Transfusion-related acute lung injury in the critically ill: a translational approach
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The practice of reporting transfusion-related acute lung injury: a national survey among clinical and pre-clinical disciplines


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Abstract

**Background:** Transfusion-related acute lung injury (TRALI) is hypothesized to be a ‘two hit’ entity, in which an inflammatory condition (e.g. sepsis) predisposes to TRALI. TRALI is a clinical diagnosis. Disciplines involved in managing TRALI may differ in decision-making on the reporting of TRALI.

**Methods:** A survey was conducted among critical care physicians, hematologists, hemovigilance workers and transfusion medicine physicians, using case vignettes and a questionnaire. The vignettes varied in patient and blood product related factors that may influence the decision to report a TRALI-case. Multiple-linear regression analysis was performed. A positive $\beta$-coefficient is in favor of reporting.

**Results:** Ninety-two questionnaires were returned (response rate 68%). For all disciplines, preferences in favor of reporting TRALI were onset of symptoms within 1 hour ($\beta$ 0.4), after transfusion of a single unit of FFP ($\beta$ 0.5), in the absence of ALI prior to transfusion ($\beta$ 1.3). An admission diagnosis of sepsis was a negative preference ($\beta$ -0.3). Massive transfusion (6 RBC + 4 FFP units) was a negative preference for transfusion medicine physicians ($\beta$ -0.3), but a positive preference for the other disciplines. The questionnaire revealed that massive transfusion and the age of blood products were considered relatively more important reasons to report TRALI by critical care physicians compared to the other disciplines ($p<0.05$).

**Conclusions:** A pre-transfusion inflammatory condition is a reason to withhold from reporting of a suspected TRALI-case. Disciplines involved in managing TRALI differ in decision-making of reporting TRALI, which may contribute to variance in incidence.
Introduction

Insight into the pathogenesis of TRALI is evolving. Leukocyte and neutrophil antibodies present in the transfusion product have long been considered the sole implicated causative agents in the development of a TRALI reaction. However, antibodies are not involved in all cases fulfilling the clinical definition of TRALI.\(^1\)\(^\text{1-4}\) Furthermore, look-back investigations reveal that even in the presence of antibody-antigen pairing of the donor and recipient, TRALI does not always occur.\(^5\)\(^,\)\(^6\) Studies indicating that TRALI may be caused by a “two hit” event are accumulating.\(^3\)\(^,\)\(^7\)\(^-\)\(^12\) The “first hit” is any inflammatory condition (e.g. pneumonia, sepsis or trauma), resulting in priming of pulmonary neutrophils. The “second hit” is the transfusion of a blood product and results in activation of the primed neutrophils, with subsequent pulmonary edema. Besides antibodies, bio-active lipids which accumulate during storage have been implicated.\(^3\)\(^,\)\(^9\)\(^-\)\(^12\) Stored blood products have been found to induce lung injury after priming of the lungs with lipopolysaccharide in ‘two hit’ animal models.\(^9\)\(^,\)\(^10\)\(^,\)\(^13\) In patients, bio-active lipids have been associated with the occurrence of TRALI.\(^3\)\(^,\)\(^11\) However, the clinical relevance of bio-active lipids is still under debate. Besides lipids, antibodies also induced lung injury in an endotoxemic “two hit” TRALI rat model, but not in healthy animals.\(^13\) These “two hit” models mimic the clinical situation of a patient suffering from an underlying inflammatory condition.\(^14\)\(^,\)\(^15\) In accordance, the presence of sepsis has been identified as a risk factor for the development of TRALI in a critically ill patient population.\(^7\) The antibody model and the two hit model may not be mutually exclusive. A threshold model of TRALI has been introduced, in which the onset of TRALI is dependent both on the severity of the underlying condition of the patient and on the severity of the transfusion mediator (antibody titer or concentration of bio-active lipids).\(^16\)

Table 1. Definition of transfusion-related acute lung injury

<table>
<thead>
<tr>
<th>TRALI</th>
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<tbody>
<tr>
<td>-Acute onset within 6 hours after a blood transfusion</td>
</tr>
<tr>
<td>-PaO2/FiO2 &lt; 300 mmHg</td>
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<tr>
<td>-Bilateral infiltrative changes on chest X-ray</td>
</tr>
<tr>
<td>-No sign of hydrostatic pulmonary edema (wedge pressure &lt;18 mmHg or CVP &lt; 15 mmHg)</td>
</tr>
<tr>
<td>-No ALI prior to transfusion</td>
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<tr>
<td>-No other risk factor for ALI present</td>
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</table>

Possible TRALI

-Other risk factor for ALI present
-Fulfillment of the definition of TRALI

Abbreviations; CVP=central venous pressure, ALI=acute lung injury
Due to a lack of diagnostic markers, TRALI is defined by clinical criteria, in which possible TRALI is defined as TRALI in the presence of another ALI risk factor (table 1). The reported incidence of TRALI varies widely, ranging from 0.0008% to 1.2% per blood product and from 0.08% to 8% per transfused patient. This 100 to 1000 fold difference in incidence may partly be explained by differences in study design and patient population. However, under-reporting has been coined as an alternative explanation. In the Netherlands, as in many other counties, reporting of TRALI is done by a multidisciplinary system (figure 1). Reporting of TRALI-cases is important for identifying and excluding involved donors with leukocyte or neutrophil antibodies to prevent future TRALI reactions. Immunologic work-up to detect antibodies is performed when the transfusion medicine physician of the blood bank agrees on the suspicion of a TRALI-case.

<table>
<thead>
<tr>
<th>Disciplines involved in reporting TRALI</th>
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<tbody>
<tr>
<td><strong>Patient</strong></td>
</tr>
<tr>
<td>Acute lung injury within 6 hours of transfusion</td>
</tr>
<tr>
<td><strong>Physician on ward</strong></td>
</tr>
<tr>
<td><strong>Hematologist</strong></td>
</tr>
<tr>
<td><strong>Hemovigilance worker</strong></td>
</tr>
<tr>
<td><strong>Transfusion medicine physician</strong></td>
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</table>

*Figure 1.* Flowchart representing the multidisciplinary reporting of a patient suspected of TRALI to the blood bank.
Insight into patient and blood product related determinants that influence the practice of reporting of TRALI is limited. Interdisciplinary differences in reporting TRALI may contribute to under-reporting and variance in TRALI incidences. Using a survey, we investigated whether clinical practice of reporting TRALI reflects a belief in the “two hit” TRALI hypothesis. Also, we investigated whether disciplines involved in handling of suspected TRALI patients differ in their decision-making regarding reporting of TRALI.

Materials and Methods

Setting
The chairs of the departments of critical care, hemovigilance and hematology in hospitals with an intensive care unit (ICU) with 5 or more beds equipped for mechanical ventilation (n=66) were asked for participation in this survey. When participation was agreed upon, the chairs of each department were asked which critical care physician, hemovigilance worker and hematologist were most consulted in identifying and reporting of a suspected TRALI case. The survey was sent to these physicians and health care workers. In addition, all transfusion medicine physicians working in the National Blood Bank (n=13) were asked for participation in this survey.

The Survey
The survey consisted of three parts: (a) characteristics of the respondent, (b) 20 clinical vignettes and (c) questionnaire with 10 questions on additional factors influencing TRALI reporting. The survey was introduced with a cover letter, providing the American-European Consensus Conference (AECC) definition for ALI to avoid unclarity about the onset of ALI. The survey was sent to all persons who agreed to participate. To enhance response, a reminder was sent after 2 weeks. After 4 weeks, non-responders were contacted by telephone.

Vignettes
To assess preferences of physicians for diagnostic determinants in reporting TRALI, vignettes were used. A vignette is a brief, written case history of a fictitious patient. Vignette-based surveys are a well-suited tool to measure practice variation in clinical decision-making. Determinants considered to influence decision-making in reporting of TRALI were identified by using previous studies which indicated patient risk factors (e.g. sepsis) and transfusion risk factors (e.g. fresh frozen plasma) for the onset of TRALI and by the clinical experience of the authors (determinants shown in table 2). Four diagnostic determinants with two levels and
one diagnostic determinant with five levels were embedded in the vignette case scenarios (case scenario shown in appendix 1). The physicians were asked whether he/she would report this patient as suspected TRALI (response options; mark on a line from 0-7 (I will report – I will not report). A full factorial design would generate 128 vignettes, which is a number too great to score. Therefore the number of vignettes was reduced to 20 from the original 128 possible vignettes using an orthogonal main effects design (SPSS version 15.1).36,37 This procedure generates a specific subset of combinations which was used for the survey, whilst still being able to infer preferences for all factors using a multiple-linear regression model. The survey was tested in a pilot study for clarity of content by an independent critical care physician, hemovigilance worker, hematologist and transfusion medicine physician. No changes were made after the pilot test.

**Questionnaire**

Next to the 20 vignettes, physicians were questioned using a list of 10 additional factors, including variables that may indicate risk factors for TRALI or for an alternative diagnosis. The questions were added because not all diagnostic determinants that may influence decision-making of the physician to report TRALI could be taken into account in the vignette. The statements had to be visually scored on a 10 cm line providing a 0% (not taken into account) – 100% (fully taken into account) scale.

**Statistics**

The influence of the TRALI-determinants imbedded in the vignette was estimated by multiple-linear regressions (mixed models). Effect sizes were expressed in beta-coefficients with 95% confidence intervals (CI). The means and standard deviations for continuous variables and distributions for frequency of categorical variables were summarized using descriptive statistics. The scores on the statements
(visual analogue scale, VAS) are given as mean ± standard error. Differences between disciplines were analyzed using ANOVA analysis followed by Bonferroni post test. A p value of < .05 was taken as statistically significant (SPSS ver. 15.1).

**Results**

Study participation was agreed upon by 30 hematologists, 41 ICU physicians and 52 hemovigilance workers of all hospitals, as well as by all transfusion medicine physicians (n=13) of the National Blood Bank. Of the 136 questionnaires sent, 92 were returned (response rate 68%), from employees in 45 hospitals. Characteristics of the responding physicians are listed in table 3.

**Table 3. Characteristics of the participating physicians in the survey.**

<table>
<thead>
<tr>
<th></th>
<th>Critical care physician n=31</th>
<th>Hematologist n=15</th>
<th>Hemovigilance worker n=37</th>
<th>Transfusion medicine physician n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical specialty</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>66%</td>
<td>100%</td>
<td>10%</td>
<td>56%</td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>24%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Clinical chemist</td>
<td>0%</td>
<td>0%</td>
<td>80%</td>
<td>0%</td>
</tr>
<tr>
<td>Other</td>
<td>10%</td>
<td>0%</td>
<td>10%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>80%</td>
<td>50%</td>
<td>40%</td>
<td>56%</td>
</tr>
<tr>
<td>Female</td>
<td>20%</td>
<td>50%</td>
<td>60%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Age (SD)</strong></td>
<td>44±5</td>
<td>46±8</td>
<td>48±7</td>
<td>47±5</td>
</tr>
<tr>
<td><strong>Experience (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>30%</td>
<td>6%</td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td>6-10</td>
<td>23%</td>
<td>31%</td>
<td>14%</td>
<td>22%</td>
</tr>
<tr>
<td>11-15</td>
<td>30%</td>
<td>25%</td>
<td>19%</td>
<td>22%</td>
</tr>
<tr>
<td>16-20</td>
<td>10%</td>
<td>13%</td>
<td>16%</td>
<td>44%</td>
</tr>
<tr>
<td>20+</td>
<td>7%</td>
<td>25%</td>
<td>30%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Hospital</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>14%</td>
<td>13%</td>
<td>16%</td>
<td>N/A</td>
</tr>
<tr>
<td>Non-Academic</td>
<td>86%</td>
<td>87%</td>
<td>84%</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>TRALI-cases reported last year (SD)</strong></td>
<td>0.7±1.3</td>
<td>0.8±1.0</td>
<td>0.8±1.0</td>
<td>4.1±3.9</td>
</tr>
</tbody>
</table>

TRALI cases reported last year = mean number of cases reported to blood bank by the participant.
The preferences of all disciplines in favor of reporting TRALI are shown in figure 2. Onset of symptoms within 1 hour was a stronger positive preference for reporting than onset within 5 hours (β 0.4 [0.2 to 0.5] vs. neutral). Transfusion of FFP or platelets was a stronger positive preference for reporting than transfusion of red blood cells (β 0.5 [0.3 to 0.7] vs. neutral). A patient with the age of 20 years was a stronger positive preference for reporting than a patient with the age of 80 years (β 0.2 [0.02 to 0.3] vs. neutral). The absence of ALI prior to transfusion was a stronger factor in favor of reporting TRALI compared to the presence of ALI prior to the transfusion (β 1.3 [1.1 to 1.4] vs. neutral). An admission diagnosis of sepsis was a negative determinant for reporting TRALI compared to an admission diagnosis of CVA (β -0.3 [-0.5 to -0.2] vs. neutral).

Then, we determined whether disciplines involved in reporting TRALI differed in preferences of diagnostic determinants. Transfusion medicine physicians scored massive transfusion (6 units of RBC + 4 units of FFP) as a negative factor (β -0.3 [-1.1 to 0.4]) to report a suspected TRALI-case (figure 3), while the hemovigilance workers, critical care physicians and hematologist scored massive transfusion as a factor in favor to report a suspected TRALI-case (β 0.5 [0.1 to 0.9], 0.3 [-0.2 to 0.8] and 0.2 [-0.4 to 0.8], respectively). The disciplines did not differ in their preference of the other diagnostic determinants (age of the patient, ALI risk factor, ALI prior to transfusion, time between transfusion and onset of TRALI).

Figure 2. Preferences of all disciplines combined for determinants on reporting TRALI. Abbreviations; FFP=fresh frozen plasma, RBC=red blood cells, PLT= platelets concentrate, ALI=acute lung injury.

Vignette

The preferences of all disciplines in favor of reporting TRALI are shown in figure 2. Onset of symptoms within 1 hour was a stronger positive preference for reporting than onset within 5 hours (β 0.4 [0.2 to 0.5] vs. neutral). Transfusion of FFP or platelets was a stronger positive preference for reporting than transfusion of red blood cells (β 0.5 [0.3 to 0.7] vs. neutral). A patient with the age of 20 years was a stronger positive preference for reporting than a patient with the age of 80 years (β 0.2 [0.02 to 0.3] vs. neutral). The absence of ALI prior to transfusion was a stronger factor in favor of reporting TRALI compared to the presence of ALI prior to the transfusion (β 1.3 [1.1 to 1.4] vs. neutral). An admission diagnosis of sepsis was a negative determinant for reporting TRALI compared to an admission diagnosis of CVA (β -0.3 [-0.5 to -0.2] vs. neutral).
Questionnaires

Additional determinants that may indicate TRALI or an alternative diagnosis that may be considered when reporting a suspected TRALI-case, were measured with the VAS (table 4). Hemodynamic variables (ejection fraction, Early diastolic / Atrial filling velocity (E/A ratio)), were added to the questionnaire as they may indicate the presence or absence of heart failure. Patients with heart failure are at risk of developing hydrostatic pulmonary edema after transfusion, called transfusion associated cardiac overload (TACO). As the clinical symptoms of TACO mimic TRALI, hemodynamic variables may influence the decision to report a patient suspected of TRALI. All disciplines considered the hemodynamic variables important in decision-making of reporting a patient suspected of TRALI. A positive blood culture or the presence of a risk factor for ALI may indicate an alternative diagnosis or an inflammatory condition. These conditions were equally considered by all disciplines.

Physicians were also questioned on blood product related factors. Plasma is the blood product most often implicated in TRALI reactions. In addition, aged blood products have been implicated in pulmonary complications, including respiratory insufficiency.38 The relative importance of the type of blood product did not differ between disciplines. Critical care physicians considered the age of the transfused products a more important factor to report a suspected TRALI-case then the other disciplines (p<0.02). Concerning massive transfusion, the questionnaire was consistent with results from the vignettes. Critical care physicians considered massive transfusion a more important factor to report a suspected TRALI-case compared to transfusion medicine physicians (P<0.05). Increased lactate dehydrogenase (LDH), which may indicate an alternative diagnosis of a hemolytic immune reaction, was considered to be of minor importance by all disciplines when reporting a TRALI-case.

Figure 3. Disciplines analyzed separately for preference of massive transfusion (6 RBC + 4 FFP) on reporting TRALI.
Recent insights in TRALI pathogenesis suggest a “two hit” entity, in which an inflammatory condition may predispose to TRALI.\(^7,^{11,12}\) The present study shows that the practice of physicians of reporting suspected TRALI-cases does not depend upon a “two hit” mechanism. This study furthermore shows that disciplines involved in managing TRALI differ in decision-making of reporting a suspected TRALI-case, which may contribute to variance in the estimated incidence of TRALI.

Determinants with a strong preference for reporting of TRALI included a young patient without a risk factor for other causes of lung injury, developing ALI within 1 hour after a single FFP transfusion. These determinants indicate a belief in the “single hit” theory, in which antibodies in donor plasma are thought to induce activation of the pulmonary neutrophils in the absence of a priming hit.\(^{39}\) In accordance, we found that the presence of an inflammatory condition prior to transfusion (sepsis) had a negative preference for reporting of TRALI, indicating that TRALI is viewed as a diagnosis by exclusion.

### Table 4. Blood product and patient related factors that are considered when reporting TRALI

<table>
<thead>
<tr>
<th>Statements</th>
<th>Percentage taken into account</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ejection fraction (Echocardiography)</td>
<td>Hematologist Critical care physician Hemovigilance Worker Transfusion medicine</td>
</tr>
<tr>
<td>2. The E/A ratio (Echocardiography)</td>
<td>55±9 60±5 53±6 45±11</td>
</tr>
<tr>
<td>3. Wedge pressure</td>
<td>43±7 40±4 49±5 36±12</td>
</tr>
<tr>
<td>4. 24 hours fluid balance</td>
<td>70±8 59±5 78±4* 57±13</td>
</tr>
<tr>
<td>5. Results of blood culture</td>
<td>56±9 53±5 57±5 58±9</td>
</tr>
<tr>
<td>6. The presence of a risk factor for ALI</td>
<td>65±9 60±5 55±7 45±11</td>
</tr>
<tr>
<td>7. The age of the transfused product(s)</td>
<td>79±6 70±4 72±5 80±5</td>
</tr>
<tr>
<td>8. Multiple transfusions (&gt;10 units)</td>
<td>33±8 50±5† 20±5 10±2</td>
</tr>
<tr>
<td>9. Plasma LDH</td>
<td>63±8 64±5‡ 43±6 36±13</td>
</tr>
<tr>
<td>10. Type of product transfused</td>
<td>37±6 40±5 32±6 13±5‡</td>
</tr>
</tbody>
</table>

Data are presented as mean percentage (SE). Data are the percentage that physicians take a factor into account when reporting TRALI (0=not taken into account, 100=always taken into account). Abbreviations; E/A =diastolic dysfunction (Early diastolic filling velocity / Atrial filling velocity, ALI=acute lung injury, LDH=lactate dehydrogenase. *p<0.01 hemovigilance worker vs. critical care physician, †p<0.02 critical care physicians vs. other disciplines, ‡p<0.05 critical care physicians vs. other disciplines, ‡p<0.05 critical care.

### Discussion

Recent insights in TRALI pathogenesis suggest a “two hit” entity, in which an inflammatory condition may predispose to TRALI.\(^7,^{11,12}\) The present study shows that the practice of physicians of reporting suspected TRALI-cases does not depend upon a “two hit” mechanism. This study furthermore shows that disciplines involved in managing TRALI differ in decision-making of reporting a suspected TRALI-case, which may contribute to variance in the estimated incidence of TRALI.

Determinants with a strong preference for reporting of TRALI included a young patient without a risk factor for other causes of lung injury, developing ALI within 1 hour after a single FFP transfusion. These determinants indicate a belief in the “single hit” theory, in which antibodies in donor plasma are thought to induce activation of the pulmonary neutrophils in the absence of a priming hit.\(^{39}\) In accordance, we found that the presence of an inflammatory condition prior to transfusion (sepsis) had a negative preference for reporting of TRALI, indicating that TRALI is viewed as a diagnosis by exclusion.
Explanations for the belief in the “single hit” TRALI theory in clinical practice may be two-fold. First, clinicians may not be convinced by the “two hit” theory. Because the pathophysiology of TRALI is incompletely understood, a case definition based on clinical and radiological parameters was agreed upon during a consensus conference in 2004. This case definition however, does not distinguish TRALI from ALI due to other aetiologies. In an effort to capture the possibility of TRALI in a patient with an underlying ALI risk factor, the term ‘possible TRALI’ was adopted. Our results indicate that possible TRALI-cases, in the presence of another ALI risk factor, are not acknowledged in clinical practice. In line with this, blood banks in some European countries, including The Netherlands, use a TRALI scoring system other than the consensus definition, which scores the imputability of symptoms to the transfused blood product. The presence of sepsis or pneumonia prior to transfusion, results in a lower imputability. A similar policy is seen among US blood banks. Almost half of the centres use a case-by-case selection instead of the consensus definition to decide when to start an immunologic work-up of the involved donors. In addition, it has been proposed that the clinical course of TRALI in critically ill patients differs from ‘classic’ TRALI. Onset of symptoms is less acute, which has led to the term ‘delayed TRALI’. Also, risk of lung injury is related to the amount of transfused blood products, whereas in ‘classic’ TRALI, usually a single unit is implicated. Together, due to a different course, lung injury following a blood transfusion in critically ill patients may not be acknowledged as TRALI requiring an immunologic work-up.

A second explanation for our findings is that clinicians may not be aware of the “two hit” TRALI hypothesis. The majority of case reports of TRALI described patients in whom other risk factors for ALI were absent, which may render clinical acknowledgement of possible TRALI more difficult. In general, changes in clinical practice often are behind changes in pathophysiology insights. Furthermore, it could be speculated that the importance of the antibody mediated TRALI is stressed out as marketing policy by producers of suggested “TRALI-free plasma” such as solvent detergent plasma.

In clinical practice, it is difficult to distinguish TRALI from other causes of respiratory distress, such as hydrostatic pulmonary edema. However, as a consequence of the vignette study design, we do not think that a failure to recognize TRALI contributed to the results of this study. Rather, either a lack of belief or a lack of knowledge in the “two hit” TRALI hypothesis may account for the results. From our data, we can not dissect between these two explanations. We do think it is important that disciplines involved in handling of TRALI are aware of changing insights in TRALI pathogenesis, including the awareness that TRALI can develop in patients in whom other risk factors for ALI are present, such as sepsis. We acknowledge that distinguishing between causative factors is a challenge. Notably, onset of ALI in the absence of transfusion
is reported in only 19% of the cases of patients with sepsis. Furthermore, it should be noted that transfusion is the most common event that precedes the development of ALI and transfusion is an independent risk factor for the development of ALI. Finally, even more important there is a dose dependent relationship for transfusion and mortality in patients suffering from ALI.

The medical disciplines involved in managing TRALI differed in their preferences for diagnostic determinants regarding the reporting of TRALI. In contrast to critical care physicians, transfusion medicine physicians considered massive transfusion a reason to withhold immunologic work-up. We suppose that the enormous time and finance consuming process of the immunologic investigation of a massively transfused patient contributes to declining of such a request. A recent summary of all TRALI cases reported in the Netherlands to the Blood Bank from 2002-2005 revealed that one third of the cases is rejected for immunologic work-up, which complies with the practice in other countries. It can be speculated that a part of these rejected cases were massively transfused.

Medical disciplines also differed in their preference of the importance of the age of blood products. A possible association between storage time of blood products and increased respiratory complications and mortality has been shown. Critical care physicians considered the age of the blood product a significantly more important determinant compared to the other disciplines when reporting a TRALI-case. Conflicting results in studies on the impact of age of blood, may contribute to the discrepancy on this topic between the disciplines.

Diagnosis or exclusion of cardiogenic pulmonary edema is limited by both the subjective interpretation of clinical findings and the invasive nature of hemodynamic monitoring. Hemodynamic variables were considered important by all disciplines when considering reporting a TRALI-case. However, in daily practice, measurement of hemodynamic variables by echocardiography or Swan-ganz catheter are not routinely performed for each patient. TRALI-diagnosing would benefit from a reliable bio-marker which can easily distinguish TACO from TRALI. Natriuretic peptides are of limited diagnostic value. IL-6 may be a promising candidate, but requires future validation studies.

The results of this study may have several implications. Our data indicate that patients suffering from an underlying condition or receiving massive transfusion will probably be withheld from immunologic diagnosing of TRALI. We consider it important that all patients suspected for TRALI are dealt with in a same fashion. We propose that the international consensus case definition should be applied rather than national TRALI scoring systems. Also, it is of importance that a suspected
TRALI case in the presence of another ALI risk factor (possible TRALI) is reported to the blood bank. When considered appropriate and feasible, analysis of neutrophil and leukocyte antibodies should be initiated, in order to exclude implicated donors to prevent future TRALI reactions. Besides implications concerning patient care, consistent reporting of TRALI cases will provide reliable data on incidence and may increase insight in risk factors for acquiring TRALI.

The survey design of this study has several limitations. Firstly, although vignettes have been recognized as a valid tool to assess preferences in clinical practice, we can not rule out a discrepancy between practice of disciplines involved in reporting TRALI-cases and their answers to vignettes with hypothetical patients. Secondly, diagnostic determinants influencing reporting of TRALI are many. A vignette survey is limited to a number of determinants to generate an optimal number of vignettes which respondents can adequately evaluate. Lastly, although the response rate of individual participants was good, surveys were not returned from all centers. However, assuming that the opinions of the respondents are consistent within one discipline, the results of this study reflects the opinion of Dutch physicians and hemovigilance workers on what determinants are considered important when reporting a TRALI-case.

**Conclusion**

Medical disciplines involved in reporting and diagnosing TRALI consider an inflammatory condition prior to the transfusion a reason not to report a suspected TRALI-case. Furthermore, the disciplines were mutually divergent in their preference of factors on amount and age of products transfused for reporting suspected TRALI-cases and asking for an immunologic work-up. These differences in decision-making, regarding reporting of TRALI, may partly explain under-reporting of TRALI and may contribute to variance in estimated TRALI incidence reports.
Reference List


34. Transfusion for massive blood loss: www trauma org 2009


