Review

TRANSFUSION-RELATED ACUTE LUNG INJURY

Transfusion-related acute lung injury (TRALI) is best described as a clinical constellation of signs and symptoms including dyspnoea, hypotension and fever with bilateral pulmonary oedema that usually develops within 4h of a transfusion (Popovsky & Moore, 1985). Patients with TRALI often require respiratory support, but symptoms tend to resolve within 96h. TRALI is most often associated with transfusion of whole blood, packed red blood cell (pRBCs) and fresh frozen plasma (FFP). There are also reports of TRALI following transfusion of granulocytes (O'Connor et al., 1988), cryoprecipitate (Reese et al., 1975), platelet concentrates (Ramanathan et al., 1997; Vircich et al., 1997) and plateletpheresis (Eastlund et al., 1988). Infusion of even small volumes of blood can trigger a reaction (Brittingham, 1957). Estimates of frequency have ranged from 0-014% to 0-02% per unit transfused (Popovsky & Moore, 1985; Ausley, 1987) and from 0-04% to 0-16% per patient transfused (Popovsky & Moore, 1985; Ausley, 1987; Weber et al., 1995). Of particular concern is that TRALI has been reported as the second most common cause of fatal transfusion reactions (Sazama, 1990). The syndrome is fatal in approximately 5% of cases (Wolf & Canale, 1976; Popovsky & Moore, 1985).

The first published report of fatal pulmonary oedema related to transfusion was in 1951 (Barnard, 1951). Over the subsequent 30 years numerous reports of pulmonary oedema associated with transfusion have appeared in the literature. These cases were assigned various designations including: noncardiogenic pulmonary oedema (Ward, 1970; Carilli et al., 1978; Culliford et al., 1980), pulmonary ‘hypersensitivity’ (Thompson et al., 1971; Wolf & Canale, 1976) and severe allergic pulmonary oedema (Kernoff et al., 1972). The underlying cause of the pulmonary oedema was attributed to incompatibility of an undetermined nature (Phillips & Fleischner, 1966), non-HLA leucoagglutinins (Thompson et al., 1971), pulmonary allergic reaction (Kernoff et al., 1972; Culliford et al., 1980; O’Connor et al., 1981) and undefined granulocyte leucoagglutinins (Dubois et al., 1980). The term TRALI was coined by Popovsky et al. (1983). The aetiology of the syndrome was attributed to leucoagglutinating and/or lymphocytotoxic antibodies in the plasma from multiparous donors, directed against the white blood cells of patient recipients.

Clinical, radiologic and laboratory findings

Clinical findings. The clinical presentation of TRALI is indistinguishable from adult respiratory distress syndrome (ARDS) (Popovsky et al., 1983). Symptoms include dyspnoea, cyanosis, hypotension, fever, chills, cough and production of fluid from the endotracheal tube in intubated patients, along with physical findings of bilateral pulmonary oedema. The symptoms often commence within 1–2 h of transfusion and are usually present by 4–6 h (Popovsky & Moore, 1985). An alternate, less common, presentation consists of mild (Levy et al., 1986; Ward, 1970) or no (Kernoff et al., 1972) initial symptoms, with the development of full-blown TRALI as late as 2 d following transfusion (Levy et al., 1986). The severity of symptoms can range from relatively mild to severe, but is primarily related to the degree of hypoxaemia.

The syndrome is often associated with significant morbidity: In a series of 36 patients with TRALI (Popovsky & Moore, 1985), all required oxygen support for a mean of 40 h. Mechanical ventilation was required by 72%; TRALI was determined to contribute significantly to mortality in 6%.

Radiologic findings. The development of bilateral pulmonary infiltrates after infusion of blood containing a leucoagglutinin was first described by Brittingham (1957). Pulmonary infiltrates appear at the time of the reaction and resolve within 96 h in about 80% of affected patients (Popovsky & Moore, 1985) (Fig 1). Arterial blood gas values also tend to become altered but return to baseline within this time frame. Infiltrates persist for at least 7 d in the remaining 20%. Persistence of infiltrates has been associated with difficulty weaning patients from mechanical ventilator support (Popovsky & Moore, 1985). The radiographic findings tend to be more remarkable than the physical findings (Phillips & Fleischner, 1966; Popovsky & Moore, 1985).

Laboratory findings. White blood cell antibodies are frequently identified in donor serum as part of a transfusion reaction evaluation following an episode of TRALI. The first documented leucoagglutinin as the cause of a post-transfusion respiratory reaction was reported by Brittingham (1957). A volunteer was administered plasma, from two patients, containing a weak leucoagglutinin; a mild respiratory reaction occurred after both infusions. Whole blood (50 ml) from a patient with hypoplastic anaemia and a strong leucoagglutinin was subsequently given to the same volunteer; a marked respiratory reaction, associated with bilateral pulmonary infiltrates, ensued.

In the largest documented series of cases (Popovsky & Moore, 1985), granulocyte antibodies were identified, in the serum of at least one donor, in 89% of the 36 cases. Lymphocyte antibodies were identified in at least one donor in 72%. The blood products implicated were whole blood (21), pRBCs (10) and FFP (five). There are several other small series of cases or case reports in which granulocyte
Fig 1. Sequence of chest X-rays taken of a patient with transfusion related acute lung injury (TRALI). Left: normal chest X-ray prior to transfusion; centre: chest X-ray, 2 h after transfusion, showing bilateral pulmonary infiltrates consistent with pulmonary oedema; right: chest X-ray, 48 h after transfusion, showing clearing of pulmonary infiltrates. (Reprinted with permission from Popovsky et al. 1985.)

and/or lymphocyte antibodies were identified in at least one donor (Felbo & Jensen, 1962; Ward, 1970; Thompson et al., 1971; Carilli et al., 1978; Dubois et al., 1980; Campbell et al., 1982; Popovsky et al., 1983; Geeken et al., 1984; Levy et al., 1986; Latson et al., 1986; Ausley, 1987; Fitzgerald et al., 1988; Kawamata et al., 1995; Lindgren et al., 1996; Ramana reaction to occur subsequent to the infusion of a pool of platelet concentrates. The platelet pool was composed of plasma from a single donor, in which platelets from the plasma donor and three other donors were suspended. The plasma donor was strongly positive for anti-HLA-A2 and A28. The recipient patient was negative for the HLA-A2 and A28 antigens. However, the donor of one of the platelet concentrates was positive for HLA-A28. WBCs from this donor were strongly reactive by lymphocytotoxicity and leucoagglutination with serum from the plasma donor.

Popovsky et al (1992) have hypothesized that donor antibodies more commonly cause TRALI than recipient antibodies because the former are able to react with the entire circulating (and marginating) pool of WBCs in the recipient. Antibodies in the recipient have a much smaller pool of WBCs in a blood component with which to react.

**Diagnosis and laboratory confirmation**

The diagnosis of TRALI is based primarily upon clinical signs and symptoms, not laboratory findings. It is important to determine that the pulmonary oedema is noncardiogenic, because it is treated differently than cardiogenic or volume overload types of pulmonary oedema. The laboratory investigation, although important to confirm the diagnosis of TRALI, is performed at a later date. The presence of noncardiogenic pulmonary oedema following a transfusion should prompt immediate medical treatment of this type of pulmonary oedema with subsequent laboratory confirmation of the presumed TRALI reaction.

**Confirmation.** Popovsky et al (1992) have suggested a stepwise approach to confirm the diagnosis of TRALI. First, the gender of the donors of all components transfused within the 6 h prior to the reaction should be determined. All female
donors are then questioned regarding pregnancy and transfusion history; initially, such donors with four or more pregnancies are tested for HLA and granulocyte antibodies. If negative, donors with one to three pregnancies are then tested. When antibodies are found, a lymphocytotoxicity crossmatch between donor serum and recipient WBCs is performed. If the crossmatch is positive, the diagnosis of TRALI is confirmed. If the crossmatch is negative, TRALI is still presumed in the appropriate clinical setting (see subsequent discussion on pathophysiology regarding another postulated mechanism for TRALI).

**Distinguishing TRALI from other types of pulmonary oedema**

Pulmonary oedema can be classified into three types (Milne et al., 1985): cardiogenic, secondary to myocardial or valvular heart disease; overhydration, secondary to excess intake and/or inadequate output of fluid; and noncardiogenic, secondary to increased vascular permeability due to a variety of pathologic, traumatic and infectious causes. TRALI, a form of noncardiogenic pulmonary oedema, is clinically distinguished from other forms of pulmonary oedema based upon normal (Culliford et al., 1980; Dubois et al., 1980; Popovsky et al., 1983) to decreased (O'Connor et al., 1981) pulmonary capillary wedge pressure (PCWP), normal pulmonary artery pressure (Dubois et al., 1980), absence of jugular venous distention (Carilli et al., 1978), absence of murmurs or gallops (Carilli et al., 1978), normal cardiac silhouette (Dubois et al., 1980; Yomtovian et al., 1984), absence of pulmonary vascular congestion (Dubois et al., 1980) and no evidence of myocardial infarction on EKG (O'Connor et al., 1981).

Intubated patients who develop TRALI are typically described as producing copious quantities of frothy oedema fluid from the endotracheal tube (Culliford et al., 1980; Popovsky et al., 1983; Hashim et al., 1980; Kawamata et al., 1995). The protein content of the oedema fluid can be used to help distinguish between types of pulmonary oedema. The protein content of oedema fluid in TRALI is elevated (Culliford et al., 1980; Hashim et al., 1984). The ratio of protein in oedema fluid to protein in blood is usually >0.7 in noncardiogenic pulmonary oedema and <0.5 in cardiogenic pulmonary oedema (Sprung et al., 1981). The relative increase in protein content in noncardiogenic pulmonary oedema, compared to cardiogenic pulmonary oedema, is thought to be due to increased vascular permeability. In fact, increased vascular permeability was demonstrated in TRALI by Carilli et al. (1978). Contrast agent was injected into a patient’s main pulmonary artery shortly after a TRALI reaction began; the late arterial and venous phases showed extravasation of the contrast agent into alveoli.

**Treatment**

Corticosteroids, epinephrines and diuretics were traditionally used to treat TRALI. However, O’Connor et al. (1981) described a patient with TRALI who responded poorly to treatment with diuretics. Although the patient had PE, he was not overhydrated. Treatment with diuretics led to decreased PCWP, decreased cardiac output and hypotension. However, subsequently, the patient promptly responded to saline infusion. Hashim et al. (1984) made a similar observation in a series of eight patients who experienced a total of nine episodes of TRALI after receiving FFP during cardiopulmonary bypass. In the first six patients there was a progressive decrease in PCWP and cardiac output, not improved with an intra-aortic balloon pump or the administration of catecholamines. Three deaths occurred secondary to decreased cardiac output in this group. The last two patients, one of whom had two reactions, were treated with saline infusion to restore adequate left-sided filling pressure and achieve adequate cardiac output. Symptoms resolved rapidly, after saline infusion, in the patient with a single episode of TRALI. The patient who had two episodes responded promptly to treatment with saline infusion the first time. The second episode occurred a few hours later, when another transfusion of FFP was administered. The patient’s cardiac output again rapidly improved with saline administration, but he needed ventilatory support for 5 days.

Levy et al. (1986) and Fitzgerald et al. (1988) have also published case reports describing the attributes of treatment with respiratory support plus fluid administration versus potentially dangerous treatment with diuretics, antibiotics and invasive procedures. Culliford et al. (1980) described three cases of TRALI during cardiopulmonary bypass that responded dramatically to infusion of albumin solution. However, treatment with albumin may be difficult to recommend at this time due to a recent meta-analysis that found increased mortality in critically ill patients treated with albumin solution versus crystalloid (Cochrane Injuries Group Albumin Reviewers, 1998).

Since the pulmonary oedema in TRALI is not related to fluid overload or cardiac dysfunction, but to altered vascular permeability in the lungs, with exudation of fluid and protein into the alveoli, it is logical that maintenance of haemodynamic status is the most beneficial and appropriate therapy. Ventilatory assistance and saline infusion are probably the only therapies that can be recommended, as standard therapy, for the treatment of TRALI. The use of corticosteroids remains controversial, and the use of diuretics may be detrimental.

**Implicated donors and prevention**

The donor of the implicated blood component is usually multiparous (Ward, 1970; Thompson et al., 1971; Kernoff et al., 1972; Popovsky et al., 1983; Eastlund et al., 1989). This is primarily related to antibody formation in female donors, due to exposure to paternal leucocyte antigens from the fetus, during pregnancy. Payne (1962) demonstrated that leucoagglutinins are present in approximately 18% of parous women. The percentage of women with leucoagglutinins increases with increasing number of pregnancies (Payne, 1962). Payne also demonstrated that 55% of women tested still possessed leucoagglutinins 3 years after initial testing and up to 8 years after the last potential exposure (pregnancy). Clay et al. (1984) studied serum from 2313 postpartum women; lymphocytotoxic antibodies were present in 17.2% and granulocyte agglutinating antibodies in 12.6%. For the latter, only two were determined to have...
an identifiable specificity: one was anti-NA1 and the other anti-NB1.

Several Popovsky et al (1983) and Popovsky & Moore (1985) have suggested that blood from implicated donors should only be used as frozen-deglycerolized or washed RBCs. A more recent publication (Popovsky et al, 1992) suggested that implicated donors should be told not to donate again. Additionally, it was recommended that blood from unscreened multiparous donors, defined as having three or more pregnancies, should be diverted to recovered plasma and not used as whole blood, FFP, or pheresis platelets. The use of plasma-poor cellular components (platelet concentrates, volume reduced or albumin resuspended platelets and pRBCs stored in protein poor solutions) was neither advocated nor discouraged. This is estimated to affect about 5% of all volunteer blood and component donations. Other authors (Ramanathan et al, 1997) have suggested that plasma from implicated donors should only be used for fractionation into plasma protein derivatives and all cellular components should be plasma free (i.e. either saline washed or frozen/deglycerolized).

Given the rarity of TRALI, a more moderate approach is probably more realistic. Plasma from implicated donors should be diverted for protein fractionation. Transfusion of pRBCs from such donors when preserved in an anticoagulant-preserve solution like AS-2 (e.g. Adsol solution) is probably acceptable due to the small volume of plasma present in this component. The idea of deferring all unscreened multiparous women as blood and pheresis donors is particularly disturbing, considering the ongoing difficulties with blood shortages.

Particular caution may need to be taken in cases of patient-directed donation of blood and blood components from relatives, particularly if the donor is the mother of the intended recipient. Campbell et al (1982) and Goecken et al (1984) reported two cases of TRALI subsequent to donor-specific blood transfusion, in preparation for living-related renal transplantation. In both cases the implicated donor was the patient’s mother, whose plasma had an antibody specific for her child’s WBCs. This antibody was presumably acquired during pregnancy. Transfusion in this setting, as well as any transfusion from mother to child, is the perfect setup for TRALI. The mother has already been exposed to the child’s WBCs, and has therefore had the opportunity to develop specific antibody to the recipient’s maternal WBC antigens, which makes the recipient a prime candidate for TRALI. Theoretically, patient designated donation of blood from a woman to the father of her children could also result in a TRALI reaction, if the donor had formed antibodies to the recipient’s leucocytes during pregnancy.

Autopsy findings

Several case reports of TRALI included gross and/or microscopic descriptions of the lungs at autopsy (Felbo & Jensen, 1962; Kernoff et al, 1972; Wolf & Canale, 1976; Popovsky & Moore, 1983; Aasley, 1987; Eastlund et al, 1989; Silliman et al, 1997). The lungs were typically described as firm, heavy, consolidated and congested (Aasley, 1987). Microscopically, the tissue showed diffuse alveolar damage (DAD) with intra-alveolar oedema and haemorrhage, hyaline membrane formation, alveolar cell hypertrophy and scant interstitial inflammation (Fig 2) (Silliman et al, 1997). DAD is a pattern of pulmonary injury that is also seen in ARDS (Kobzik & Schoen, 1994). Bronchopneumonia can be superimposed on the DAD if the patient lives for several days after the TRALI reaction (Aasley, 1987).

Pathophysiology

As noted previously, the aetiology of TRALI has long been attributed primarily to the interaction of antibodies, usually of donor origin, with WBCs of the patient recipient. When an extensive search for WBC antibodies is performed, they are identified, in at least one donor, in approximately 90% of cases of TRALI (Popovsky & Moore, 1985).

McCullough et al (1986) demonstrated that 111Indium-labelled granulocytes localize to the lungs, when transfused to recipients with granulocyte antibodies. Although this is the reverse of the usual TRALI situation, it does show that the presence of leucocyte antibodies can cause pulmonary sequestration of WBCs; and the complexes of antibodies with leucocyte antigens are therefore probably responsible for the respiratory symptoms of TRALI.

Seeger et al (1990) have reproduced TRALI in an ex vivo rabbit lung model. When the lung is perfused with plasma containing anti-5b, accompanied by 5b-positive granulocytes and rabbit plasma as a source of complement, severe PE results after a latent period of 3–6 h. The pulmonary oedema is associated with an increase in lung vascular permeability. If 5b-negative granulocytes are infused or if complement is not provided, the pulmonary reaction does not occur. This suggests concomitant activation of complement, which is not usually thought to occur with granulocyte–antibody interaction; however, Yomtovian et al (1984) and Kawamata et al (1995) have reported transient hypocomplementaemia early in the course of a TRALI reaction. Yomtovian et al (1984) attributed the hypocomplementaemia in their case to the presence of a woven Dacron aortic bifurcation graft. Yomtovian et al (1984) and Brittingham (1957) also observed a transient leucopenia. Transient neutropenia has been reported by Aasley (1987).

Although WBC–antibody interaction, with subsequent sequestration of WBCs in the pulmonary microvasculature, leading to increased vascular permeability and exudation of fluid and protein into the alveoli, appears to be the cause of TRALI, two questions remain unanswered. Specifically, why are leucocyte antibodies not identified in all cases of TRALI?

Van Buren et al (1990) reported a case of TRALI associated with transfusion of pRBCs from a donor with NR2 antibody into an NR2-positive patient. But the implicated donor had previously donated 21 times and was never implicated in a TRALI reaction, even though the frequency of
Fig 2. Histology of the lung during transfusion-related acute lung injury (TRALI). Thin sections of fixed lung tissue (A, 40×; B, 440×), stained with haematoxylin and eosin showing diffuse alveolar damage with intra-alveolar oedema and haemorrhage, hyaline membrane formation, and relatively scant interstitial inflammation. (Reprinted with permission from Silliman et al, 1997.)
NB2 is 32% (Lalezari et al., 1982). The authors suggested the patient’s pre-existing condition, thrombotic thrombocytopenic purpura (TTP), predisposed her to develop TRALI.

Popovsky & Moore (1985) first observed that the majority of TRALI reactions occur in the setting of general anaesthesia. This led to the hypothesis that hypoxia itself may ‘predispose’ to TRALI. Silliman et al. (1997) studied 10 patients with TRALI and 10 patients with febrile or urticarial reactions as a control group. All 10 patients with TRALI had a predisposing condition. These included infection, cytokine administration, recent surgery, or massive transfusion. Only two patients from the control group had a predisposing condition. Thus, Silliman et al. (1997) advanced a ‘two-hit hypothesis’ to explain the aetiology of TRALI. The first hit consists of a predisposing condition. The second hit is the infusion of biologically active lipids in stored blood components. This is primarily based upon the observation that stored cellular blood components, at the time of outdate, contain a ‘priming agent’ that enhances polymorphonuclear cell (PMN) NADPH oxidase activity (Silliman et al., 1992). This priming activity is not present in fresh cellular blood components or non-cellular blood components. These researchers demonstrated that there was significantly more PMN-priming activity present in post-transfusion samples from the 10 patients who had TRALI reactions compared to their pre-transfusion samples and pre- and post-transfusion samples from the 10 control patients with just febrile or urticarial transfusion reactions (Silliman et al., 1997). This group has also reproduced a two-hit mechanism of TRALI in a perfused rat lung model (Silliman et al., 1998). The rats were pretreated with endotoxin to simulate pre-existing sepsis. Their lungs were subsequently perfused, ex vivo, with either saline, fresh plasma, plasma from stored RBCs on the day of collection or the day of outdate (day 42), lipid extracts from day 42 plasma or lysophosphatidylcholines. Acute injury was not produced in lungs perfused with saline, fresh plasma or plasma from day 0 pRBCs. Conversely, it was produced in lungs perfused with day 42 plasma from pRBCs, lipid extract from day 42 plasma or lysophosphatidylcholines.

This ‘two-hit theory’ as the main cause of TRALI reactions fails to take into account a fundamental that we know about TRALI and so has its own shortcomings. The almost consistent presence of leucocyte antibodies is ignored; their detection in TRALI investigation is too frequent to be coincidence. The presence of biologically active lipids in post-transfusion TRALI samples may well be effect, not cause. Silliman et al. (1992) did not find significantly greater PMN NADPH priming activity in fresh plasma or FFP, despite the fact that TRALI may occur secondary to infusion of FFP (O’Connor et al., 1981; Hashim et al., 1984; Popovsky & Moore, 1985). If the required two hits are: (1) a significant illness, and (2) transfusion of blood products at or near outdate, TRALI should be an extremely common event in ill patients, do not cause TRALI. There may not be enough biologically active lipid present to cause a reaction in the absence of donor leucocyte antibody to a patient’s WBCs.

Conclusions
TRALI is a clinical constellation of signs and symptoms, related to noncardiogenic pulmonary oedema, that occurs subsequent to transfusion. Antibodies to leucocytes, usually of donor origin, are identified in the majority of cases, provided their presence is sought. Treatment should never be delayed pending laboratory confirmation, which typically occurs at a later date. Treatment should be initiated when TRALI is first suspected and consists of fluid support to maintain blood pressure and cardiac output plus ventilatory assistance. Diuretics have no role in the treatment of TRALI; their use may actually be detrimental.

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