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Recommendations in the event of a suspected transfusion-related acute lung injury (TRALI)

2 March 2011

1. INTRODUCTION

Transfusion-related acute lung injury (TRALI) is a disorder with a potentially serious evolution that arises during or shortly after administering blood components (Kleinman et al, 2004, Goldman et al, 2005, Saidenberg et al, 2010). The differential diagnosis with other lung disorders is not an easy one to make. It is therefore likely that its incidence, which varies significantly from country to country, is being underestimated. The aim of this project is to draw up an advisory report on the clinical diagnosis of TRALI and on the laboratory investigations that can support it.

In Belgium, national haemovigilance reports for 2006-2008 (FAMHP, 2007; FAMHP, 2008; FAMHP, 2010) mention 11 cases of suspected TRALI: 3 in 2006, 4 in 2007 and 4 in 2008. For none of these cases was it possible to show that there were any HLA/HNA antibodies present (FAMHP, 2010). This surveillance concerns 1,997,005 blood components distributed with a frequency of 0.65/100,000 blood components.

One of the known causes of TRALI is the presence of anti-leukocyte antibodies in the plasma of the administered blood components (Benson et al., 2009; Silliman et al., 2009; Nuffermans, 2010). Not only HNA (human neutrophil antigen)-antibodies have been incriminated, but also HLA (human leukocyte antigen) class I and II antibodies. We hope that drawing attention to this condition will improve haemovigilance notifications, thus enabling us to obtain a better assessment of its incidence in this country and to verify whether the anti-leukocyte antibodies found in the blood components play a part in it. The data obtained will allow for measures to be sought that will reduce its incidence.

In order to provide an answer to the question, a working group was set up which consisted of experts in blood transfusion, haematology, clinical biology, anaesthesiology and intensive care.

2. ADVICE

TRALI is a clinical syndrome characterised by the occurrence or the worsening of acute respiratory distress associated with the development of noncardiogenic pulmonary oedema within six hours after the completion of a plasma-containing blood component transfusion.

The diagnosis of TRALI is mainly made clinically and laboratory testing can, in some cases, contribute to it. TRALI should be distinguished from other potential causes of acute respiratory distress, especially from transfusion-associated circulatory overload (TACO).

The treatment of TRALI is mainly symptomatic.

The laboratory tests required within the framework of an immunological investigation (search for HLA and HNA antibodies) should be carried out in reference laboratories with the necessary expertise.

The use of fresh frozen plasma from non-immune male or female donors currently provides the most effective preventive measure.

The SHC recommends that there should be a more stringent surveillance of patients who receive a blood component transfusion. The clinician should pay very close attention to any change in the patient's respiratory status (cf. dyspnoea and desaturation), which should be notified systematically to the haemovigilance contact person in the hospital.

3. FURTHER DETAILS AND ARGUMENTATION

Abbreviations used: ALI = acute lung injury ; BNP = B-type natriuretic peptide; DNA = deoxyribonucleic acid ; HLA = human leukocyte antigen ; HNA = human neutrophil antigen; NT-proBNP = N-terminal-pro-B natriuretic peptide; SHOT = Serious Hazards Of Transfusion; TACO = transfusion associated circulatory overload; TRALI = transfusion-related acute lung injury

3.1 Methodology

The advisory report is based on an overview of the scientific literature as well as on the opinion of the experts. The systematic review is the result of a careful assessment of the reference lists of all relevant articles and articles available on-line prior to publication in the main journals in the field of clinical transfusion. These data have been augmented with the search for related articles via the PubMed database.

3.2 Further details

3.2.1. Introduction

TRALI is a clinical syndrome characterised by the occurrence or worsening of acute respiratory distress associated with the development of noncardiogenic pulmonary oedema within six hours after the completion of a plasma-containing blood component transfusion (AFSSAPS, 2006).

In retrospect, the first description of TRALI appears to have been that by Barnard in 1951, before the concept of ALI (acute lung injury) had even been established (Barnard, 1951). Several subsequent publications mentioned pulmonary manifestations under different labels: pulmonary infiltrates associated with leucoagglutinin transfusion, pulmonary hypersensitivity reaction induced by the transfusion of non-HLA agglutinins, pulmonary oedema after transfusion with no circulatory overload, pulmonary infiltrates with HLA-specific antibodies, fulminating noncardiogenic pulmonary oedema after cardiac surgery.

Popovsky et al. (1985) were the first to identify TRALI as a distinct syndrome in 1983 and, in 1985, published a series of 36 cases observed in the Mayo Clinic between 1982 and 1984. Between 1985 and the mid-nineties, relatively little interest was taken in the syndrome, possibly as a result of the mistaken notion that acute post-transfusion complications could not affect the lungs. This view has changed since, following the publication of reports and studies which have clearly shown that lung damage plays a part in the occurrence of serious and even fatal post-transfusion complications.

When TRALI became the leading cause of post-transfusion acute mortality in the United States and the United Kingdom, the medical community took the problem much more seriously.

The haemovigilance systems in France and Canada have confirmed that TRALI poses a significant problem. Nowadays, it is generally agreed that TRALI is the leading cause of severe post-transfusion morbidity and acute mortality in countries with a high development index (Popovsky et al., 2008). In addition, research into this syndrome has revealed the existence of other pulmonary complications associated with transfusion, such as overload oedema or TACO (transfusion-associated circulatory overload).

At the same time as data about the morbidity and mortality associated with TRALI were becoming available, several epidemiological and pathophysiological studies increased the knowledge about this syndrome's mechanisms and triggering factors. Also the association observed between TRALI and plasma-containing blood components from multiparous women has dramatically changed the approach taken by blood collection facilities. In some countries, several strategies for detecting high-risk donors have been identified and implemented.

3.2.2. Definitions

TRALI is a special form of ALI. At the North-American and European consensus conference (Bernard et al., 1994), ALI was defined as acute hypoxaemia characterised by a partial arterial oxygen tension (fraction of inspired oxygen $\text{PaO}_2/\text{FiO}_2$) index inferior to 300 mmHg and associated with bilateral infiltrates on the chest X-rays without any signs of pulmonary vascular overload. On the other hand, several risk factors for TRALI have been identified. Most of them are recognised causes of the development of lesional pulmonary oedema, especially

1. Direct pulmonary lesions
 - a. infections;
 - b. aspiration pneumonia;
 - c. fat embolism;
 - d. amniotic fluid embolism;
 - e. pulmonary contusion;
 - f. toxic inhalation;
 - g. lung transplant;
 - h. drowning.

2. Indirect lesions
 - a. severe sepsis;
 - b. shock;
 - c. salicylate overdose;
 - d. intravenous drug addiction;
 - e. acute pancreatitis;
 - f. multiple trauma;
 - g. extracorporeal circulation.

On this basis, two definitions for TRALI were proposed: one during the Canadian consensus conference in Toronto (Kleinman et al., 2004), the other by the NHLBI (National Heart, Lung and Blood Institute) (Goldman et al., 2005). Both refer to the onset of a new ALI within 6 hours after the completion of a blood component transfusion when there are no other risk factors present for the development of ALI. When there are one or more other risk factors present for the development of ALI within six hours after a transfusion, the Canadian consensus conference speaks of “possible” TRALI, whereas the NHLBI takes the view that there is a TRALI when the clinical circumstances suggest that there are no other risk factors for ALI involved.

TRALI is not clinically different from other forms of ALI and is severe from the outset. Patients usually exhibit severe dyspnoea and/or cyanosis. As regards intubated patients, pink frothy secretions may appear around the endotracheal tube and/or they may require an increased FiO₂. Hypoxaemia is immediately severe (PaO₂ between 30 and 50 mmHg in the ambient air). Tachycardia, a 1 or 2 °C rise in body temperature, hypotension or even hypertension can also be observed, though this is not invariably the case. The chest X-rays show alveolar-interstitial infiltrates that are sometimes difficult to differentiate from a cardiogenic pulmonary oedema. When present, the hypotension is usually moderate and does not correspond to blood volume expansion. Administering diuretics to the normo- or hypertensive patient can hasten the onset of hypotension. All these symptoms occur within 1 to 6 hours after the transfusion of a plasma-containing blood component (in 90 % of the cases within 1 to 2 hours). Unlike other forms of ALI that are characterised by a serious morbidity and mortality, 80 % of TRALI patients show a weakening of their symptoms within 48 to 96 hours after the initial insult, provided they received appropriate respiratory support. Whereas the pulmonary lesions resolve more slowly in ALI patients, they are temporary in TRALI patients. The PaO₂ will soon assume values identical to those prior to the insult and the chest X-rays will reveal that the oedemic fluid is quickly eliminated. Nonetheless, in about 20 % of the cases the pulmonary infiltrates can persist for 7 days without leaving permanent pulmonary sequelae. In addition to the clinical symptoms described above, transitory leukopenia and neutropenia have been described in TRALI patients (Popovsky et al., 2008; Renaudier et al., 2009). This can last for 2 to 16 hours. Therefore, the evaluation of patients with suspected TRALI can include selective leukocyte counts. Depending on the studies, the TRALI mortality rate varies from 5 to 24 %. TRALI is the leading cause of acute mortality associated with transfusion in the United States. Nevertheless there are probably more moderate forms of TRALI that do not correspond entirely to the definition of the Toronto consensus and are under diagnosed.

For a variety of reasons, the precise incidence of TRALI is poorly known: no unequivocal definition prior to 2004, lack of data concerning the number of blood components transfused each year and, above all, the failure to recognise and the under-reporting of TRALI due to possible confusion with other clinical syndromes such as TACO (Popovsky et al., 2008). These factors account for the highly divergent incidences mentioned in the literature.

In the United States, studies mention an incidence between 1/1,300 and 1/5,000 transfusions of plasma-containing blood components. A study carried out in an English hospital reports an incidence of 1/7,900 units of fresh frozen plasma (Juvin et al., 2000). The blood components most commonly involved are fresh frozen plasma, blood platelets from multiple donors, apheresis platelets and finally units of red blood cell concentrates. A recent study on a consecutive series of intensive care patients who did not require mechanical breathing prior to transfusion mentions a TRALI-incidence of 1/534 transfusions (Gajic et al., 2007). This observation suggests that TRALI is probably more frequent in specific clinical circumstances. However that may be, most authors agree that the actual incidence of TRALI remains considerably underestimated due to the failure to recognise and report it (Popovsky et al., 2008; Renaudier et al., 2009).

TRALI is equally frequent in both sexes and occurs in all age groups.

3.2.3. Diagnosis

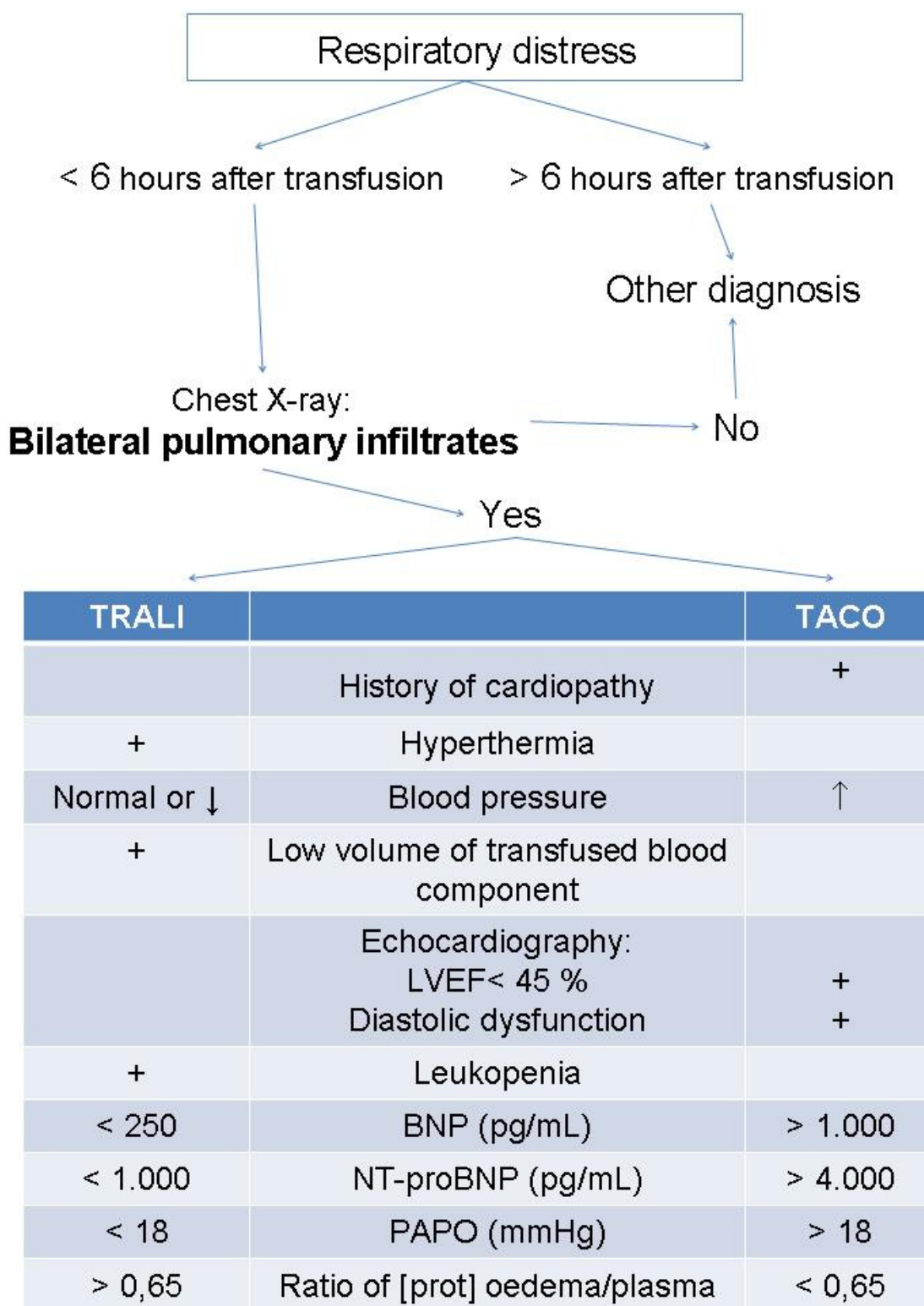
The differential diagnosis should, first of all, include the following clinical syndromes: transfusion-associated circulatory overload (TACO), lesional oedema of another origin, severe anaphylactic transfusion reaction, transfusion reaction as a result of bacterial contamination and haemolytic reaction due to ABO incompatibility (Popovsky et al., 2008; Renaudier et al., 2009; SHC, 2010).

- 3.2.3.1. *Transfusion-associated circulatory overload* (TACO) is characterised by increased pulmonary capillary wedge pressure and left atrial pressure. This diagnosis is supported by a previous history and/or clinical signs of left ventricular insufficiency. An abnormal electrocardiogram can direct the diagnosis towards a cardiogenic cause. The chest X-rays (front view) are also part of the differential diagnosis (Table 1). The echocardiography has become the reference examination: it investigates the presence or absence of signs suggesting ventricular insufficiency and/or increased left atrial pressure. On the biological level, there is an increased plasma concentration of brain natriuretic peptide (BNP) or its N-terminal (NT-proBNP) (Renaudier et al., 2009). However, the sensitivity and specificity of the BNP in the diagnosis of TACO are still subject to debate. In the case of TACO, the pulmonary capillary wedge pressure, if measured, would be over 18 mmHg, whereas it would be normal or even low in the case of TRALI. In actual practice, however, it is increasingly less frequent for the pulmonary capillary wedge pressure to be measured. From a therapeutic point of view, an overload oedema usually responds quickly to diuretics and vasodilator treatment, in contrast to TRALI, where these treatments can worsen the haemodynamic instability.
- 3.2.3.2. *A lesional oedema of another origin* also needs to be ruled out: the most frequent aetiologies are mentioned above.
- 3.2.3.3. *A severe anaphylactic transfusion reaction* usually occurs very early, without delay after the transfusion. Bronchospasms with tachypnoea, expiratory wheezing, stridor and cyanosis are uppermost in the respiratory picture. Symptoms that contribute to the diagnosis may also affect the skin and mucous membranes, such as urticaria or erythema, mainly in the face, the neck and the anterior chest region. Quincke's oedema can develop, bringing about a risk of asphyxia. There can also be a state of shock and even cardiac arrest. There is usually no pulmonary oedema, at least not in the initial phase of the reaction.
- 3.2.3.4. *A transfusion reaction as a result of bacterial contamination* is accompanied by fever, shivering, mottled skin, hypotension and/or vascular collapse with possible septic shock. The clinical picture can contain an ALI, but in most cases the pulmonary affection does not occur until several hours later.
- 3.2.3.5. *A haemolytic reaction due to ABO incompatibility* can usually be ruled out easily as a result of the clinical context of acute intravascular haemolysis and by checking the transfusion documents and the transfused red blood cell bags and by carrying out a final verification at the patient's bedside.

In practice, there are forms that are more difficult to diagnose because lesional and haemodynamic factors co-occur in the same patient. This is also the case when this complication concerns a patient already suffering from a lesional pulmonary oedema of another origin. Depending on the case, the anamnesis, the circumstances in which the symptoms appeared and especially their chronological relation with the transfusion, the (para)clinical investigations will make it possible to confirm or reject the diagnosis of "possible" TRALI. In unclear cases immunohaematological tests can help making a presumptive clinical diagnosis. In a patient who already has an ALI, especially one that has an infectious origin, a significant worsening of the respiratory status (deterioration of the PaO₂/FiO₂ ratio) within six hours after a transfusion should evoke a diagnosis of TRALI.

A flow chart with decision points for diagnosing and ascribing the pulmonary oedema to the transfusion is presented in figure 1 and tables 1 and 2 (Ozier et al., 2010).

Figure 1. Decision points for diagnosing a post-transfusion pulmonary oedema (adapted from Ozier et al., 2010).



+ = present; ↓ = down; ↑ = up; LVEF = left ventricular ejection fraction; PAOP = pulmonary artery occlusion pressure; [prot] = protein concentration.

Table 1. Elements for a differential diagnosis between overload oedema (TACO) and TRALI on the chest X-ray (front view) (based on Ware et al., 2005).

Appearance on the X-rays	Overload oedema	TRALI
Heart shape	Normal or enlarged	Normal
Hilar size	Enlarged	Normal
Vascular distribution	Equalisation or redistribution to the upper lung zones	Normal
Distribution of the oedema	Perihilar	Fluffy, peripheral
Pleural bleeding	Present	Usually none
Peribronchial oedema	Present	Usually none
Kerley lines	Present	Usually none
Air bronchogram	Usually none	Usually present

Table 2. Causal link for TRALI (based on Ozier et al., 2010).

Causal link	Comments	Definition
0		ALI not linked to transfusion
1	Presence of another ALI cause	“possible” TRALI
2	TRALI without indication of immunological conflict (negative, incomplete or no screening)	“likely” TRALI
3	TRALI with immunological conflict	“confirmed” TRALI

3.2.4. Treatment

The treatment for TRALI is primarily based on an aggressive tackling of the respiratory distress with oxygen therapy and mechanical ventilation (non-invasive or with endotracheal intubation) (Wheeler et al., 2007; Khan et al., 2008). For moderate forms of TRALI, oxygen therapy can be sufficient, either via an endonasal catheter or via a mask when the administered flow is over 6 L/min. As mentioned above, the differential diagnosis between TRALI (“confirmed” or “possible”) and TACO is crucially important, since diuretics play a key role in the treatment of TACO, but can worsen the haemodynamic instability in case of TRALI. Nevertheless, once the respiratory distress has been recognised and the haemodynamic instability has been mastered (if necessary with the help of vasopressors) it can be useful to adopt a restrictive fluid strategy in order for the pulmonary oedema to resolve more quickly, thus reducing the duration of mechanical ventilation. In any event, once TRALI has been diagnosed, the principles for treating respiratory distress are identical to those of the other forms of ALI. They include a low-tidal-volume strategy in the event of invasive mechanical ventilation (6 – 8 mL/kg body weight), use of standard sedation and ventilator weaning protocols and the use of appropriate measures to prevent nosocomial complications. Immunological treatment, such as corticotherapy, has not proved to be effective and is therefore not recommended (Steinberg et al., 2006; Wheeler & Bernard, 2007).

In case of “confirmed” or suspected TRALI, the transfusion of blood components, especially in its initial phase, should be evaluated very carefully. The indication for transfusion needs to be clearly defined, especially as regards high-risk blood components, i.e. those that contain significant amounts of plasma. In order to reduce recipient exposure to other biological causal factors to an absolute minimum, some authors propose the use of blood components that contain “young” cellular elements, i.e. red blood cells that have been preserved for less than 3 weeks or blood platelets that are less than 3 days old (Khan et al., 2008). However, at the moment, this proposal is not grounded on solid scientific data.

3.2.5. Pathophysiological mechanisms

Clinical observations and experimental data have led most authors to suggest that the sequential combination of two factors is responsible for the occurrence of TRALI (Renaudier et al., 2009; Looney et al., 2010). The first factor is related to the patient’s pathology (sepsis, cardiac surgery with extracorporeal circulation, etc.), which causes a systemic inflammatory reaction. This is responsible for endothelial activation, which delays lung transit and results in long-lasting polynuclear neutrophil sequestration in the capillary vessels. At this stage there is no lesion of the alveolo-capillary basement membrane, the patient is simply at risk of developing a TRALI. The second factor has to do with the activation of the sequestered polynuclear cells through the transfusion of a blood component. Contact with the endothelium will cause the activated polynuclear cells to release oxygen radicals and granular enzymes, leading to lesions in the capillary basement membrane and to the appearance of the alveolar oedema. The latter is made of a serous and cellular exudate with the formation of hyaline membranes, which is typical of a lesional pulmonary oedema. This exudate and oedema are at the basis of a ventilation-diffusion disorder, the extent of which is proportional to the seriousness of the respiratory distress.

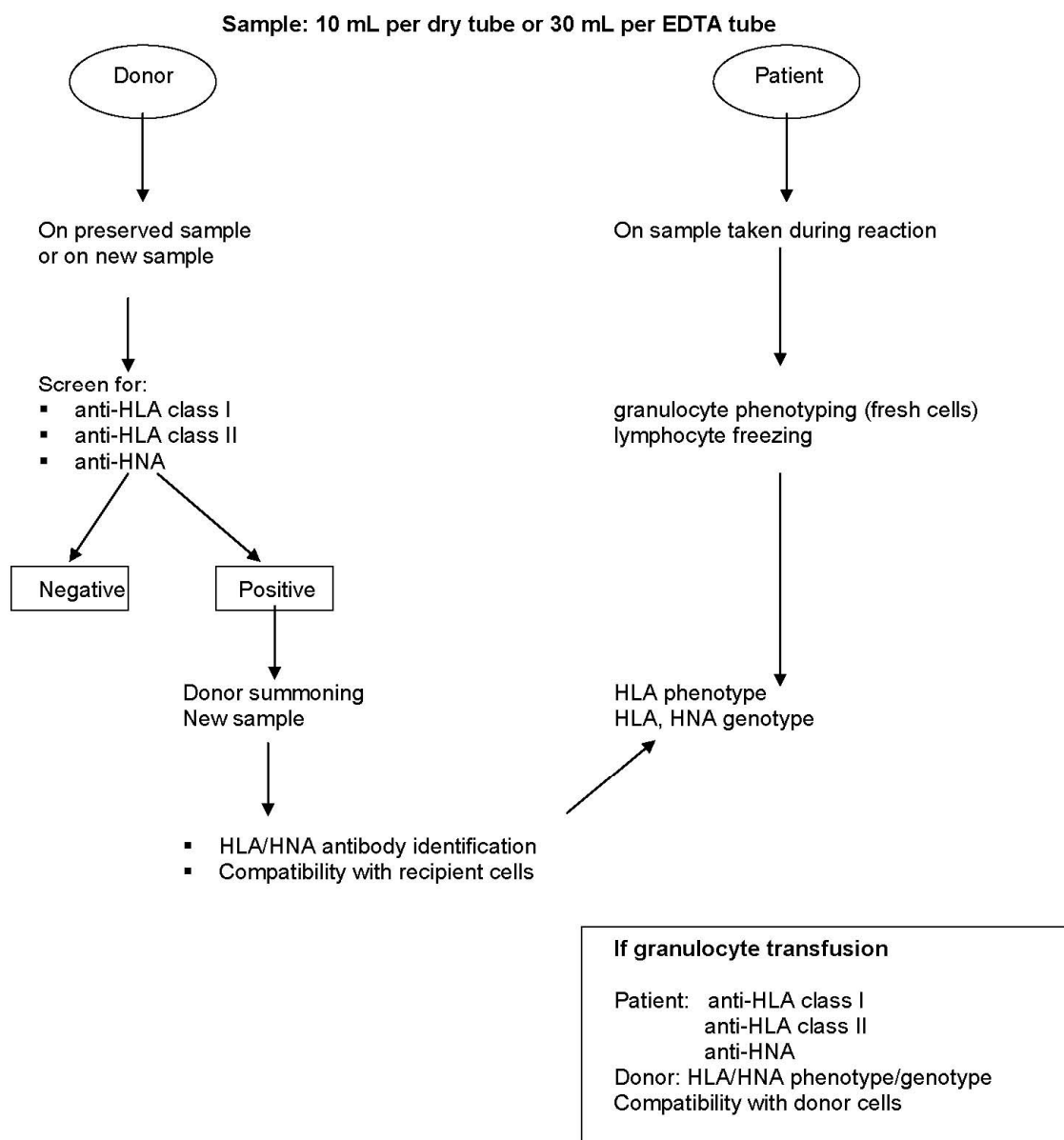
As regards TRALI, it has been known for a long time that anti-granulocyte antibodies emanating from the transfused component are responsible for the *in vivo* activation of polynuclear cells. This concerns either anti-neutrophil antibodies (HNA-antibodies) or HLA-class I antibodies, which cause complement activation by binding to the polynuclear cells, or HLA-class II antibodies. Apart from the auto-antibodies, five activation mechanisms for polynuclear cells were eventually identified (Renaudier et al., 2009):

- neutral lipids and phosphatidylcholines accumulate in cellular blood components (i.e. red cell and platelet concentrates) during storage.
- the red blood cells release free oxygen radicals in the event of pulmonary hypoxaemia, resulting in an inflammatory reaction and causing the mobilisation of polynuclear cells. This free radical release is all the more marked with cellular concentrates in which the red blood cells have a reduced oxidising capacity.
- the vascular endothelial growth factor (VEGF) and HLA class II antibodies enhance endothelial cell permeability. HLA class II antibodies are believed to act either directly on the neutrophils in the event of a severe inflammatory reaction or via the monocyte-macrophage cell lines.
- the soluble CD40 ligand (sCD40L) is a proinflammatory mediator that is released by the blood platelets and found in blood components. By binding to the CD40 present on the polynuclear cells, it is capable of triggering their activation.
- antibodies present in the recipient that are directed against a donor leukocyte antigen can trigger a “reversed” TRALI, with the transfused leukocytes causing a pulmonary insult in the recipient.

3.2.6. Significance of biological donor and recipient testing

Since the Toronto consensus conference in 2004, the definition of TRALI has been clinical. TRALI results from several mechanisms in which the activation of granulocytes accumulated in the pulmonary capillaries is central. The part played by the anti-granulocyte antibodies in the activation has been known for a long time. This can concern anti-neutrophil antibodies (HNA) or HLA class I and II antibodies. The first studies reported the presence of antibodies in 89 % of the donors implicated (Popovsky et al., 2008). The HNA antibodies (nomenclature HNA-1 to 5) (Bux, 2008) are more frequently implicated in the most serious cases, in particular anti-HNA-3a (the former anti-5b) (Reil et al., 2008). Detecting these antibodies is therefore important for the follow-up of the donor(s) implicated (figure 2).

Figure 2. Immunological investigation among donors and recipients (based on SHC, 2010).



EDTA = ethylenediaminetetraacetic acid

The presence of anti-leukocyte antibodies has been detected more frequently in female donors. Thus, according to a European study (Insunza et al., 2004), this frequency increases with the number of pregnancies: 9 % after one pregnancy, 18 % after two and 23 % after three pregnancies. An American study carried out on 5,841 female donors shows an overall prevalence of HLA antibodies of 17.3 %, of which 1.7 %, 11.2 %, 22.5 %, 27.5 % and 32.2 % were found after 0, 1, 2, 3 or 4 pregnancies, respectively (Triulzi et al., 2009).

As regards the specificities of the antibodies, the search for HLA class I and II antibodies and HNA antibodies in 5,532 female donors with a history of one or several pregnancies has revealed the presence of anti-leukocyte antibodies in 8.9 % of them. Amongst these antibodies, 63 % were HLA class I, 19 % HLA class II, 19 % HLA classes I and II and 5 % anti-HNA (Reil et al., 2008). When carrying out such an investigation, one should therefore favour screening for antibodies in female donors with a history of one or several pregnancies.

As for the rare cases of “reversed” TRALI, the antibodies are present in the patient and are directed against a leukocyte antigen of the donor. In the first TRALI cases described, up to 6 % of the cases were attributed to the presence of antibodies in the patient (Popovsky et al., 2008). In many countries, including Belgium since 2004, red blood cell and platelet concentrates are systematically leukodepleted (residual white blood cell count < 1.10^6 per blood component). Therefore, this mechanism is probably little implicated, except in the case of granulocyte transfusions.

3.2.7. Immunological investigations among donors and recipients

These investigations (AFSAPPS, 2006; Bierling et al., 2009) are only carried out with “likely” or “possible” cases of TRALI diagnosed according to the recognised criteria (Kleinman et al., 2004; Goldman et al., 2005; Chapman et al., 2009; Ozier et al., 2010). These immunological investigations are to be carried out in reference laboratories with the necessary expertise for carrying out serological testing, typing and genotyping of the HLA and HNA antigens (SHC, 2010).

The donors

The immunological investigation contains 2 steps:

- a. Screening for HLA class I and II antibodies and for HNA anti-neutrophils. These tests can be carried out either on a donor sample preserved in the blood establishment in a fresh or frozen state (serum library) or on a new blood sample.
- b. Verifying and identifying antibodies, as well as lymphocyte or granulocyte crossmatching with recipient cells in the corresponding systems if the results are positive. This should be done with a new blood sample from the donor, who should be summoned to this end.

The recipients

The blood samples taken from the recipient during the incident should be quickly transported to the reference laboratory (within 48 hours at the latest).

The immunological investigation contains 2 steps:

Step 1 – to be carried out systematically

- a. Granulocyte phenotyping by means of serological techniques. If they cannot be brought to the reference laboratory within the time limit, the typing should be done by means of molecular biology (see point c) and this on account of the fragility of the granulocytes.
- b. Lymphocyte freezing in order to carry out a lymphocyte crossmatch depending on the results of the donor investigation.

- c. Preserving the blood samples for DNA extraction and for potential HLA and HNA genotyping depending on the results of the donor investigation.
- d. Screening and identifying HLA class I and II antibodies as well as HNA antibodies; mainly to be carried out in case of TRALI following a granulocyte transfusion.

The frozen lymphocytes and the recipient's DNA should be preserved until the donor investigation is completed.

Step 2 – to be carried out in the event of HLA/HNA antibodies being found in the donor or the recipient

- a. Determining the HLA/HNA phenotype and genotype in the corresponding system;
- b. Lymphocyte or granulocyte crossmatching in the corresponding system;
- c. If the outcome of the screening for anti-leukocyte antibodies in the recipient is positive, summoning the donor(s) implicated and taking a blood sample for phenotyping/genotyping and lymphocyte or granulocyte crossmatching in the corresponding system.

3.2.8. Attitude regarding blood components and donors

Blood components

As soon as a TRALI or "possible" TRALI is suspected, the person in charge of haemovigilance in the hospital should contact the person in charge of haemovigilance in the transfusion centre/ blood establishment (SHC 2010) The latter should make a list of the blood components and the corresponding donors and block and/or recall all **blood components and products from the same donation**.

If the suspected TRALI is confirmed, the blood components from male donors with no transfusion history may be released, but the blood components originating from female donors should only be released if the outcome of the antibody search is negative.

If the suspected TRALI is not confirmed, all blood components may be released.

Donors

As soon as the case is sufficiently well documented and the TRALI diagnosis is confirmed, **all female donors** are temporarily contra-indicated until the immunological investigation has been completed.

According to the Canadian consensus conference (Kleinman et al., 2004; Goldman et al., 2005) the donor can be involved in either of two ways:

- either the donor is **associated** with TRALI if one or several of his or her blood components were transfused within the six hours previous to the first symptoms of TRALI;
- or the donor is **implicated** if HLA/HNA antibodies were found and match the patient's leukocyte antigens.

Several approaches can then be taken into consideration, the most frequently recommended being the following (Reil et al., 2008; Bierling et al., 2009):

- "associated" donors are not contra-indicated;
- the "implicated donors for whom immunological screening has led to a suspected causal link between the donor and the incident", should be permanently deferred from giving blood.
- the detection of an HNA antibody, especially anti-HNA-3a, should also always result in the donor being permanently deferred.
- donors with HLA antibodies should be deferred if they exhibit strong reactivity and may possibly continue to give blood components that contain little plasma.

For the moment, this deferral is not based on any prospective studies and has not proved to be effective in reducing TRALI. Rather, it is based on the precautionary principle and on the principle of empirical logic that holds that if a donor has been implicated in a TRALI reaction, he or she is more likely to be so again. As far as “implicated” donors are concerned, there should be retrospective studies carried out on transfusions with blood components that were prepared previously.

3.2.9. Strategies for reducing the risk of TRALI

All blood components (red cell concentrates, platelet concentrates and virus-inactivated fresh frozen plasma) are concerned. The incidence of TRALI, which varies from one study to another, is in the region of 1/100,000 (variation 1/400 to 1/500,000) transfused blood components, with a risk 7 to 8 times higher for the blood components that contain large volumes of plasma, i.e. virus-inactivated fresh frozen plasma and platelet concentrates (Kleinman et al., 2008; Popovsky et al., 2008).

In Belgium, national haemovigilance reports for 2006 – 2008 (FAMHP, 2007; FAMHP, 2008; FAMHP, 2010) mention 11 notifications of suspected TRALI: 3 in 2006, 4 in 2007 and 4 in 2008. For none of these cases was it possible to show that there were any HLA/HNA antibodies present, nor could they be identified (FAMHP, 2010). This surveillance concerns 1,997,005 distributed blood components with a frequency of 0.65/100,000 blood components.

On the other hand, the French haemovigilance report of 2009 mentions 42 TRALI cases with 2 up to 4 deaths caused by it, which amounts to a frequency of 1.4/100,000 blood components. This corresponds to 0.7 % of the transfusion reactions (AFSSAPS, 2010).

Between January 2005 and July 2007, 49 cases of TRALI were reported in the Netherlands, including 10 deaths (van Stein et al., 2010). In 48 % of the cases, anti-leukocyte antibodies with proved incompatibility were detected. Its frequency is 3/100,000 blood components.

Reducing the risk of TRALI

Reducing the risk of immune TRALI is based on all measures that aim at bringing down the presence of HLA class I and II antibodies and HNA antibodies in the blood components, especially in virus-inactivated fresh frozen plasma and platelet concentrates, but also red cell concentrates. Measures aimed at reducing the patient’s immunity also need to be taken.

As regards non-immune TRALI due to biological factors, it is possible to propose safety measures like washing the red cell concentrates or possibly bringing forward the expiry date of the blood components, but not a single measure is currently being recommended or applied.

The main measure for reducing patient immunisation is blood-component leukocyte depletion. This measure has been applied in Belgium since 2004 (SHC, 2010).

Other measures pertaining to the deferral of high-risk donors, especially female donors with a history of pregnancy (Insunza et al., 2004; Reil et al., 2008; Triulzi et al., 2009) can be considered and are already being implemented in the United Kingdom and Germany (Barnard, 1951; Reil et al., 2008).

Regarding single-donor platelet concentrates, samples should only be taken from male donors, possibly also from nulliparous women. This measure will result in the loss of about 50 % of platelet donors. An alternative is using female donors but replacing their plasma with plasma from male donors with no transfusion history. However, this requires additional processing and can lead to a loss in quality. Reducing the plasma in cellular blood components involves using a SAG-M (saline, adenine, glucose, mannitol) solution for the red cell concentrates, and resuspending

platelet concentrates in a PAS (platelet additive solution; 1/3 plasma, 2/3 PAS) preservation solution. An alternative is using plasma from “no-risk” female donors.

The detection of “high-risk donors”, mainly non-nulliparous female donors, can be done by screening for HLA/HNA antibodies. This is already being done in Germany (Reil et al., 2008) and France is currently assessing this possibility (AFSSAPS, 2010). A recent study shows no significant increase in the prevalence among donors with a transfusion history compared to those without. Therefore, it does not recommend searching for antibodies (Kakaiya et al., 2010). In addition to the significant costs involved, searching for antibodies also poses a number of technical problems. Thus, it is problematic to use highly sensitive tests to screen for HLA antibodies when there is no standardisation, no clear definition of the significant cut off value and no identification of the importance of transfusion in a context other than that of organ or haematopoietic stem cell transplantations (AFSSAPS, 2010; Kakaiya et al., 2010; Lopes et al., 2010; Hashimoto et al., 2010). As regards the tests used to screen for HNA antibodies (agglutination, fluorescence, MAIGA (monoclonal antibody-specific immobilisation of granulocyte antigens)), they require the use of fresh granulocyte panels, since these cannot be frozen. This technical constraint considerably reduces the number of laboratories capable of carrying out these tests in appropriate conditions. New techniques using HNA antigen binding to the microbeads for HNA antibody screening are currently being evaluated. As a result, it will no longer be necessary to use fresh granulocytes (Fromont et al., 2010).

Two teams have recently described the molecular characterisation of the HNA-3a antigen on the CTL-2 protein (choline-transporter like protein 2) and identified the polymorphism at the gene level (Curtis et al., 2010; Greinacher et al., 2010). This will make it possible to screen for antibodies by means of the techniques described above and to determine the genotype of donors and HNA-3a negative patients (around 5 %), for whom immunisation is possible.

For platelet concentrates obtained from buffy coats from 5 or 6 donors, the theoretical risk is even lower than for single-donor platelet concentrates as a result of the smaller quantity of residual plasma per donor. The English have favoured this platelet concentrate since 2003 (Hume, 2009). However, the minimum quantity of plasma necessary for triggering a TRALI is not known to date.

The highest risk for TRALI is found with single-donor fresh frozen plasma, where it is 20 to 30 times higher than for red cell concentrates. Not a single case of TRALI has been declared after transfusing virus-inactivated fresh frozen plasma from a large donor pool that was subjected to the “solvent-detergent” method (Renaudier et al., 2009).

In 2003, the United Kingdom decided to exclude women from donating plasma on the basis of the SHOT haemovigilance data (Chapman et al., 2009). This decision clearly proved to be effective and resulted in a reduction of the number of TRALI cases notified. Other European countries and the United States have implemented or recommend the deferral of non-nulliparous women as well as women with anti-leukocyte antibodies (cf. section 3.2.6).

Ever since virus-inactivated fresh frozen plasma has been prepared from a single donor (1 April 2004), the Belgian blood establishments have only been using plasma from male donors with no transfusion history or female donors with no pregnancy or transfusion history.

CONCLUSION

1. TRALI is a clinical syndrome characterised by the occurrence or the worsening of acute respiratory distress associated with the development of noncardiogenic pulmonary oedema within six hours after the transfusion of a plasma-containing blood component.

2. The diagnosis of TRALI is made on clinical grounds and laboratory research can, in some cases, contribute to it. TRALI should be distinguished from other potential causes of acute respiratory distress, especially transfusion-associated circulatory overload (TACO).

3. The laboratory tests required within the framework of an immunological investigation (screening for HLA and HNA antibodies) should be carried out in reference laboratories with the necessary expertise.

4. The treatment of TRALI is mainly symptomatic.

5. Using fresh frozen plasma from non-immune male or female donors is currently the most effective preventive measure.

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5. COMPOSITION OF THE WORKING GROUP

All experts joined the working group *in a private capacity*. The names of the members and experts of the Superior Health Council are indicated with an asterisk*.

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About the Superior Health Council (SHC)

The Superior Health Council is a federal body that is part of the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC takes no decisions on the policies to follow, nor does it implement them. It does, however, aim at giving guidance to political decision-makers on public health matters. It does so on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, members of scientific institutions), 200 of whom are appointed experts of the Council. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, a referring committee) and 4) the final endorsement of the advisory reports by the Board (ultimate decision-making body). This coherent set of procedures aims at allowing the SHC to issue advisory reports based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

These advisory reports are submitted to the Board. Once they have been endorsed, they are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.css-hgr.be), except as regards confidential advisory reports. Some of them are also communicated to the press and to target groups among healthcare professionals.

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