary edema, as occurs in TRALI, was until recently often thought to be of cardiac origin – even in cases without any evidence of overtransfusion or heart failure.

This review is based on a systematic analysis of the literature from 1951 to 2006, with particular attention to international haemovigilance reports. The authors have also brought their personal experience into the analysis.

**Definition of TRALI**

The European Haemovigilance Network (EHN) defines TRALI as a clinical entity consisting of acute shortness of breath during or in the first 6 hours after blood transfusion, combined with the new appearance of bilateral pulmonary infiltrates (pulmonary edema) on chest x-ray, and in the absence of evidence of heart failure due to volume overload (7). Because pulmonary edema is the key pathological feature of TRALI, this entity was often called “transfusion-related, non-cardiogenic pulmonary edema” before the introduction of the term TRALI in 1983. The North American TRALI Consensus Conference Committee has recommended that proof of hypoxemia, as well as the exclusion of further risk factors for acute lung injury (ALI), such as sepsis, shock, aspiration, etc., should be adopted as additional criteria for the definition of TRALI (box 1). Yet, because patients with additional risk factors for lung injury are particularly vulnerable to TRALI, the Committee suggests that cases in which some of these risk factors are present should still be reported as “possible” (but not definite) TRALI.

The differential diagnosis of TRALI includes not only transfusion-related heart failure due to volume overload (“transfusion-associated circulatory overload,” TACO), but also a transfusion-induced attack of bronchial asthma. For cases of transfusion-related shortness of breath that cannot be attributed to TRALI, TACO, or an asthma attack, the EHN recommends the designation “transfusion-associated dyspnea” (TAD) (box 2).

**BOX 1**

<table>
<thead>
<tr>
<th>Criteria for the diagnosis of a TRALI reaction</th>
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<tbody>
<tr>
<td>European Haemovigilance Network (EHN)</td>
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<tr>
<td>● Sudden shortness of breath</td>
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<tr>
<td>● New bilateral pulmonary infiltrates in chest x-ray</td>
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<tr>
<td>● Onset during or within 6 hours after a blood transfusion</td>
</tr>
<tr>
<td>● No evidence of cardiogenic pulmonary edema or volume overload</td>
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Further criteria proposed by the North American TRALI Consensus Conference Committee

● Hypoxemia (\( \text{PaO}_2/\text{FiO}_2 < 300 \text{ mmHg} \) or \( \text{O}_2 \) saturation < 90% or other clinical evidence)

● No other risk factors for acute lung injury (ALI) – specifically, absence of:
  - aspiration
  - multiple trauma
  - pneumonia
  - cardiopulmonary bypass
  - burn injury
  - toxic inhalation
  - lung contusion
  - acute pancreatitis
  - drug overdose
  - near drowning
  - shock
  - severe sepsis

● If one or more of these ALI risk factors is present, the case should be designated as “possible TRALI”.

Clinical features and diagnostic evaluation

TRALI typically manifests itself as acute shortness of breath (or sudden hypoxemia in an intubated patient) during or shortly after a transfusion. A drop in blood pressure and fever are frequent accompanying manifestations. Pulmonary edema can be radiologically demonstrated about 15 minutes after the onset of shortness of breath or hypoxemia. The pulmonary infiltrates seen on chest x-ray may be quite extensive, often more so than the clinical symptoms alone would suggest. Frequently, a dramatic drop of the leukocyte count is also observed at this time; this can be taken as evidence of the immune pathogenesis of pulmonary edema (9). TRALI is often hard to distinguish from non-transfusion-related ALI or its maximal variant, the acute respiratory distress syndrome (ARDS), on clinical findings alone (10).

A search for the cause of pulmonary edema is the essential next step. In patients without pre-existing cardiac dysfunction, the cardiac silhouette on chest x-ray is essentially normal in TRALI (as opposed to cardiogenic pulmonary edema). Left ventricular function, as assessed by transthoracic or transesophageal echocardiography, is also normal, and the pulmonary artery occlusion pressure is below 18 mmHg (11, 12).

Further useful information can be obtained by measuring the concentration of brain natriuretic peptide (BNP), which is elevated in cardiogenic pulmonary edema or volume overload, but under 100 pg/ml in TRALI (11). The differential diagnosis of TRALI is, of course, more difficult in patients with an already abnormal heart, but TRALI should always be thought of among the diagnostic possibilities when such patients suffer an inappropriately marked worsening of respiratory function shortly after a transfusion (especially when fresh plasma has been transfused).

It is important for blood to be drawn from the patient at the time of the transfusion reaction for laboratory analysis and to be submitted together with the containers of all of the transfused blood products (which must, in any case, be stored for 24 hours after transfusion at 4 °C ± 2 °C).

Three sample cases will serve to illustrate the types of course that TRALI reactions can take (see case illustrations).

Pathophysiology

Most TRALI reactions are thought to develop as follows (diagram): leukocyte antibodies in the donated blood product – usually fresh plasma or platelet concentrate – are transfused into the recipient's blood circulation, where they bind to the recipient's neutrophilic granulocytes, which are thereby either activated or agglutinated. Granulocytes are less readily deformed than erythrocytes and therefore travel slowly through the narrow pulmonary capillaries even under normal conditions; activated and, in particular, agglutinated granulocytes are often unable to pass through the pulmonary capillary system (13). The oxygen radicals and enzymes released by the adherent granulocytes damage the endothelial cells, and, as a result, capillary permeability increases. An outflow of plasma into the interstitial space and alveoli results, causing pulmonary edema. In severe cases, granulocytes also enter the interstitial space and the alveoli. This type of antibody-mediated (immunogenic) TRALI has been repeatedly produced in animal models (14, 15).

The leukocyte antibodies responsible for TRALI are directed against antigens found on the granulocyte membrane, among which are human neutrophil alloantigens (HNA) and human leukocyte antigens (HLA) (table). In particular, anti-HNA antibodies directed against the HNA-3a site (previous designation: 5b) are not uncommonly the cause of

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BOX 2

**Pulmonary transfusion reactions (7)**

1. Transfusion-associated acute lung injury, TRALI
2. Transfusion-associated circulatory overload, TACO
3. Transfusion-associated attack of bronchial asthma
4. Transfusion-associated dyspnea (TAD) (diagnosis of exclusion if 1–3 are not present)
severe, often fatal TRALI reactions (16,17). HLA class I antibodies are commonly found in TRALI; those that are specifically directed against HLA-A2 often cause life-threatening reactions, because such antibodies are usually powerful granulocyte agglutinins, with only rare exceptions (12,18). Recently, HLA class II antibodies have also been under discussion as possible triggers of TRALI reactions (19). HLA class II molecules, however, are not found on resting neutrophil granulocytes, and thus a more complex pathophysiological mechanism must be assumed if class II antibodies are to set off a TRALI reaction. The significance of HLA class II antibodies for the generation of TRALI reactions has not yet been conclusively established.

**CASE ILLUSTRATIONS**

**Case 1**

**The patient:** A 46-year-old man, active in sports and otherwise healthy, underwent operative correction of a dilated aortic root. The surgical procedure was performed without complication.

**Course:** 3 units of fresh plasma, 1 of platelet concentrate, and 2 of autologous erythrocyte concentrate were transfused. Within 2 hours of the last transfusion, the arterial partial pressure of oxygen fell from 224 to 34 mmHg and the leukocyte count fell from 5.4 to 0.9 × 10⁹/l. A chest x-ray revealed bilateral pulmonary infiltrates. Transesophageal echocardiography showed normal myocardial function; the pulmonary artery occlusion pressure was below 17 mmHg. The patient’s condition improved over the following 2 days after treatment with mechanical respiration with positive end-expiratory pressure (PEEP) and the administration of fluids and methylprednisolone.

**Antibody testing:** Strongly agglutinating HLA class I antibodies were found in one of the transfused units of fresh plasma. The donor was a woman with 2 children (12).

**Case 2**

**The patient:** A 66-year-old woman underwent a spinal fusion procedure.

**Course:** 2 units of erythrocyte concentrate and 5 of fresh plasma were given during the operation. While the procedure was still in progress, hypoxia and massive pulmonary edema developed, less than 3 hours after the last transfusion. There was no evidence of heart failure due to volume overload. Despite intensive treatment, the patient died the same day.

**Antibody testing:** Agglutinating HLA-3a antibodies were found in one of the units of fresh plasma. The donor was a woman with one child who had earlier received multiple blood transfusions.

**Case 3**

**The patient:** A 49-year-old woman with cirrhosis of the liver, hypoalbuminemia, and mild pulmonary edema.

**Course:** 2 hours after 2 units of fresh plasma were transfused, the patient suddenly became short of breath. The auscultatory findings suggested rapidly progressive pulmonary edema. The patient was intubated. The chest x-ray revealed new, massive bilateral infiltrates. The patient was mechanically ventilated, recovered rapidly, and was extubated.

**Antibody testing:** Agglutinating HNA-1a antibodies were found in one of the units of fresh plasma. The donor was a woman with 2 children.

**Comment**

In patients with hepatic cirrhosis, just as in patients with preexisting heart disease TRALI is difficult or impossible to distinguish from non-transfusion-associated worsening of pulmonary edema. The major clinical finding of TRALI in such cases is acute worsening of pulmonary edema to a greater degree than would be expected from the underlying illness, in close temporal association with a blood transfusion. In this situation, the finding of leukocyte antibodies in a blood donor makes a TRALI reaction highly probable. Whether or not the ultimate diagnosis is a TRALI reaction, it is useful to identify antibody-positive donors, so that TRALI reactions in future recipients can be prevented.
A further, antibody-independent triggering mechanism for TRALI was described by Silliman and colleagues (20), who showed that certain substances, particularly biologically active lipids (phosphatidyl choline), are formed and/or released in platelet and erythrocyte concentrates during storage and that these substances can activate neutrophilic granulocytes and thereby potentially set off a TRALI reaction. This so-called “non-immunogenic” form of TRALI after platelet or erythrocyte transfusion seems to take a generally milder course. Unlike immunogenic TRALI, which has been observed in healthy persons, non-immunogenic TRALI has only been found to occur in predisposed individuals. Furthermore, among the affected patients, only 3% required mechanical ventilation, a figure considerably lower than the 70% seen in immunogenic TRALI (10, 21). For this reason, among others, the postulated non-immunogenic mechanism of TRALI is still controversial at present and remains to be independently confirmed.

**Treatment**

Patients with sudden shortness of breath occurring during or shortly after blood transfusion should first be given oxygen by the nasal route. In severe TRALI reactions, early intubation and artificial ventilation are of decisive importance for the outcome (22). The administration of high-dose steroids, e.g., 500 mg of methylprednisolone, is sometimes recommended, even though the clinical utility of this has not been demonstrated and the use of steroids is known not to improve survival in ARDS (23). Most experts advise against giving diuretics – in a few cases, improvement was even reported after the administration of fluids (24). When adequately treated, patients usually recover rapidly (22).

**Prevention**

Many severe antibody-associated TRALI reactions have been observed after fresh plasma transfusion (25). The donors of blood products causing TRALI are usually women who have developed immunity against leukocyte antigens (HNA and HLA) over the course of several pregnancies (9, 12, 15, 20). Thus, the risk of TRALI can be reduced by transfusing plasma or platelet concentrate derived from male donors, female donors who have never been pregnant, or female donors whose blood has been checked for leukocyte antibodies.

In particular, female multiple donors who donate blood products via apheresis procedures (thrombocytapheresis, plasmapheresis) should be checked for leukocyte antibodies to reduce the risk of TRALI because, in comparison to whole-blood donation, these procedures generate a 7- to 18-fold greater quantity of plasma-containing blood products for transfusion. A test for leukocyte antibodies needs to be performed only once on each female multiple donor and does not have to be repeated with each donation, unless the donor has been pregnant since the last one. Thus, the cost of testing is relatively low. Nonetheless, comprehensive leukocyte antibody screening has not yet become an established procedure.

**Model for the pathogenesis of immunogenic TRALI.** Leukocyte antibodies in blood products containing plasma are transfused into the recipient’s bloodstream, where they bind to the recipient’s neutrophilic granulocytes (if they express the corresponding antigen). The activated or agglutinated granulocytes become stuck in the pulmonary capillaries and damage them through the release of oxygen radicals and enzymes in an amount sufficient to induce pulmonary edema. FFP, fresh frozen plasma; PC, platelet concentrate.
except in a small minority of blood donation services, because no testing systems for leukocyte antibodies are commercially available at present.

A study of blood donations from 1,500 female potential apheresis donors who had been pregnant 2 or more times before donation revealed the presence of leukocyte antibodies in only 8%. Thus, if all multiparous women were to be excluded as donors without testing, 92% of them would be needlessly lost from the pool of apheresis donors. The loss of potential donors would be even higher if plasma and platelets from female donors were generally not accepted (as is now the case for plasma in the United Kingdom). Users of blood products can also make an important contribution to the prevention of TRALI by immediately reporting suspected cases and saving blood specimens in such cases for further analysis.

**Laboratory testing**

The laboratory investigation of a transfusion reaction fulfilling the criteria for TRALI (box 1) involves testing the involved blood products that were transfused 6 hours or less before the onset of the reaction (or the donor or donors of these products) for leukocyte antibodies, i.e., for antibodies to HNA and HLA (box 2) (3). If a TRALI reaction has occurred in the aftermath of an erythrocyte transfusion, then the patient’s blood should also be tested for leukocyte antibodies, because, in very rare cases, TRALI can also be set off by the patient’s own leukocyte antibodies reacting with contaminant leukocytes in the transfused erythrocyte concentrate. (This constellation of events has not been observed in Germany since 2001, when leukocyte depletion came into general use.)

In the absence of a commercially available testing system for leukocyte antibodies, it may be necessary to study the donors, to a degree depending on their probability of anti-leukocyte immunization, if a TRALI reaction has occurred and a large number of blood products are considered to be potential triggers. Fresh plasma and platelet concentrates from donors who have been pregnant or who have themselves received blood transfusions should be studied with the highest priority, and transfused erythrocyte concentrates from such donors should be studied next. If no carriers of antibodies are identified in these groups, then, if the TRALI has been life-threatening (requiring intubation) or fatal, the blood products derived from donors with no history of pregnancy or transfusion should be studied next.

If a leukocyte-reactive antibody is identified, the corresponding antigen should be demonstrated on the cells of the patient who has suffered the TRALI, or else a leukocyte cross-match should be performed, if possible. No further fresh plasma or thrombocyte concentrates should be prepared from donors who have been shown to possess leukocyte antibodies. If an antibody in an erythrocyte concentrate has set off a TRALI reaction, then the donor of the erythrocyte concentrate should be disqualified from donating blood for as long as leukocyte antibodies can still be demonstrated in his or her bloodstream.

<table>
<thead>
<tr>
<th>Leukocyte antigens involved in TRALI</th>
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<tr>
<td><strong>Human leukocyte antigens (HLA)</strong></td>
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<tr>
<td>HLA class I</td>
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<tr>
<td>HLA class II</td>
</tr>
<tr>
<td><strong>Human neutrophil alloantigens (HNA)</strong></td>
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<tr>
<td>New Name</td>
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<tr>
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</tr>
<tr>
<td>HNA-1a</td>
</tr>
<tr>
<td>HNA-1b</td>
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<td>HNA-2a</td>
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<td>HNA-3a</td>
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Conflict of Interest Statement
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