Coagulopathy and plasma transfusion in critically ill patients

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Chapter 13

Prevention of immune-mediated transfusion-related acute lung injury; from bloodbank to patient

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Abstract

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion related morbidity and mortality. Immune-mediated TRALI is caused by leucocyte and neutrophil antibodies in the transfused blood products that react with white blood cell antigens of the recipient, hereby inducing endothelial damage and lung injury. About two thirds of TRALI cases are thought to be immune-mediated. Both Human Leucocyte Antibodies (HLA Class I and II) and Human Neutrophil Antibodies (HNA) are involved in TRALI. Most antibodies result from allo-exposure of the blood donor, with multiparous donors having the highest incidence of antibodies. Detection of anti-leucocyte and anti-neutrophil antibodies is complex and many uncertainties still exist regarding the interpretation of the test results.

In this review we discuss the evidence and effectiveness of measurements to prevent immune-mediated TRALI from a bloodbank and bedside perspective. From a bloodbank perspective various preventive measures have been implicated. In some countries bloodbanks have successfully implemented donor selection strategies, ranging from testing of allo-exposed donors for leucocyte antibodies to the exclusion of all females from donating high plasma volume products. Another strategy involves dilution of antibodies present by pooling of plasma donations of multiple donors.

From a bedside view, the most important measure to prevent TRALI is to limit patients’ exposure to allogenic blood products. Furthermore recognition and awareness of the syndrome need to be heightened among clinicians.
Introduction

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related morbidity and mortality [1-4]. Although traditionally regarded as a rare syndrome, recent studies show that the incidence is high in specific patient populations such as critically ill patients [5-7] and significantly contributes to adverse outcome [7,8]. A two-event hypothesis has been postulated that may explain the high incidence in the critically ill [9,10]. The first event is an underlying inflammatory condition, causing priming of the pulmonary neutrophils and the pulmonary vascular endothelium. The second event is the transfusion of a blood product containing either antibodies or factors that accumulate during storage, providing additional signals for neutrophil-mediated endothelial damage and lung injury. In general the mediators of the second hit can be divided into immune-mediated onset of TRALI (human leucocyte antibodies and human neutrophil antibodies) and non-immune-mediated (factors that accumulate during storage of cell containing blood products such as lysophosphatidylcholines, sCD40L). In line with the two-event model, critically ill patients are at high risk for acquiring TRALI. Incidences up to 8% of patients transfused have been reported for this patient population [5,7]. Generally stated to have a good prognosis, recent studies show that development of TRALI has a significant effect on morbidity and mortality. At this time, treatment of TRALI is directed to supportive care as no therapeutic strategy exists. From this point of view, countries started preventive measurements including donor exclusion policies. In the present review the focus will be on the prevention of immune-mediated TRALI, the prevention of non-immune-mediated TRALI will be discussed elsewhere in the issue. The perspective of this review will be from a bloodbank and a bedside view.

Methods and Materials

The Medline database was used to identify medical subject’s headings (MeSH) to select search terms. In addition to MeSH terms, we also used free-text words. Search terms referred to aspects of the condition (“TRALI”, “prevention”) as well as related topics (“human neutrophil antibodies”, “human leucocyte antibodies”, “fresh frozen plasma” and “platelet transfusion”). Relevance of each paper was assessed using the
on-line abstracts. In addition, the reference lists of retrieved papers were screened for potentially important papers.

**Background**

In 1983 Popovsky et al. published the first landmark report on the association between the presence of leucocyte antibodies in the donor serum and onset of acute lung injury (ALI) in the recipient of the transfusion [11]. They described 5 cases of transfusion-related ALI in which in all cases leuco-agglutinating and lymphocytotoxic antibodies were found in plasma of the transfused blood products. In 3 cases, the antibodies corresponded to the HLA antigens of the recipient. It was also recognized that multiparous blood donors whose plasma contained these antibodies represented a potential transfusion hazard. A following report of the same group first identified TRALI as a distinct clinical entity, they reported granulocyte-reactive and lymphocytotoxic antibodies in the sera of 89% and 72% of the blood donors implicated in 36 cases of TRALI, respectively. Subsequently, many other authors have reported on the association between the presence of antibodies against human leucocyte antigens (HLA) or human neutrophil antigens (HNA) in donor blood and the onset of TRALI in the recipient [2,12,13]. Although elucidation of the pathogenesis of TRALI is not complete, the role of transfused blood donor HLA and HNA antibodies is widely accepted.

**Leucocyte antibodies involved in TRALI**

Antibodies in transfused blood products against HNA, HLA-class I and HLA-class II can cause TRALI in the recipient. The antibodies involved are mostly IgG alloantibodies produced after pregnancy, transfusion or transplantation, but can also be present in a small percentage of apparently non-immunized donors [14-16]. The number of TRALI cases due to antibodies in the recipient binding to the cognate antigens on the white cells in the blood products is reduced after the introduction of leuco-depletion of blood products [17].

Up to now, eight HNA are known [18,19]. Furthermore, a small percentage of Caucasians is deficient for FcγRIIIb which can lead to immunization and FcγRIIIb alloantibody production (tables 1 and 2) [20]. Of these antibodies, HNA-1a, 1b, 2
Table 1: Overview of Human Neutrophil Antigens [16].

<table>
<thead>
<tr>
<th>Antigen System</th>
<th>Carrier glycoprotein</th>
<th>CD</th>
<th>Antigen</th>
<th>Allele</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNA-1</td>
<td>FcγRIIIb</td>
<td>CD16b</td>
<td>HNA-1a</td>
<td>FCGR3B*01</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HNA-1b</td>
<td>FCGR3B*02</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HNA-1c</td>
<td>FCGR3B*03</td>
<td></td>
</tr>
<tr>
<td>HNA-2</td>
<td>CD177 glycoprotein</td>
<td>CD177</td>
<td>HNA-2*</td>
<td>CD177*01</td>
<td></td>
</tr>
<tr>
<td>CD177 deficient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>incorrect splicing process**</td>
</tr>
<tr>
<td>HNA-3</td>
<td>CTL2</td>
<td></td>
<td>HNA-3a</td>
<td>SLC44A2*01</td>
<td>SLC44A2*461G</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HNA-3b</td>
<td>SLC44A2*02</td>
<td>SLC44A2*461A</td>
</tr>
<tr>
<td>HNA-4</td>
<td>MAC-1;CR3;αmβ2-integrin</td>
<td>CD11b</td>
<td>HNA-4a</td>
<td>ITGAM*01</td>
<td>ITGAM*230G</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNA-5</td>
<td>LFA-1;αLβ2-integrin</td>
<td>CD11a</td>
<td>HNA-5a</td>
<td>ITGAL*01</td>
<td>ITGAL*2372G</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* In HNA-2 positive individuals negative neutrophil subpopulations are present due to lack of gene transcription caused by three mutations: A793C, G1084A and possibly C49G. Furthermore, atypical HNA-2 expression causing two distinct HNA-2 positive neutrophil populations can be due to the mutations A134T, G156A and G1333A [91].

**Incorrect splicing process generating premature stop codons [92].

Table 2: HNA-1 polymorphisms

<table>
<thead>
<tr>
<th>Nucleotide/AA Position/position</th>
<th>HNA-1a</th>
<th>HNA-1b</th>
<th>HNA-1c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nucl/AA</td>
<td>Nucl/AA</td>
<td>Nucl/AA</td>
</tr>
<tr>
<td>141/36</td>
<td>G/Arg</td>
<td>C/Ser</td>
<td>C/Ser</td>
</tr>
<tr>
<td>227/65</td>
<td>A/Asn</td>
<td>G/Ser</td>
<td>G/Ser</td>
</tr>
<tr>
<td>266/78</td>
<td>C/Ala</td>
<td>C/Ala</td>
<td>A/Asp</td>
</tr>
<tr>
<td>277/82</td>
<td>G/Asp</td>
<td>A/Asn</td>
<td>A/Asn</td>
</tr>
<tr>
<td>349/106</td>
<td>G/Val</td>
<td>A/Ile</td>
<td>A/Ile</td>
</tr>
</tbody>
</table>

and especially the strong neutrophil agglutinating HNA-3a antibodies have been implicated in TRALI [16,21,22]. This is somewhat biased as antibody detection and identification until recently were mostly limited to these antigens as antibody identification panels (including antigen negative donor neutrophil suspensions) for HNA-3b, 4a and 5a were not available.
Detection of antibodies involved in TRALI

Guidelines for the detection of granulocyte specific antibodies are given by the International Granulocyte Immunology Working party [23]. The use of the Granulocyte ImmunoFluorescence Test (GIFT)[24], the Granulocyte Agglutination Test (GAT)[25] and the Monoclonal Antibody Immobilization of Granulocyte Antigens (MAIGA)[26] assay are advised. In the GIFT, antibody binding on complete neutrophils is tested. In the GAT, microscopically visible agglutination of neutrophils in the presence of the investigated serum is scored. Both the GIFT and the GAT can be used to screen for the presence of antibodies and identification of these antibodies depending on the typed donor panels used. Both tests are scored semi-quantitatively with the possible reaction strength variation of weak to strong positive ((+), 1+, 2+, 3+ and 4+). In the GAT agglutination of neutrophils can be scored. This agglutination is seen for all HNA antibodies and for several HLA antibodies. The MAIGA is a glycoprotein specific ELISA based on the Monoclonal Antibody Immobilization of Platelet Antigen (MAIPA), a test used to identify platelet-reactive antibodies [27]. MAIGA can be used for the identification of all HNA antibodies, except for HNA-3 antibodies as Choline Transporter-Like protein 2 (CTL2, the carrier for HNA-3), specific monoclonal antibodies that can be used in the MAIGA are not available yet. In most laboratories screening and identification of granulocyte specific antibodies in TRALI cases was limited to the GIFT and GAT, after which some laboratories confirmed the detected antibodies in the MAIGA. Both for HLA and granulocyte specific antibodies it is assumed that the amount of antibodies in the blood product is of importance to overcome a certain threshold to induce TRALI. For this reason, in several countries female plasma, with a higher risk of containing antibodies due to immunization during pregnancies, is limited to less than 30 ml per blood product intended for transfusion [28-30]. A decrease in reported TRALI cases in the different hemovigilance schemes shows a positive effect of this intervention [31,32]. However, this measurement will not prevent all immune-mediated TRALI as TRALI-cases after transfusions of blood products containing less than 30 ml plasma have been reported [16,33]. It seems also plausible that HNA antibody reaction strength plays a key-role in the occurrence of TRALI, but until now no granulocyte specific antibody reaction strength studies have been performed. Most granulocyte specific antibodies
implicated in TRALI cases are IgG antibodies. Quite often weak, a-specific granulocyte reactive IgM antibodies are detected in sera of TRALI associated donors and random screened donors, but our personal opinion is that these (very) weak a-specific antibodies do not cause TRALI [15].

Both HLA-class I and –class II antibodies can cause TRALI. Class I antibodies can activate neutrophils [34,35] by binding to their cognate antigens expressed on neutrophils or on endothelial cells after which neutrophils can be ‘trapped’ by binding via the Fc receptors. However, a recent study in mice showed that macrophages and complement activation are important in the onset of HLA Class I induced TRALI [36]. HLA class II antigens are not expressed on neutrophils but can cause TRALI by binding to the recipient monocytes leading to activation, release of soluble mediators and activation of neutrophils [37-40]. Frequently detected HLA antibodies in TRALI implicated donors have specificity for HLA-A2 and HLA-DR4 [21,37] which is partly due to the high antigen frequency (in the Caucasian population 48% is HLA-A2 and 23% HLA-DR4 positive) causing frequent exposure to the antigens in pregnancy and after transfusion or transplantation. However, this cannot be the only explanation for the high frequency of these antibodies as other antibodies against equally frequent antigens are detected less in TRALI implicated donors.

Several different antibody detection techniques, such as the Lymphocyte ImmunoFluorescence Test (LIFT) [41], HLA antibody ELISAs [42], Complement Dependent Cytotoxicity (CDC) assay [43,44] and HLA specific flow cytometry beads assays [45,46], are available for detection of HLA antibodies. In many laboratories, the easy to perform, flow cytometric beads assays replaced the CDC in the past five to ten years. Both beads with multiple HLA antigens for the screening of HLA class I and II antibodies and single antigen beads for antibody identification are available [47]. Results are expressed in mean immunofluorescence intensity (MFI). Since the introduction of these beads assays many more HLA antibodies are detected. The high sensitivity can be due to the concentration of antigens on the beads but seem to be strongly dependent of the cut-off values used. The specificity and clinical importance of these extra antibodies is still unclear and needs to be studied [48-51].

A recently published study by Hashimoto et al. [52] shows significant stronger mean HLA antibody reaction strength in donors implicated in TRALI cases compared with a non-hemolytic transfusion reaction (NHTR) group. This is a first indication that
antibody reaction strength is important, but although the means differed significantly, individual antibodies varied in the TRALI group from strong to weak reactive and further studies are necessary.

To confirm the imputability of the detected antibodies, a cross match between leukocytes (lymphocytes and neutrophils) of the patient and serum of the donors is necessary. Cross matching with neutrophils of the patient can be done in the GIFT, GAT and MAIGA. Cross matching with lymphocytes is not possible in the beads assays, and must be done in the CDC or LIFT.

If cross matching is not possible, HLA and HNA genotyping can show if the patient is positive for the cognate antigens for the detected antibodies in donor blood.

**Donor characteristics**

Important in prevention of immune-mediated TRALI is to understand which donors have a high incidence of HLA or HNA antibodies. Donor risk factors for HLA Class I and HLA Class II antibody formation include allo-exposure to white blood cells. Taking this into account two groups could be at risk; multiparous donors and donors exposed to blood transfusion.

**Multiparous donors**

Densmore *et al.* investigated whether the likelihood of HLA allo-immunization increases with the number of pregnancies. In multiple reports it is shown that the likelihood of HLA allo-immunization increases with the number of pregnancies from 1-9% in the absence of previous pregnancies up to 32-38% of multiparous women harboring HLA antibodies [15,53,54]. The clinical significance of donor gender was furthermore demonstrated in two studies in critically ill patients reporting worsened oxygenation after FFP transfusion from (multiparous) female donors [6,55]. From these results it can be concluded that exclusion of female or more specific multi-parous women from high volume plasma products may result in prevention of TRALI. Effect of such strategies will be discussed later on in this review.
**Donors previously exposed to transfusion**

Allo-exposure by transfusion can induce antibody formation in donors, however the prevalence of HLA antibodies in previously transfused donors is low [54]. For the prevention of variant Creuzfeldt-Jakobs disease, all individuals transfused after 1980 have been excluded from donation in the UK since 2004 and in The Netherlands since February 2005. However, this is not a wide spread donor exclusion strategy and due to the low prevalence of allo-immunization it is unlikely that a significant percentage of donors harbouring antibodies is excluded.

HLA antibody formation after blood transfusion occurs from exposure to HLA antigens present on the transfused leucocytes. From this point of view it could be hypothesized that leucocyte-reduced blood components, would reduce the rates of allo-immunization. A meta-analysis however showed that allo-immunization varied considerably between studies and range from 7% to 44% among recipients of leucocyte-reduced blood transfusions and from 20% to 50% among control recipients of non-leucoreduced blood components [56]. Therefore leucoreduction of blood components is not likely to reduce TRALI due to HLA antibodies from previously transfused donors. Other factors that influence the rate of HLA allo-immunization from transfusion include the number of units transfused, the underlying clinical condition resulting in transfusion, the time since transfusion and the method used for detecting HLA antibodies [57,58].

Until recently, the prevalence of HLA antibodies in transfused donors was not well characterized. However, a recent study obtained from 7,920 donors (2,086 males and 5,834 females) transfusion and pregnancy history and tested them for HLA Class I and Class II antibody presence [53]. Of interest, HLA antibody prevalence did not significantly differ between 895 transfused (1.7%) and 1138 non-transfused males (1.0%), [OR 1.75; 95%CI 0.80-3.82]. Prevalence in 45 transfused nulliparous females (4.4%) was not statistically different from the 1.6% prevalence in 1732 non-transfused nulliparous females [OR 2.94, 95% CI 0.68-12.74]. However, Middelburg et al. showed a positive association between transfusion and the presence of leucocyte antibodies in 148 transfused donors in a total cohort of 6034 tested donors. They showed the highest risk difference (3.0) for granulocyte specific antibodies and an overall risk difference of 5.8 for any leucocyte antibodies after transfusion [15].
Epidemiology of immune-mediated TRALI

According to the consensus definition TRALI develops within 6 hours of a transfusion, however some authors advocate an extension of the definition with a “delayed TRALI syndrome”. This delayed form of TRALI that can arise up to 72 hours after transfusion, is thought to result from non-immune mediated TRALI in the majority of the cases [59]. However, clinically it is impossible to distinguish if a case of TRALI is immune or non-immune mediated.

Although, from a blood bank view, immunologic work-up of reported TRALI cases and involved donors reveals the approximate percentage of immune-mediated TRALI, still these data should be considered with caution as reporting is often passive and different definitions of TRALI are applied, sometimes even dependent whether the immunologic work-up was positive. However, in general it is assumed that up to two thirds of TRALI-cases can be explained by presence of HLA or HNA antibodies. In line with this, the exclusion of female donors (the highest risk population among donors to have HLA-HNA antibodies) from donation of high plasma volume products has resulted in a decrease of approximately 66% of reported TRALI cases [60-62]. Probably, these numbers still do not reflect the real incidence of immune- and non-immune-mediated TRALI as most of the reports are based on passive reporting to the blood bank, which was shown to be non-representative [63].

Taking into account these limitations, immune-mediated TRALI reflects approximately two thirds of all TRALI cases. Studies reporting TRALI-cases show donor antibodies against cognate antigens present on leucocytes of the affected recipients for approximately 25-41% of HLA Class I antibodies, in 52-68% of HLA Class II antibodies, and 8-28% for granulocyte antibodies [21,64-66].

Prevention of immune-mediated TRALI from a bloodbank perspective

Excluding donors
The alarming TRALI figures in haemovigilance schemes were reason for blood supply organizations to introduce TRALI preventive measures based on donor exclusion strategies [28,32,67]. Based on results of TRALI series and observational cohort
Table 3: Overview of results of male only donor strategies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study and inclusion</th>
<th>Population</th>
<th>Country</th>
<th>Study year</th>
<th>Endpoint</th>
<th>Effect size</th>
<th>Effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palfi [55]</td>
<td>RCT active</td>
<td>ICU</td>
<td>Sweden</td>
<td>1995-1997</td>
<td>P/F</td>
<td>N/A</td>
<td>yes</td>
</tr>
<tr>
<td>Wright [62]</td>
<td>Retrospective active</td>
<td>Surgery</td>
<td>UK</td>
<td>1998-2006</td>
<td>onset TRALI</td>
<td>OR (95% CI) 0.39 (0.16-0.90)</td>
<td>yes</td>
</tr>
<tr>
<td>SHOT [28]</td>
<td>Retrospective passive</td>
<td>National</td>
<td>UK</td>
<td>2002-2005</td>
<td>onset TRALI</td>
<td>N/A</td>
<td>yes</td>
</tr>
<tr>
<td>Vlaar [7]</td>
<td>Retrospective active</td>
<td>ICU</td>
<td>Netherlands</td>
<td>2004-2007</td>
<td>onset TRALI</td>
<td>RR (95% CI) 0.35 (0.14-0.88)</td>
<td>yes</td>
</tr>
<tr>
<td>Eder [78]</td>
<td>Retrospective passive</td>
<td>National</td>
<td>US</td>
<td>2006-2008</td>
<td>onset TRALI</td>
<td>OR (95% CI) 0.21 (0.08-0.45)</td>
<td>yes</td>
</tr>
<tr>
<td>Wiersum [61]</td>
<td>Retrospective passive</td>
<td>National</td>
<td>Netherlands</td>
<td>2002-2009</td>
<td>onset TRALI</td>
<td>PAR (95% CI) 0.33 (0.09-0.51)</td>
<td>yes</td>
</tr>
<tr>
<td>Vlaar [81]</td>
<td>Retrospective active</td>
<td>Surgery</td>
<td>Netherlands</td>
<td>2006-2009</td>
<td>onset TRALI</td>
<td>N/A</td>
<td>no</td>
</tr>
<tr>
<td>Nakazawa [93]</td>
<td>Prospective active</td>
<td>Surgery</td>
<td>Japan</td>
<td>2008-2008</td>
<td>P/F&lt; 300</td>
<td>N/A</td>
<td>yes</td>
</tr>
<tr>
<td>Toy [94]</td>
<td>Prospective</td>
<td>General hospital population</td>
<td>United States</td>
<td>2006-2009</td>
<td>onset TRALI</td>
<td>Incidence (95% CI) before 2.57 (1.72-3.86), after 0.81 (0.44-1.49)*</td>
<td>yes</td>
</tr>
</tbody>
</table>

P/F=PaO2-FiO2 ratio, RCT=randomized controlled trial, PAR=population-attributable risk, RR=relative risk, CI=confidence interval, N/A=non-applicable, * TRALI incidence % (95% CI) per 10,000 units transfused before (2006) and after (2009) introduction of a male only donor strategy.

studies [18,27] exclusion of blood components with HLA and/or HNA antibodies containing high plasma volumes was considered. As large scale antibody screening was laborious and expensive the known high HLA immunization rate for ever pregnant women was reason for many blood centers, starting in the UK in 2003, to preferentially use plasma from male donors for the production of high plasma volume blood components (whole blood, FFP, multi donor buffy-coat platelet concentrates). This preventive transfusion strategy resulted in a decline in antibody
mediated TRALI cases as was shown in different haemovigilance schemes (see also table 3)[60-62,68,69].

**Testing donors for antibodies**

A less rigorous policy than the above mentioned one is testing all donors or at risk donors for presence of HLA or HNA antibodies. Except for the high labor and costs involved, large scale HLA and HNA antibody screening possibilities were not readily available in 2003. In recent years this partly changed with the introduction of the beads based flow cytometry HLA antibody screening techniques. Unfortunately, in most laboratories the introduction of these techniques was not in time to influence the TRALI prevention policy and screening for HLA class I and HLA class II antibodies is only used (in a growing number of laboratories) on top of the female exclusion strategy for the female apheresis blood components. The apheresis donation loss due to positive results in these beads based antibody screening techniques largely depends on the number of pregnancies and assay cut-offs used. A recent study by Carrick *et al.* showed a donation loss varying from 0.9% to 5.8% [70].

Up to now, no large scale antibody screening techniques for the clinically important HNA are available. Only a few blood centers test female apheresis donors for the presence of antibodies against HNA-1a, 1b, 2a and 3a.

**Pooling**

In order to prevent immune-mediated TRALI, high plasma volume containing blood products can be prepared from a pool of multiple donors. By pooling of up to hundreds donations, dilution of any leucocyte antibodies present occurs, in addition antibodies may be neutralized by soluble HLA antigens in the pool. Concerns of pooling are multiple donor exposure and transmission of viruses and prion diseases. Therefore Solvent/Detergent treatment is a prerequisite when pooled plasma is used.

Solvent Detergent plasma (S/D plasma) is prepared from pools of 500 to 1600 single donor units. Sachs *et al.* screened 20 batches of S/D plasma and could not detect HLA class I and II antibodies, nor did they demonstrate granulocyte-agglutinating antibodies [71]. Norway implemented the use of S/D plasma (Octaplas®) in 1993 and no cases of TRALI have been reported after the use of more than 300,000 units
[29,72]. Of note, it has not been determined if S/D plasma also prevents TRALI in recipients with a lowered threshold (e.g. critically ill) to develop TRALI, since even small amounts of antibodies might elicit TRALI in these patients. In addition, the use of S/D plasma is costly. In the UK it was calculated that replacement of FFP by S/D plasma in order to prevent 107 cases of TRALI would cost up to £9.2 million/year [73]. Since this report, a male-only FFP policy was instituted in the UK resulting in a striking reduction of TRALI, making the use of S/D plasma to prevent a case of TRALI even more costly.

Platelets can be collected by apheresis from a single donor or from pools of buffy-coat derived platelets. Single donor apheresis is preferred in the US, while in Europe it is more common to use pooled platelets. To prevent immune-mediated TRALI from apheresis platelets, allo-exposed donors are tested and those harboring leucocyte antibodies are deferred [74]. The deferral of all female platelet apheresis donors, as with plasma donations, is likely to hamper the adequate supply of platelets and is considered not feasible [75]. Alternatively, platelets can be derived from whole blood and pooled, to overcome the risk of TRALI by dilution of potential leucocyte antibodies present in any of the donors’ plasma, the platelets should be re-suspended in male plasma or platelet additive solution (PAS). However, multiple donor exposures increase the risk of viral infection and whether pooled platelets carry a lower TRALI risk compared to apheresis platelets, remains to be determined. Recently, the French Hemovigilance Network reported 18 cases of TRALI due to apheresis platelets and none after the transfusion of pooled platelets [76]. However, a systematic review based on the limited available data demonstrated that the risk was approximately equal for both products [77].

In conclusion, the use of S/D plasma may prevent immune-mediated TRALI due to plasma transfusion, but implementation is currently not cost-effective. Furthermore, it is not clear whether the beneficial effect also holds true for high risk TRALI patient populations such as critically ill. It remains to be determined if TRALI risk differs among pooled and apheresis platelets. Although, current measures to prevent immune-mediated TRALI by deferral of antibody positive or allo-exposed apheresis donors is proving effective [21,78].
Prevention of immune-mediated TRALI from a bedside perspective

Recognition and awareness of TRALI
To prevent TRALI, identification of donors implicated in a case of TRALI is essential; therefore recognition of TRALI by clinicians is vital. Furthermore, diagnostic work-up needs to be complete and donors should only be deferred if causality is proven by antibody testing including cross-matching or recipient typing. However, among clinicians there is a lack of awareness of TRALI and underreporting is confirmed by look back investigations and retrospective studies [6,12]. Lack of knowledge about TRALI among clinicians has shown to be an important contributor to underreporting [79]. Furthermore, despite the consensus definition [1] differences in local diagnostic criteria still exist (e.g., use of imputability criteria in certain countries). Also, even if the consensus definition is applied mild cases and patients who develop symptoms more than 6 hours after transfusion will be missed. It should be kept in mind that the consensus definition does not exclude inter-observer variability in classifying cases of respiratory distress after transfusion. Respiratory deterioration can be attributed to other causes (e.g., trauma, sepsis or pneumonia), which may lead to misclassification of TRALI cases, in particular in ICU patients. TRALI is considered to be a diagnosis of exclusion by some physicians and a pre-transfusion inflammatory condition is even a reason to withhold from reporting of a suspected TRALI case [63]. In the near future, increasing knowledge and subsequent recognition of TRALI among clinicians is warranted in order to prevent multiple TRALI cases from a single donor. To achieve this it is important to educate physicians on the incidence, pathogenesis and diagnosis of TRALI. Furthermore, insight how to process a suspected TRALI case through the haemovigilance schemes in the hospitals might also be a good source for education purposes.

Identifying patients with first hit
As stated earlier TRALI incidence is higher in critically ill patients [5,7]. These patients are frequently exposed to allogenic blood products, in addition they often have an underlying condition that induces priming of neutrophils (e.g., sepsis, cardiac surgery or the need for mechanical ventilation) in pulmonary capillaries. These primed neutrophils may be prone to HLA and/or HNA antibodies in the blood product, which
mediate activation and additional lung injury after transfusion. Patient factors associated with an increased risk of ALI after transfusion, include sepsis, mechanical ventilation, trauma and hematological malignancies [5,80]. This also applies to patients undergoing cardiac surgery, in whom TRALI significantly contributes to an adverse outcome [81]. However, most of these factors cannot be modified, but measures that attenuate ALI possibly raise the threshold for TRALI. Protective mechanical ventilation strategies using low tidal volumes reduce mortality with 22% in ALI/ARDS [82] and injurious mechanical ventilation with high tidal volumes aggravates experimental TRALI [83]. Therefore, it seems reasonable to apply lung protective ventilation strategies in patients subjected to a blood transfusion.

Transfusion-related risk factors for the development of TRALI are the amount of blood products, larger volumes of plasma containing products, donor sex and parity. In patients with an increased risk for TRALI (e.g., those with a ‘first hit’), it might be plausible to introduce a ‘tailor made’ transfusion policy. This would include transfusion of plasma containing components from male only donors. Of note, such strategy has been shown to reduce the incidence of TRALI in the general patient population [21,61]. However, in a cohort of cardiac surgery patients use of male plasma only was not shown to reduce TRALI incidence [83]. It should be mentioned that this study was not designed to demonstrate such an effect and the number of included patients was relatively low.

In conclusion, host factors contribute to increased susceptibility for immune-mediated TRALI. Although the underlying condition cannot be modified, supportive care and treatment modalities need to be applied cautiously. To date, evidence for utility of a ‘tailor made transfusion’ strategy in high-risk patients is lacking.

**Restrictive transfusion practice**

From a bedside perspective, the most important measure to prevent TRALI is to limit patient’s exposure to allogenic blood products. In critically ill, the incidence of ALI is reduced when a restrictive transfusion policy is applied [84] and such strategy is associated with decreased mortality [85].

Blood products highly associated with the onset of immune-mediated TRALI are high volume plasma products such as platelet concentrates and fresh frozen plasma [5]. Prevention of immune-mediated TRALI should be focused on minimizing the use
of these blood products. Although it is not feasible to completely avoid the use of these blood products in daily practice, the use of plasma rich blood components can be reduced by using alternatives. A recent trial showed that the use of tranexamic acid in trauma patients significantly reduced mortality [86]. Furthermore, the use of FFP should be limited to bleeding patients, since evidence for prophylactic use of FFP to prevent bleeding is lacking. However, a recent survey among UK ICUs indicated that up to 50% of FFP is administered to non-bleeding patients, either to prevent bleeding in patients with prolonged coagulation parameters or to reverse warfarin therapy [87]. In addition, despite a more restrictive transfusion trigger in the critically ill, multiple unit transfusion to correct for anaemia is still common practice. The inappropriate use of blood products can be limited by the use of computerized transfusion algorithms [88]. In trauma and cardiac surgery, the use of point of care coagulation tests (e.g. ROTEM®) combined with transfusion algorithms also reduces the amount of transfused blood [89,90].

In order to prevent immune-mediated TRALI and to limit inappropriate use of blood products, transfusion algorithms need to be implemented and clinicians’ awareness of appropriate and restrictive use of these products needs to be heightened.

**Conclusion**

TRALI is a serious complication of transfusion and significantly increases morbidity and mortality. Currently, from a blood bank perspective two major strategies exist which have proven to prevent immune-mediated TRALI. The first strategy is aimed at exclusion of allo-exposed donors from donating high volume plasma containing blood products, the second strategy is aimed at dilution of antibodies present in high volume plasma products by means of pooling. From a bedside perspective, TRALI can be prevented by limiting inappropriate use of blood products. A future bedside perspective might involve tailor made blood products for patients at risk for developing TRALI.
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