

## **Transfusion Related Acute Lung Injury (TRALI)**

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# **TRANSFUSION RELATED ACUTE LUNG INJURY (TRALI)**

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## Transfusion Related Acute Lung Injury (TRALI)

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### Purpose

To provide background information supporting NHSBT procedures for investigation and further transfusion of suspected cases of Transfusion Related Acute Lung Injury and subsequent management of implicated donors.

### Method

Recommendations are based on review of the literature and accepted current clinical practice. The definitions of the types of evidence and the grading of recommendations used in this document originate from the US Agency for Health Care Policy and Research and are provided in the Appendix.

### Consultation

NBS Transfusion Medicine Clinical Policies Group

NBS Transfusion Medicine Clinical Policies H&I / PGI (TRALI) Subgroup (Membership: Geoff Lucas, Sheila MacLennan, Edwin Massey, Cristina Navarrete, Willem Ouwehand, Nay Win)

NBS Components Strategy Group

### Status

Approved by the Transfusion Medicine Clinical Policies Group on 5<sup>th</sup> March 2003. Updated by Edwin Massey, 2006 and Catherine Chapman 2010, 2011 and 2014.

### Summary

TRALI is a serious complication of blood transfusion which is thought to arise as a result of the interaction of specific leucocyte antibodies with leucocytes in most cases (Evidence Level Ib). Susceptibility of some patients may be increased by contributory factors such as underlying disease or modes of treatment, though these factors are as yet poorly defined (Evidence Level IV). Patients present with dyspnoea, hypoxia and symptoms and signs of pulmonary oedema. Diagnosis is made on clinical grounds, which may later be supported by demonstrating the presence of donor leucocyte antibodies. Rarely, patient leucocyte antibodies may be implicated following transfusion of non-leucodepleted components (apheresis or buffy coat granulocytes). Treatment requires stopping the transfusion and giving oxygen and cardio-respiratory support. Most cases require mechanical ventilation for several days.

Investigation of each case should be undertaken by designated NHSBT staff so that each case is uniformly and appropriately investigated. Samples from the patient and donors (restricted initially to female and transfused male donors) of components transfused in the 6 hours preceding the onset of TRALI are obtained and investigated for the presence of leucocyte antibodies as required (1). The relevance of a positive donor antibody result is confirmed by either demonstrating that the patient is positive for the corresponding antigen, or that a crossmatch between donor and patient is positive.

A donor who has been implicated in a case of TRALI is resigned from donation of therapeutic blood components but may still donate blood for quality control/quality assurance

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if eligible. A donor who is found to have HNA antibodies with an identified HNA specificity is resigned from future donation for clinical use even if concordance with the patient is not found. (Grade of Recommendation C, Evidence Level IV).

### 1. Introduction

TRALI is a life threatening complication of transfusion which is clinically indistinguishable from Acute Lung injury (ALI) or Acute Respiratory Distress Syndrome (ARDS) due to other causes (2). Although rare, TRALI is a significant cause of transfusion associated morbidity and mortality and has been reported as the leading causes of transfusion associated death in the UK based on cumulative data from 1996 to 2008 from the Serious Hazards of Transfusion (SHOT) haemovigilance scheme (16). In recent years deaths reported to SHOT as at least possibly due to Transfusion Associated Circulatory overload have exceeded reported deaths at least possibly due to TRALI (17, 18).

### 2. Pathogenesis

TRALI is thought to result from the interaction of specific leucocyte antibodies with leucocytes and pulmonary endothelium. Human Leucocyte Antigen (HLA) antibodies, both Class I and Class II, and antibodies to Human Neutrophil Antigens (HNA) have all been implicated (3). Multiparous women have been shown to have a higher rate of HLA sensitisation with increasing number of pregnancies (4) and plasma from multiparous women has been demonstrated to play a part in causing impairment of pulmonary function in a randomised controlled trial (5) (Evidence Level Ib). The antibodies are usually donor-derived, though there have been occasional reports of the syndrome occurring after transfusion of donor leucocytes which have interacted with either patient-derived antibodies or antibodies transfused in a second donation, or the presence of HLA antigen/antibody incompatibility in a pooled platelet concentrate. Since 'universal' leucodepletion was introduced in late 1999 these mechanisms are considered unlikely except when non leucocyte depleted components have been transfused (apheresis or buffy coat granulocytes). (Grade of Recommendation C, Evidence Level IV).

Look-back studies have demonstrated that not all transfusions from donors found to have leucocyte antibodies result in TRALI – even if there is a match of antigen and antibody specificity overt lung injury does not always ensue (14). It is likely, although not proven, that patient factors may contribute to the development of the syndrome and a two event model has been postulated. In this model, the first event is the clinical condition of the patient resulting in pulmonary endothelial activation and neutrophil sequestration; the second event is transfusion of a biologic response modifier such as antibodies or biologically active lipids. (6). Hypoxia, recent surgery, cytokine therapy, active infection or inflammation, and massive transfusion have all been suggested as predisposing factors (7,8). It is known that recipient morbidity is not a prerequisite for TRALI because this has been clearly described in healthy volunteers (9).

TRALI is clinically indistinguishable from ALI and ARDS due to other causes which include a number of direct and indirect insults to the lung (10). Post-mortem studies show the pathophysiology of ARDS as being one of diffuse damage to the lung (8). Both epithelial and endothelial injury occurs and the alveolar spaces are filled with fluid and proteinaceous debris. Histology shows an intense acute inflammatory cell infiltrate composed of neutrophils and monocytes migrating across the pulmonary vascular bed into the alveolar spaces. The disease is thought to result from initial activation and damage to the pulmonary endothelial/epithelial interface by systemic inflammatory stimuli (both the cellular and

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circulating mediators) which then stimulate production of further pro-inflammatory mediators and further recruitment of inflammatory cells. ALI/ARDS is therefore, the final common presentation following a range of insults. The question why the lungs are predominantly affected has remained unanswered. A simple explanation may be that when an activating antibody is infused the first microcirculatory encounter is with the narrow diameter capillaries in the lungs. Secondly, the binding of antibodies to mononuclear and polymorphonuclear cells may cause activation partially via the binding of the Fc domain of the antibody to the Fc $\gamma$  receptor and possibly via the activation of complement. Activated granulocytes and monocytes become stickier as adhesion molecules change from their non-active to their active configuration.

### 3. Clinical presentation and management

TRALI is characterised by symptoms and signs of dyspnoea, cyanosis, hypotension, fever, (none of these is universal) and pulmonary oedema. The full blood count may show a transient drop in neutrophil and monocyte counts (11,14). The onset of symptoms occurs usually within 6 hours of a transfusion episode (1,2). All blood components including red cells, platelets, granulocytes, plasma and cryoprecipitate have been reported to cause TRALI. There has been a single case report of the pooled blood product Intravenous Immunoglobulin (IvIG) containing measurable leucocyte antibodies (13).

The problem for clinical diagnosis is that there is no definitive test and often transfusion has been performed in clinical settings where other causes of Acute Lung Injury are present (e.g. trauma, sepsis). The differential diagnoses include acute pulmonary oedema due to fluid overload/left ventricular failure or ALI/ARDS secondary to other causes. The distinction between TRALI and cardiac failure may be aided by measurement of the pulmonary capillary wedge pressure which is typically raised in circulatory overload. A low PaO<sub>2</sub>/FiO<sub>2</sub> Index (<300 mmHg – acute lung injury, <200 acute respiratory distress syndrome) is helpful (1). The development of pulmonary infiltrates on chest X-rays are not specific and radiological abnormalities due to other causes may also cause confusion (e.g. pneumonia, poorly penetrated films, malignancy). Comparison with a recent pre-transfusion film is important. The diagnosis is essentially a clinical one and should be suspected if other reasons to explain the severity of pulmonary oedema are not present. Later, investigations for leucocyte antibodies may support the diagnosis.

There is no specific treatment for TRALI. If the transfusion is still continuing, it should be stopped and oxygen and supportive therapy started. Thereafter treatment is largely supportive to allow time for lung injury to subside. Most cases require mechanical ventilation for several days and cardiovascular support should be given as required. Steroids have been advocated but proof of efficacy is lacking.

### 4. Data from Serious Hazards of Transfusion haemovigilance scheme (SHOT)

TRALI has been included in SHOT reports since this began in 1996. Over the first ten years of SHOT 195 evaluable cases were reported (12). Cases from 1999 were classified according to the probability of TRALI. Forty-nine percent of these cases were highly likely or probable and 51% possible or unlikely illustrating the difficulty of making a positive clinical diagnosis of the condition. In 40 cases, TRALI was thought to have at least contributed to the patient's death. Patients treated by Haematology/oncology and Surgical specialties were the most frequently reported (40% for each). However, denominator data are not available to assess whether these specialties are truly over-represented or whether they simply reflect groups of patients heavily exposed to FFP/platelets.

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### 5. Implicated components and risk reduction

TRALI has been reported to occur after transfusion of all the following blood components; plasma, platelets, whole blood, cryoprecipitate, concentrated red cells and blood in additive solution (Evidence Level III). Proportionate to the numbers of different components transfused, components containing more plasma such as platelets and FFP have been more likely to cause TRALI but the syndrome may also occur after transfusion of components containing smaller volumes of plasma, e.g. SAG-M red cells (15). One case of TRALI following infusion of IvIg has been reported (Evidence Level III) (13). TRALI has not been reported following the transfusion of other pooled plasma products, e.g. solvent-detergent treated FFP. Theoretically, the pooling process may be considered to reduce the risk due to dilution of donor leucocyte antibodies and adsorption by soluble antigens.

NHSBT introduced policies to minimise the use of female plasma for FFP and for the plasma contribution to platelet pools in 2003. SHOT data have shown that the reported risk of highly likely or probable TRALI dropped from 15.5 before this policy to 3.2 per million components FFP/cryosupernatant plasma issued ( $p = 0.0079$ ) afterwards and from 14 to 5.8 per million issued for platelets ( $p = 0.068$ ).

Preferential use of male plasma was also introduced for cryoprecipitate production in 2009. NHSBT figures for components produced from male plasma are now 100% FFP, 100% cryoprecipitate and 100% main plasma contribution to platelet pools.

Female platelet apheresis donor recruits must be screened and found negative for HLA and HNA antibodies before acceptance. Testing of previously accepted female platelet apheresis donors for these antibodies commenced in October 2011.

### 6. Referral of Cases

TRALI should be suspected and investigation considered for patients fulfilling the following criteria:

1. Hypoxia
2. Bilateral pulmonary infiltrates on CXR
3. Lacking clinical evidence of fluid overload or other cause of pulmonary shadowing
4. Occurrence during or within 6 hours of blood component transfusion

Any suspected case should be referred initially to one of the medical staff in the local Blood Centre by the hospital blood transfusion department or clinician, who will refer the case to a designated Diagnostics consultant. Full clinical details will be requested in order to assess the likelihood of the reaction having been due to TRALI. Details obtained should include the following:

- patient demographic details
- consultant / hospital
- nature of transfusion reaction and time in relation to transfusion
- components transfused (including donation numbers) in the 24 hours preceding the reaction
- treatment given including ventilation

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- clinical response / outcome

Referring consultants should be encouraged to report the incident to SHOT if TRALI remains the most likely diagnosis and they should be reminded of this in the final report following laboratory investigations.

On receipt of the referral, the designated NHSBT consultant will:

- open an investigation file
- inform the H&I laboratory in Bristol by e-mail about the case
- request samples from the patient
- review clinical details, obtaining more from other sources if necessary (e.g. ITU staff) to assess likelihood of the reaction being TRALI
- forward anonymous clinical details to TRALI expert panel for opinions on the clinical likelihood of TRALI and recommendations on whether or not to proceed with a full TRALI investigation
- if TRALI is considered a possible diagnosis, determine donations/donors to be investigated (initially those from female or transfused male donors transfused within 6 hours of onset of TRALI – if these investigations give negative results but TRALI is strongly suspected clinically, investigation should be extended to include donations from apparently untransfused males)
- withdraw and / or recall other plasma rich components (platelets, plasma or cryoprecipitate but not SAG-M red cells) from same donation(s)
- temporarily suspend female and transfused male donor(s) pending investigation results

### 7. Samples

The NHSBT laboratory investigations for TRALI are undertaken by H&I laboratories at NHSBT Bristol. The investigations aim to identify the presence of leucocyte antibodies (HLA class I, HLA class II and HNA) in the implicated donor samples. Patient samples will only be tested for antibodies if the transfused component was not leucodepleted (apheresis or buffy coat granulocytes). If leucocyte alloantibodies are detected then appropriate tests for the presence/absence of the antigen or allele in the patient/donor will be performed.

It is important to note that there is a possibility of finding donors with HLA or HNA antibodies by chance. It is therefore essential that investigations should determine whether the patient is positive for the cognate antigen. Even if this is the case, the observed incompatibility may have nothing to do with the clinical picture as many patients, who may be positive for the cognate antigen, are transfused with leucocyte antibodies and TRALI does not ensue. The limited diagnostic specificity of the laboratory investigations should be taken into account when reporting. The interpretation of the laboratory results must be in the context of a well-documented clinical case history.

#### 7.1 - patient

6 mL clotted and 6 mL EDTA blood samples should be obtained from the patient for:

1. Investigation for HLA class I & class II & HNA antibodies if indicated.
2. HLA and HNA typing.

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### 7.2 – donor(s)

Donor samples are required for investigation for the presence of HLA & HNA antibodies and for defining HLA and HNA antigens if required. The latter can only be performed if fresh donor samples are obtained as donor DNA is not routinely archived after donation. The ideal samples are 6 mL clotted and 6 mL EDTA blood obtained from the donor.

If many donors have been identified as possibly implicated then it may be simpler to first screen the archived samples from these donors for leucocyte antibodies. Although false positive reactions can be obtained the number of donors which do not require re-sampling can be reduced significantly thus reducing the amount of time it will require to resolve the case. Any positive result from an archived sample should be confirmed on a fresh donor sample if possible.

As leucocyte antibodies are produced as a result of pregnancy or transfusion, it is pragmatic to investigate only female donors and male donors with a history of transfusion, initially.

### To crossmatch or not to crossmatch

It is logistically complex to perform a lymphocyte and granulocyte cross match and this is rarely required.

#### No cross match

If leucocyte antibodies with an obvious allo-specificity are detected in a donor sample and the patient tests positive for the cognate allele or alloantigen then a cross match is not required.

#### Crossmatch

Rarely, HLA or other leucocyte antibodies are detected to which no clear specificity can be assigned. In such cases, a crossmatch of donor serum with recipient leucocytes should be performed to confirm incompatibility. If there are no stored recipient lymphocytes or if there is granulocyte specific reactivity in donor serum that reacts independently of known HNA specificities a fresh 20 ml EDTA blood sample will need to be obtained. A sample from the patient should be sent to the TRALI Laboratory in Bristol and must arrive there within 24 hours of sampling.

## 8. Reporting Of Results

All results on patient and donor samples will be collated on the H&I computer database. A single report will be prepared collating the scientific findings and conclusion. The final version of the report will be issued with a covering letter from a TRALI Medical Consultant to the referring clinician and SHOT.

The report will indicate whether or not the scientific findings are consistent with immunologically mediated TRALI.

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### 9. Management of Donors

The management of the donors should be as follows:

- Resign donors who are positive for leucocyte antibodies which are concordant with recipient antigen or who have a positive crossmatch with recipient.
- Resign donors with HNA antibodies with identified HNA specificity
- Do not resign donors with HLA antibodies which are not concordant with recipients but allocate them, on PULSE, to red cell use only (Pack type code A)
- Do not resign donors who are found negative for leucocyte antibodies; they may continue to donate as routine.

### 10. Subsequent transfusion management of patients diagnosed with TRALI

There is no good evidence on which to base transfusion support policy for patients who have experienced TRALI. However, the hypothesis that there may be patient factors which contribute to the risk of TRALI is generally accepted. Based on this reasonable assumption it makes sense to try to avoid further transfusion during the period of illness following the reaction if at all possible.

It is no longer considered necessary to advise hospitals to contact NHSBT to request male donor plasma rich components specifically for these patients. This is based on the low risk of a subsequent plasma rich component containing concordant leucocyte antibodies. Necessary transfusion could also be delayed by this advice (Grade of Recommendation C, Evidence Level IV).

The evidence that biologically active lipids play a causal role in TRALI is limited and insufficient to support the use of recently donated or washed cellular components.

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### Key to evidence statements and grades of recommendations

The definitions of the types of evidence and the grading of recommendations used in this guideline originate from the US Agency for Health Care Policy and Research and are set out in the following tables.

#### STATEMENTS OF EVIDENCE

- |     |   |
|-----|---|
| Ia  | Evidence obtained from meta-analysis of randomised controlled trials.   |
| Ib  | Evidence obtained from at least one randomised controlled trial.  |
| IIa | Evidence obtained from at least one well-designed controlled study without randomisation.   |
| IIb | Evidence obtained from at least one other type of well-designed quasi-experimental study.   |
| III | Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies. |
| IV  | Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.                             |

#### GRADES OF RECOMMENDATIONS

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- A** Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation.  
(Evidence levels Ia, Ib)
- B** Requires the available of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.  
(Evidence levels IIa, IIb, III)
- C** Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.  
(Evidence level IV)