Coagulopathy and plasma transfusion in critically ill patients

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Transfusion-related acute lung injury: a preventable syndrome?

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Abstract

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related morbidity and mortality. Recent insights into the pathophysiology of TRALI have led to various preventive strategies. Strategies in donor management range from antibody testing of sensitized donors to the deferral of female plasma donors altogether. However, knowledge on the efficacy of measures to reduce TRALI is limited. In addition, the various measures may lead to a substantial loss of donors, hampering steady blood supply. Thereby, consensus among countries and blood collecting facilities regarding the optimal strategy to prevent TRALI is lacking. In this review, the advantages and disadvantages of various preventive measures to prevent TRALI are discussed, related to both patient factors as well as blood component-processing strategies, including transfusion policy, donor management and practices of preparation and storage conditions of blood components.
Introduction

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related morbidity and mortality. Any plasma-containing blood product, non-cellular and cellular, can elicit a TRALI reaction and even small volumes can trigger the reaction. TRALI is defined as the onset of Acute Lung Injury (ALI) [1] in temporal relationship to a blood transfusion, characterized by pulmonary edema resulting in decreased oxygenation and bilateral infiltrates on a chest radiograph [2,3].

TRALI is generally considered to be under-reported, underlined by the finding that the incidence in TRALI cases reported to the blood bank is increasing [4,5]. Given the persistent finding of an association between blood transfusion and the occurrence of ALI in observational studies [6], it is probable that TRALI cases reported to the blood bank represent the “tip of the iceberg”. Although it is not known whether adverse outcome in patients that develop TRALI is causal or merely reflective of underlying disease severity, the clear association between transfusion and adverse outcome [6-8] highlights the need for preventive measures.

Although the exact pathophysiology of TRALI is not known, there is near-universal agreement that anti-leukocyte antibodies play a role. Human Leukocyte Antibodies (HLA) and Human Neutrophil Antibodies (HNA) have been found in up to 85% of sera of donors implicated in a TRALI reaction. HLA and HNA are thought to activate pulmonary neutrophils in the recipient, resulting in endothelial damage and pulmonary edema. However, antibodies are not detected in all TRALI cases [9]. Also, many antibody-containing blood products fail to produce TRALI [10]. These supposed differences in susceptibility between individuals have led to the alternative hypothesis of a ‘two-event’ model, in which the first hit is determined by recipient factors at the moment of transfusion (e.g., mechanical ventilation or infection) causing priming of the neutrophils. The second hit consists of the transfusion of antibodies present in the blood product. Alternatively, biologically active substances which accumulate during storage of blood products may provide additional signals in the activation of neutrophils [11].

In recent years, there has been evolving interest in the prevention of TRALI. One of the most important preventive measures has been the exclusion of female plasma donors, which has led to a relevant reduction of the incidence of (reported)
TRALI [4,12], as well as a reduction of respiratory complications following multiple blood transfusions [13,14]. In addition to the antibody hypothesis, the ‘two-hit’ concept may have several implications for efforts to prevent TRALI. Recipient factors can be modified aiming to reduce susceptibility for TRALI as much as possible. Furthermore, optimization of preparation and storage conditions of blood products may attenuate the second hit.

This review will focus on strategies to prevent TRALI. Advantages and disadvantages of various preventive measures will be discussed, related to both patient factors and blood component-processing strategies, including donor management and practices of preparation and storage conditions of blood components and transfusion policy.

Incidence of TRALI

Hemovigilance programs report variable TRALI incidences, ranging from 1:29,000 to 1:260,000 for all transfused blood products [5,15-17], suggesting that TRALI is a rare complication of transfusion. Other data suggest much higher incidences with TRALI occurring in 1 per 1120-5000 transfused products [18,19].

For several reasons, records from hemovigilance programs may underestimate TRALI incidence. Hemovigilance programs rely on spontaneous reporting. Active follow-up of transfused patients with computer-assisted screening showed a TRALI incidence of 0.85%, in contrast to the spontaneously reported incidence that was only 0.24% [20]. Look-back investigations and retrospective studies confirm under-reporting of TRALI [10,21]. A lack of knowledge among clinicians further contributes to under-recognition [22]. Also, despite the consensus definition, imputability criteria exist in various countries. These differences in local diagnostic criteria (i.e., France and UK take the presence of antibodies into account) contribute to variance in reported incidences and probably to underdiagnosing, in particular of nonimmune TRALI. Of note, some of the criteria of the consensus definition are subjective, leading to inter-observer variability in classifying cases of respiratory distress after transfusion.

TRALI incidence may be higher in critically ill patients and cardiac surgery patients. Not only are these patients frequently exposed to allogenic blood products, they often have an underlying condition (e.g., sepsis or mechanical ventilation) that promotes sequestration and priming of neutrophils in pulmonary capillaries. In line with
the ‘two-event’ hypothesis, primed neutrophils may be prone to signals in the blood product that mediate activation and additional lung injury after transfusion. Prospective cohort studies showed an incidence of 5-8% in transfused intensive care unit (ICU) patients, with an incidence of TRALI per transfused unit of approximately 1% [7,8].

Outcome of TRALI

Most patients who develop TRALI need some kind of respiratory support; indeed up to 70% require invasive mechanical ventilation [18] and subsequent ICU admission. When TRALI develops in critically ill patients, duration of mechanical ventilation is prolonged and ICU and hospital length of stay increased compared to controls [8,23]. The mortality of TRALI is considerable; up to 21% of TRALI patients die [4]. In the critically ill, TRALI is an important contributor to mortality, with 42-47% mortality in TRALI patients compared to 23-25% in transfused controls who did not develop ALI [7,8]. In addition to increased hospital mortality, long-term survival is also significantly decreased for critically ill medical patients with TRALI compared to critically ill transfused controls without TRALI [23]. Taken together, TRALI may not be a rare disorder and the syndrome contributes to adverse outcomes. Therefore, efforts to decrease TRALI are mandatory.

Pathogenesis of TRALI

Immune-mediated TRALI

In 65-85% of TRALI cases, antibodies to HLA or granulocytes can be demonstrated in one of the administered blood products [18,24,25]. Involved antibodies are mainly directed against HLA class I, HLA class II or HNA and are thought to react with the cognate antigen on the recipients’ neutrophils [26,27]. This interaction triggers a cascade of inflammatory responses, culminating in pulmonary endothelial damage leading to an increase in pulmonary vascular permeability and subsequent leakage of a protein-rich pulmonary exudate [28]. In approximately 60% of the recipients, presence of the cognate antigen can be demonstrated [18]. Most involved donors in immune-mediated TRALI are multiparous women, since pregnancy is strongly
associated with allo-immunization [29]. Both HLA class I and HLA class II antibodies are implicated in TRALI. Antibodies against HNA-3a (5b) are less frequently involved but associated with more severe cases of TRALI [30-32].

**Non-immune-mediated TRALI**

As antibodies do not seem to play a role in a substantial number of TRALI cases [8], an alternative pathophysiological explanation implicates a ‘two event’ model [11], in which the underlying condition of the patient predisposes to a TRALI reaction [33]. In primed recipients, biological response modifiers that accumulate during storage of cellular blood components have been implicated, including lysophosphatidylcholines (LysoPCs), nonpolar lipids (arachidonic acid and 5-, 12-, and 15-hydroxyeicosatetraenoic acid) [34-36], inflammatory cytokines and soluble CD40 ligand (sCD40L) [37]. These substances induce activation of primed neutrophils in the recipient, resulting in release of inflammatory cytokines and endothelial damage [11,35,38].

Results from experimental studies show that transfused antibodies also function as the second hit [27], implicating that the two hit concept and the immune-mediated concept are not mutually exclusive. A threshold model has been suggested [39], in which a threshold must be overcome to induce a TRALI reaction. Whether TRALI evolves, depends both on the presence of primed neutrophils in the recipients as well as the potential of the transfused product to activate these neutrophils.

**Prevention of TRALI using donor-management strategies**

Ideally, donor-management strategies should be consistent within individual organizations and across transfusion medicine [40]. However, there is a lack of consensus among institutions and different countries regarding the management of donors implicated in TRALI [41,42]. In 2006 and 2007, the American Association of Blood Banks (AABB) recommended US blood-collecting facilities to take actions to mitigate the risk of TRALI [43,44]. By 2009, 90% of blood centers instituted a platelet and/or plasma risk-reduction policy, although a wide variation regarding the type of implemented measures exists [42].
Screening all donors for HLA and/or HNA antibodies

Various cohort studies have shown that the prevalence of HLA antibodies ranges from 1 to 7% in individuals who have never been alloexposed [45-47]. An important limitation of antibody screening is the lack of a gold standard and uniformity in antibody testing. To detect HLA antibodies, many different tests are available, with various cutoff values. Currently there are no published data to assess the sensitivity of a particular assay cutoff value for preventing TRALI [42,46]. Thereby, consensus regarding deferral of donors who test positive for antibodies is lacking [41,48]. Testing for granulocyte antibodies is time consuming and requires large amounts of test cells. Novel, more efficient assays for HLA and HNA antibody detection are under way [49,50], but not yet widely available.

In conclusion, testing of all donors for antibodies is a costly and time consuming strategy to prevent TRALI, due to both the low prevalence of antibodies in unexposed donors as well as the limitations of the available assays [51].

Screening previously alloexposed donors for HLA and/or HNA antibodies

Transfusion can lead to sensitization of recipients, albeit with very different reported numbers, ranging from 1 to 12% [45,51]. Pregnancy is the most important reason for sensitization of the donor population [29,45,51,52]. About 10% of previously pregnant women have HLA-antibodies [32,53] and this number increases to 26-39% in women who have had three or more pregnancies [29,45,51,52].

In 2009, a US survey on TRALI risk-reduction strategies showed that some, but not all centers, tested for leukocyte allo-antibodies in alloexposed donors [42]. Although indications for HLA testing varied widely (e.g., number of pregnancies, history of transfusion or transplantation), the most common scenario was to screen women with one or more pregnancies [42]. None of the centers screened for HNA antibodies. Powers et al. demonstrated that donor history indeed is a reliable predictor of HLA alloimmunization [51]. In addition, the predictive value of a positive HLA antibody screen increases when the test is restricted to individuals with a higher pretest probability of HLA sensitization [47,51]. However, it is still unclear if alloexposed donors who harbor antileukocyte antibodies should be deferred.
**Donor deferral based on antibody screening**

Prospective follow-up of transfusion outcomes suggests that HLA antibodies infrequently cause TRALI [50] and deferral of all donors that test positive for HLA antibodies could result in an unnecessary loss of donors. In contrast to HLA antibodies, HNA-3a (5b) antibodies are associated with more severe cases of TRALI [30,32]. In 2008, the International Society of Blood Transfusion recommended to consider deferral of donors with HNA-3a antibodies from blood donation [54].

To establish if a TRALI case is antibody mediated, implicated donors and recipients should be tested to detect antibody and cognate antigen interaction. However, investigations are often incomplete as recipient samples for HLA and HNA typing can be obtained only in a minority of TRALI cases [40]. Therefore, it was recommended not to test donors for leukocyte antibodies in clinically unsubstantiated cases of TRALI, or in cases in which critical information is lacking [40].

In conclusion, it is obvious that donors implicated in a proven case of TRALI should be permanently deferred from further donations [10]. Donors with HLA or nonspecific HNA antibodies who are implicated in a case of TRALI, could be directed to donating low plasma-volume products if causation is excluded by cross-match or recipient typing studies [40]. Finally, it seems reasonable to defer all donors who test positive for HNA-3a antibodies.

**Donor deferral based on alloexposure**

In Europe, most previously transfused donors are already deferred, in order to decrease the risk of prion transmission [47,55]. In the USA, donors are deferred for 12 months after receiving a transfusion. As less than 5% blood donations are made by previously transfused donors [56] and the rate of alloimmunization is low after previous transfusion [45], the deferral of transfused blood donors is not considered to be an effective TRALI mitigation strategy.

As noted, alloexposure also occurs after pregnancy. Transfusion of plasma from multiparous female donors led to a significant worsening in oxygenation and increased inflammatory response compared to control plasma of non-alloexposed donors [14]. Furthermore, a case referent study of 83 TRALI cases showed that the relative risk of developing TRALI was 19 (CI 95% 1.9-191) after transfusion of plasma-rich products from female donors [12]. In addition, in 71% of TRALI fatalities reported
to the American Red Cross, a female antibody-positive donor was identified [57]. Thereby, a strategy could be to defer women reported to have been pregnant.

Half of blood donations in the USA are made by female donors, of which two thirds reported one or more pregnancies [45,51]. In 2006, in the USA it was recommended to exclude parous women as fresh frozen plasma (FFP) and platelet apheresis donors, as one of the several possible interventions to prevent TRALI [44]. This led to a reduction in reported TRALI cases from plasma transfusion [58]. Also, in 2007, Switzerland adopted a policy to exclude parous women and donors testing positive for HLA antibodies from the production of quarantine FFP [55].

A limitation to deferring parous women only will be the failure to defer female donors with antibodies, who could not or did not accurately inform the blood bank on abortion or miscarriages. About 8% of nulliparous women have HLA antibodies, probably owing to missed ectopic pregnancies and premature abortions [29]. Thereby, an alternative strategy is to defer all women from donation of plasma.

**Deferral of all female donors**

In 2003, the National Blood Service, which supplies 83% of blood components in the UK, was the first to introduce a predominantly male donor strategy for FFP production and for suspension ofuffy coat-derived pool platelets. This resulted in a significant drop in reported TRALI cases associated with transfused FFP and platelets. Since 2005, no concordant antibody-positive cases of TRALI have been reported [4]. Also, in surgical patients receiving multiple transfusions, use of predominantly male plasma significantly reduced the onset of ALI [13] or respiratory distress [59].

In 2007, The American Red Cross implemented a strategy based on preferential use of plasma collected from male donors. As a result, 95% of distributed plasma for transfusion was collected from male donors [40]. This strategy resulted in a significant reduction in TRALI associated with plasma transfusion (odds ratio: 0.21 95% CI: 0.08-0.45) [58]. Although not all blood collecting facilities in the USA implemented a gender-based donor strategy, male only was the most frequently implemented policy to reduce TRALI risk from apheresis platelets. Furthermore, 91% of the blood centers had a plasma risk-reduction policy, which in some centers included male-only plasma [42].
In conclusion, exclusion of female donors prevents the majority of TRALI cases caused by plasma rich products. However, TRALI due to red blood cell transfusion and pooled platelets are not prevented.

**Consequences of donor deferral for blood-banking practice**

Preventing TRALI by screening or excluding (sub) groups of donors will have implications for blood-banking practice. The key issue is finding a balance between safety and maintaining adequate supply of blood products.

**Deferral based on antibody screening**

Leukocyte antibody screening of only previously alloexposed and consequential deferral of those with HLA antibodies, will lead to a loss of up to 10% of apheresis donors and 7% of whole blood donations [32,51,56]. Deferral of all donors with any leukocyte antibody from donation of any blood product would result in a loss of 9% of donors [47]. An alternative option is exclusion based on the type of antibody, such as, deferral of those with HNA-3a antibodies and HLA antibodies that react with HLA antigens that are highly prevalent. Obviously, donors with circulating antibodies that have been implicated in TRALI in which the cross match with the recipient is confirmed, should be deferred from further donations [40].

**Deferral based on alloexposure**

As most previously transfused donors are already deferred to decrease the risk of prion transmission [47,55], implementation of this strategy will have limited effect on blood-banking practice. However, deferral of all previous pregnant women from donating plasma-rich blood components however, would lead to a substantial loss of donors. As discussed previously, approximately 50% of donors are female and up to 65% of them have been pregnant [29]. If all these women would be excluded, it is estimated that this would result in a loss of 30% of whole blood donations and nearly a quarter of all apheresis platelet donations [56]. In Spain, apheresis donations from females with a history of pregnancy and positive for HLA antibodies are used for plasma derivates. This led to 16% loss of transfusable apheresis plasma and 12% loss of apheresis platelets from
female donors. The latter could be compensated with platelets obtained from whole blood donors. However, the loss of transfusible apheresis plasma was temporarily troublesome and it was occasionally necessary to import FFP from other blood banks [60].

**Deferral of all women**

This strategy carries the risk of unnecessary loss of donors and blood that would be safe for most recipients. However, in the UK, the implementation of predominantly male FFP was not accompanied by loss of any donors [4]. Also in The Netherlands, the male-only plasma measure was implemented without significant costs or serious threat to the plasma supply [61]. By contrast, calculations from the American Red Cross Blood Service estimated that deferring all female donors would result in a nearly 50% reduction in the units of whole blood available for plasma manufacturing. Deferral of female apheresis platelet donors would result in a loss of 37% of apheresis platelet donations [56]. It is expected that the loss of female-derived transfusible plasma units can be compensated, but the losses of apheresis platelet would impact clinical care and are considered unacceptable.

A possible explanation for this discrepancy in loss of platelet donations is the difference in how platelets are collected. In the USA the predominant method is apheresis, while in Europe buffycoat-derived platelet pools are used. The latter also contain some residual plasma, but can be resuspended in male plasma or additive solution (AS), which has only recently became available in the USA [4]. In general, apheresis platelet risk-reduction policies led to an increased production of whole-blood derived platelets in 25% of the blood centers [42].

In conclusion, deferral of all female plasma donations is proven to be feasible and efficient in reducing TRALI. The deferral of all female platelet apheresis donations without substantial losses is currently not feasible. Furthermore, to prevent unnecessary loss of donors, it should be emphasized that female donors remain eligible to donate cellular components, but that their plasma would be preferentially diverted to fractionation rather than infusion [57].
Prevention of TRALI by modifying product preparation and storage condition

Leukoreduction

Many countries and numerous blood-collecting facilities in the USA had implemented universal prestorage leukoreduction by the end of the 1990s. Its implementation is associated with decreased in-hospital mortality, which can possibly be attributed to a decrease in the amount of inflammatory transfusion reactions [62]. According to the two-event model, TRALI can result from transfusion of bioactive lipids that accumulate during storage of cellular blood components. Prestorage leukoreduction of red blood cells reduces accumulation of cytokines [63], with a concomitant attenuation of neutrophil-priming activity compared with non-leukoreduced blood [64]. However, accumulation of non-polar lipids is not attenuated by prestorage leukoreduction of red blood cells and these lipids have been shown to induce ALI in a two-event in vivo model of TRALI [36]. In addition, observational studies on the effect of leukoreduction on ALI and TRALI incidence have shown conflicting results [65-69]. Of note, only a small minority (<10%) of TRALI cases result from the interaction of transfused white blood cells with antibodies in the recipient [60].

Blood product leukoreduction leads to reduced allo-exposure of transfused individuals, which consequently reduces the sensitization rates of these individuals [68]. However, as rates of alloimmunization are modest and transfused individuals are excluded from donation, it is doubtful whether leukoreduction attributes to a reduced incidence of TRALI.

Decreasing storage time

During storage, the erythrocyte undergoes numerous changes and acquires pro-inflammatory properties, collectively referred to as the “red cell storage lesion” [70]. In addition, bioactive lipids (LysoPCs) that accumulate in cellular blood components during storage are associated with increased neutrophil-priming activity of the blood product [71,72]. Indeed, the accumulated lipids have been shown to induce TRALI in a two-event model of TRALI in rats [35,38] and the occurrence of TRALI has been linked with transfusion of blood containing lipids with significant...
neutrophil-priming activity [34]. Of note, association of aged red blood cells and transfusion-related morbidity and mortality has mainly been found in studies performed in the USA [27,35,73], but not outside the USA [8,74], which may suggest a difference in product preparation or storing processes of red blood cells. In a study performed in The Netherlands, stored red blood cells did not show lysoPC accumulation, nor neutrophil priming [72].

Besides lipids, sCD40L has been implicated in TRALI [36-38]. Levels of sCD40L were increased in platelet products associated with TRALI compared to control platelet products and sCD40L had neutrophil-priming capacity in vitro [37]. Of note, although observational studies report associations between prolonged storage of blood products and respiratory failure in patients after cardiac surgery and trauma [73,75], storage time could not be linked to TRALI in observational trials [7,8].

**Altering storage conditions**

Of interest, the accumulation of LysoPCs depends on the percentage of plasma present in the storage medium [72]. The use of ASs for the resuspension of platelets (platelet additive solution) or erythrocytes (SAG-M) can reduce the amount of plasma content in the final product. However, since even small amounts of plasma can cause TRALI, these substances will not totally eliminate this risk [76]. Whether the use of ASs will reduce the incidence of TRALI remains to be determined.

Washing of red blood cells can reduce the concentration of HLA and HNA antibodies, which could reduce the incidence of TRALI [41]. Also, Silliman et al. demonstrated that washing of stored packed red blood cells reduces neutrophil-priming activity of the product [77]. Indeed, in a two-hit rat transfusion model, transfusion of washed red blood cells prevented onset of TRALI [78]. Whether washing can be performed without diminishing the oxygen-delivering capacity remains to be determined. At present, there are no clinical data available about washing of blood components and TRALI.

In conclusion, preparation and storage conditions of blood components are involved in the pathophysiology of TRALI. However, it is not yet known whether specific measures regarding the preparation or storage of blood products influences TRALI incidence [41].
Preparation of solvent detergent plasma
Solvent/detergent (S/D) plasma (Octaplas®) is prepared from pools containing plasma from 500-1600 donations, which leads to at least a 500-fold dilution of donations containing leukocyte antibodies. Indeed, no HLA Class I or II or granulocyt agglutinating antibodies could be detected in S/D plasma [79]. After introduction of S/D plasma in Norway [79], no cases of TRALI have been reported in recipients so far [17,80].

A concern of the use of pooled plasma has been the occurrence of prion diseases. However, to date, this has not been reported. Another limitation to implementation of S/D plasma is financial. The replacement of all units of FFP in the UK by S/D plasma is estimated to cost £9.2 million/year to prevent 107 cases of TRALI [81]. The introduction of the use of male-only FFP may further negate supposed beneficial effects of S/D plasma on the incidence of TRALI.

Reducing recipient exposure to blood products
The most important measure to prevent TRALI is to enforce appropriate use of blood products. A restrictive transfusion strategy reduces the incidence of ALI in the critically ill [82] and is associated with decreased mortality [83]. Multiple-unit transfusions to correct for anaemia are still common practice. Also, inappropriate use of blood products (i.e., outside of guidelines) is still frequent, including the use of FFP for the reversal of warfarin and for prevention of hemorrhage in case of prolonged coagulation parameters. A measure to reduce inappropriate transfusion may be the use of computerized transfusion algorithms [84]. However, blood transfusion cannot be completely avoided. Indeed, data from combat trauma patients have led to more aggressive use of FFP and platelets for the resuscitation of severe bleeding patients [85]. Thereby, FFP and platelet use in the UK has remained virtually unchanged in the past decade [86].

Of note, there is an emerging interest in the use of alternative products to correct coagulation disturbances. A recent trial showed that the use of tranexamic acid in trauma patients significantly reduced mortality [87]. Furthermore, the use of point of care tests to assess coagulation (e.g., ROTEM®) in combination with transfusion
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Modifying host factors to reduce susceptibility for TRALI

Patient-related risk factors for TRALI have recently been identified. These include mechanical ventilation, cardiothoracic surgery, sepsis, trauma and hematologic malignancy [7,8]. Most of these factors cannot be modified. However, measures that attenuate ALI are likely to raise the threshold for TRALI. Protective mechanical ventilation strategies using low tidal volumes in mechanical ventilation reduce mortality with 22% in ALI/acute respiratory distress syndrome [90] and injurious mechanical ventilation with high tidal volumes is shown to aggravate TRALI in a mouse model [91]. Therefore, it seems reasonable to apply lung protective ventilation strategies in patients subjected to a blood transfusion. In addition, fluid-restrictive management has been shown to reduce ventilation days in patients with ALI [92]. It is conceivable that these results also apply to TRALI.

Expert commentary

TRALI is a relevant clinical problem with substantial morbidity and mortality in certain patient populations. In the past decade, important preventive measures have been implemented. The deferral of female donors for FFP production has led to a reduction of TRALI cases. Depending on blood bank practices, such a policy is feasible without inferring with adequate blood supply. Preventing TRALI due to platelet transfusion is more complicated. Deferral of all women from donating apheresis platelets does not seem feasible, since this will lead to a substantial loss of donors and, consequently, clinical supply problems. Antibody testing of platelet donors can be considered, but has considerable limitations. However, at present, antibody testing of alloexposed platelet donors seems a reasonable TRALI risk-reduction strategy. Alternative measures to prevent TRALI are the resuspension of pooled platelets in male plasma, which was relatively easily implemented in the UK and The Netherlands, or the addition of platelet AS instead of plasma.
However, the above measures will only prevent immune-mediated cases of TRALI due to FFP or platelet transfusion. Also, patients with a decreased threshold to develop TRALI (e.g., those who are critically ill) are at risk to develop TRALI, even if the transfused product only contains a small amount of plasma. Further research in optimizing preparation and storage conditions with the aim to reduce accumulation of bioactive substances is warranted.

It needs to be elucidated whether it is beneficial to implement tailor-made transfusion therapy for specific patient populations at risk for TRALI. This could potentially include the preferential use of ‘fresh’ blood products, S/D plasma or washed blood products, platelets from male-only or antibody-negative donors and possibly even male-only red blood cell products.

Finally, despite extensive evidence about the harmful effects of blood products, inappropriate use is still common. Awareness needs to be heightened among clinicians and studies on the use of alternative products need to be encouraged.

**Five-year view**

Consensus needs to be reached concerning donor deferral and antibody screening of donors. To improve donor screening, standardized HLA and HNA tests are needed. In addition, stronger evidence is needed regarding the effect of deferral of donors that harbor antibodies, in order to maximize TRALI prevention with the least possible loss of donors. Furthermore, to prevent unnecessary deferral of donors with leukocyte antibodies, both donor testing and crossmatching with the recipient’s cells or typing of the recipient’s cells should be performed when TRALI is suspected. A prerequisite to prevent use of products from donors implicated in TRALI is universal use of the consensus definition for reporting of TRALI cases to the blood bank.

The deferral of female plasma donors has been shown to be effective and feasible and is expected to be applied in more countries. For other plasma-rich products (e.g., platelets), deferral of all females is not feasible. Guidelines on donor screening and deferral are warranted.

It remains to be elucidated whether the use of fresh blood products is beneficial compared with prolonged storage, which is associated with the accumulation of bio-
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active substances. Results of the ABLE trial, which compared fresh blood with standard transfusion care in critically ill patients [101], may help to answer this question. Awareness among clinicians about risk factors for TRALI needs to be heightened, especially among those who are involved in the care of high-risk patients, such as ICU physicians, anesthesiologists and hematologists. Results should be awaited of trials investigating the (preventive) use of plasma-rich products in critically ill patients with a coagulopathy [102-104]. In addition, the ongoing RELIEVE trial might clarify whether a restrictive transfusion policy in critically ill is safe and advantageous [105]. Hopefully, the results of these trials will further contribute to the appropriate use of blood products.
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