Transfusion AE

Chair: Maria Aurora Espinosa, Manuel Muñoz

Thursday 20th of April 2023

1. OVERTRANSFUSION AN AE?

Thomas Frietsch

Overtransfusion is considered an adverse event

Incidence 27-71%

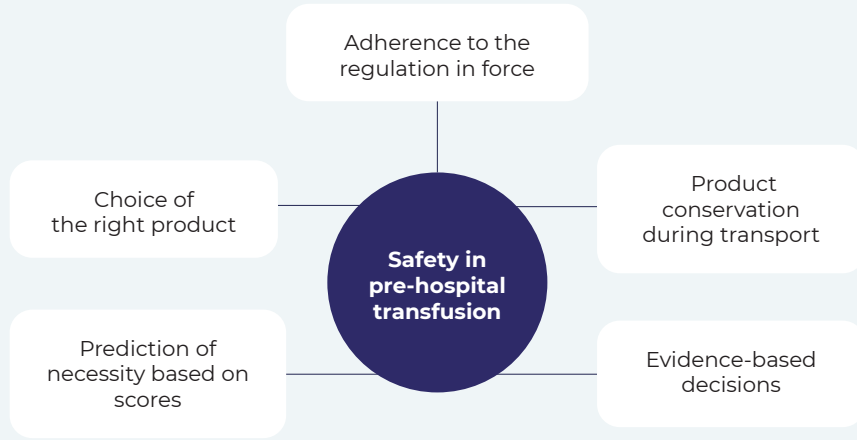
It is necessary to integrate overtransfusion into hemovigilance, to agree on a useful definition, and to work on the factors contributing to its increase

CONSEQUENCES

- Higher mortality in patients with massive transfusion
- Higher mortality in post-surgery patients

TRALI: Transfusion related acute lung injury
TACO: Transfusion associated circulatory overload

Trauma is the main cause for loss of years of life in Western countries, and also the main cause for pre-hospital transfusions, and it can be prevented by managing the hemorrhage



Main causes of transfusion-related death

TACO 3rd more common transfusion-related severe AE

TRALI 6th more common transfusion-related severe AE

Differential diagnose

TRALI (<6 hours)

- TRALI type I: without ARDS risk factors
- TRALI type II: with ARDS risk factors, but no ARDS

TACO (<6-12 hours)

TAD (<6 hours)

TACO/TRALI (<6 hours)

ARDS (worsening over 12 last hours)

Needs

Prevent the onset

Agreeing definitions and criteria

24-hour active hemovigilance with specific detection of TACO and TRALI

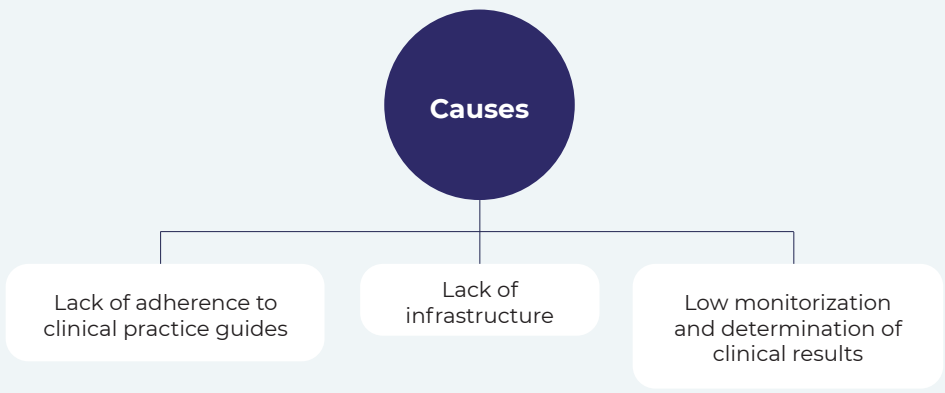
Currently, overtransfusion is underregistered and entails a significant issue, as is the case with undertransfusion[1,2]. Identification and reporting of both events should be integrated as hemovigilance strategies. Overtransfusion rates of 27-71% have been reported, depending on the intervention, the time, and the activation or not of massive transfusion protocols[3-6].

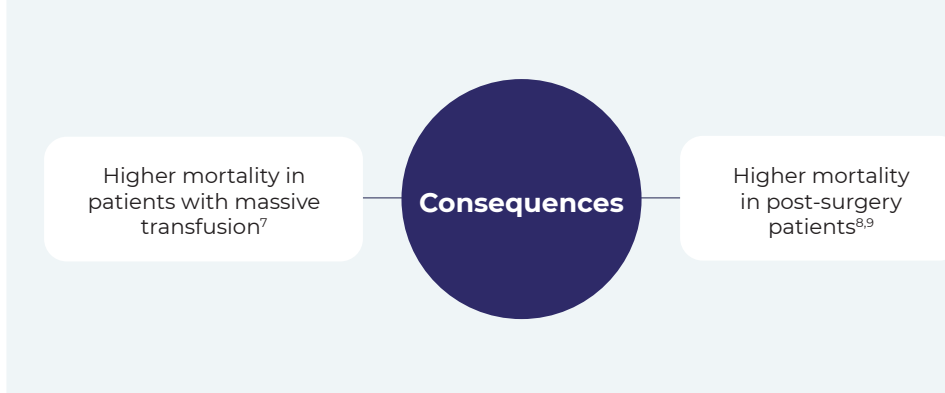
Overtransfusion is considered an adverse event, and lacking a widely agreed definition, it can be defined as follows:

Overdose of
- Blood cell products
- Plasma fluids
- Plasma proteins

in
- Standard situations
- Controlled bleeding
- Controlled volume status, stable intravascular volumen or normovolemia

as
- Treatment or prophylaxis (with no evidence of vital sign improvement)





In order to reduce overtransfusion rates and its consequences, the international working group on overtransfusion wants to include it in hemovigilance strategies, as well as to focus its current work on reaching a consensus around a useful definition for its detection, and the identification of factors contributing to its increase and related consequences.

If you are interested in this field, please register at the following address: **overtransfusion@iakh.deC**

CSL Behring

Expert Comment

Author of the comment: Dra. Sonia María Veiras.

Hospital Clínico Universitario de Santiago de Compostela. Head of Section at the Anesthesia and Resuscitation Department. Province of A Coruña.

Undertransfusion is poorly quantified and registered. The delays in the supply of the requested products, errors, transportation and storage issues, rejection by the patient, supply lower than demand, are factors for undertransfusion (TRANSFUSION, Dec 2021: "incorporating the entity of undertransfusion into hemovigilance monitoring").

Overtransfusion (OT) is also underestimated, and it is a very frequent problem in developed countries.

A search in PubMed of the term overtransfusion yields 130 results, whereas when entering the term TACO (Transfusion Associated Circulatory Overload) or TAD (Transfusion Associated Distress) yields around 25,000 results… Therefore, something is off.

The frequency of OT is unknown.

When reviewing the literature, and OT incidence value of 27% is found in the scenario of multiple trauma patients in Australian reviews (Eur J of Trauma and Emergency Surgery 2022), and up to 71% in North American reviews in scenarios of massive transfusion protocol activation (Trauma Surgery and Acute Care Open 2022). These publications define OT as a transfusion resulting in a hemoglobin value > 11 g/dl. The conclusion of these works is that OT should be followed by Blood Banks and trauma centers and studied as a potential quality measure of the resuscitation of massively transfused patients.

In scheduled surgery scenarios, such as hip replacements, OT rates reach 46.99% on average upon review of the Works published between 2011 and 2023, with a volume of 17273 patients.

As for the influence of OT on the "outcome" of patients, 2.5 odd ratios are found in terms of increased mortality, increased incidence of renal failure, infections, hospital admissions… even though some works do not find such negative influence on the evolution of their patients.

The first pitfall is the lack of definition of the term overtransfusion. There are in fact several definitions:

- High transfusion dose, inappropriate for the needs of the patient (SHOT Report 2011)
- Transfusion for hemoglobin threshold >2g/dl versus pre-transfusion level, in cases of reversible anemia (Warburton KB et al, Future Hospital Journal , 2016)
- Post-transfusion Hb level >10g/dl (levels > 11g/dl will be considered major overtransfusion) (Stokes A et al, Clin Med (Lond) 2015)
- Hb > 12gr/dl on discharge after elective hip replacement (Joshi G et al, Ir J Med Sci 1997)

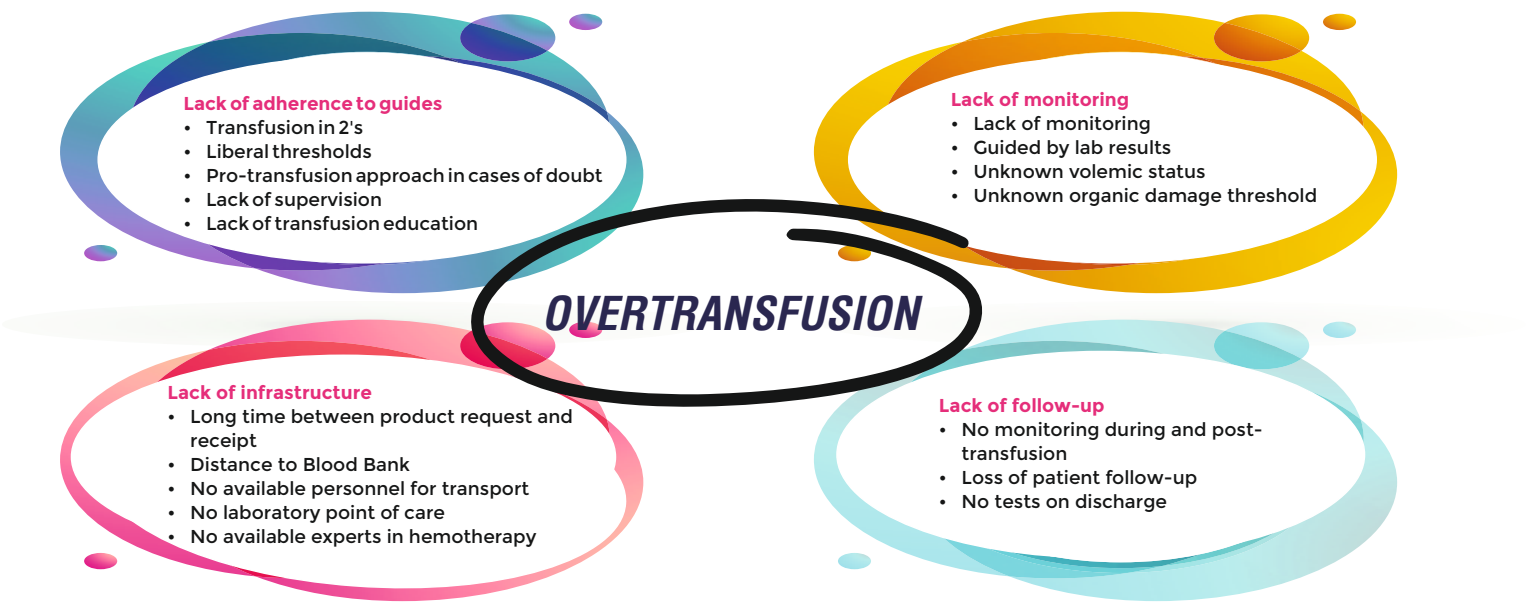
A possible definition of OT (under construction):

Overdose of:
- Blood products (whole blood, red blood cells, platelets)
- Plasma-derived fluids (FPC, albumin)
- Plasma proteins (cryoprecipitates, factor concentrates, CCP)

In:
- Standard situations
- Controlled bleedings
- Normovolemia and stability situations

As:
- Superfluous therapy or prophylaxis (with no evidence of vital sign improvement)

Resulting in adverse events (TACO, TAD, Thrombosis/embolism, alloimmunization, transfusion reaction, HBP, Component errors, tissue ischemia).



The difficulty to administer the product when needed results in overtransfusion.

A NATA working group on overtransfusion is suggested, aimed at defining OT, analyzing contributing factors, reasons for OT, frequency and patient outcome.

OVERTRANSFUSION WORKING GROUP

(contact by e-mail: overtransfusion@iakh.de)

Transfusion AE

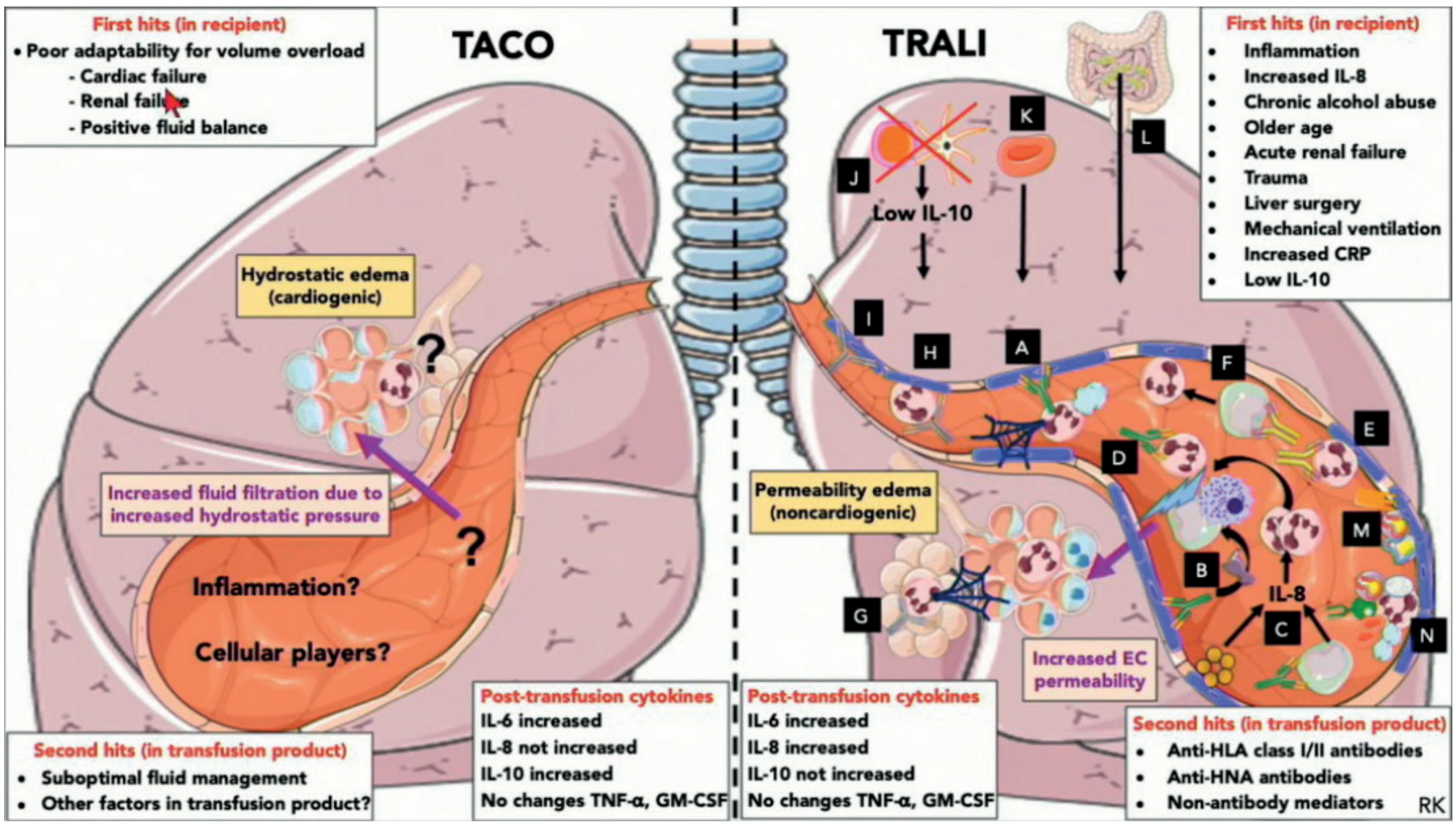
Chair: Maria Aurora Espinosa, Manuel Muñoz

Thursday 20th of April 2023

2. TACO AND TRALI - TWO BREATHTAKING SYNDROMES

José Antonio García Erce

Syndromes causing shortness of breath within 6 hours (approximately) of receiving a transfusion:



TRALI: Transfusion Related Acute Lung Injury

TACO: Transfusion Associated Circulatory Overload

Extracted from Tung et al. Blood Rev, 2022[7]

Presentation

TRALI is presented as an edema with increased permeability (non-cardiogenic), and TACO as a hydrostatic edema (cardiogenic)[8].

Pathophysiology

The pathophysiology of TRALI and TACO is complex and not well defined; the assumption is that is responds to a *2-hit*[7,8] model:

Hit 1: Clinical condition of the patient → **Hit 2:** Transfused product, generally allogeneico

Diagnose

- At the time of the diagnose, it is hard to distinguish between them and from other underlying causes for pulmonary damage[8-10].
- Different definitions and diagnostic criteria for each scientific society.
- 24-hour active hemovigilance programs ➡ crucial in the detection of pulmonary adverse events, less frequent than febrile or allergic ones, but less serious and with a higher impact on mortality.
- Criteria:

TRALI (<6 hours)

- TRALI type I: TRALI type I: without acute respiratory distress syndrome (ARDS) risk factors
- TRALI type II: with ARDS risk factors but no ARDS

TACO (<6-12 hours)

TAD (<6 hours)

TACO/TRALI (<6 hours)

ARDS (worsening in the last 12 hours)

Reach

These are the main causes of transfusion-related death[11].

- TACO was the third most common transfusion-related serious adverse event, and TRALI was the sixth one, according to the old classification[12].
- The lower incidence of TRALI registered can emerge from the implementation of preemptive measures in the selection of blood donors or the new classification put forward by Vlaar in 2019.

Treatment

There are no specific therapies for the treatment of TACO and TRALI and, therefore, the most important thing is to prevent their onset.

CSL Behring

Expert Comment

Author of the comment: Dra. Sonia María Veiras.

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TRALI is the acronym for Transfusion Related Acute Lung Injury. TACO stands for Transfusion Associated Circulatory Overload.

Why do these happen? The most widely accepted theory is that of "double hit," the first hit representing the clinical condition of the patient and the second hit given by the transfusion of the blood product.

In Blood (25 April 2019, Vol 133, Number 17), the pathophysiology of both syndromes is clearly explained.

Vlaar et al (Lancet Vol 382, Sept 14, 2013) explains that the severity of TRALI is related to the antibody titer emerging from the transfusion.

Six potential development paths have been described for TRALI (John Paul Tung et al, Blood reviews), related to monocytes, the endothelium, neutrophyles, the complement... These are complex mechanisms that may explain the theory that receiving blood from female donors leads to a higher risk of respiratory distress.

One of the issues is diagnosing these cases, since there is not a single criterion. Subsequently, a unified definition for TACO was suggested in 2018 (Lancet Haematol 2019) from the International Haemovigilance Network and the American Association of Blood Banks. The fundamental point is for symptoms to be identified within 12 hours from the transfusion.

Vlaar et al (Transfusion vol59, July 2019) suggests a consensus definition for TRALI type I and type II depending on whether patients present risk factors for respiratory distress. Symptoms should be identified within 6 hours from the transfusion. In case the symptoms appear from 6-12 hours after transfusion, we describe it as Transfusion Associated Dyspnea (TAD).

How frequent are these cases? An incidence is reported of 1 TACO case per 13,843 transfusions, which becomes 1 per 33 in perioperative scenarios. Similarly, one TRALI case per 63,940 transfusions, which becomes 1 per 71 in perioperative situations.

According to the WHO, 10% of reported transfusion reactions are TACO, while 3% are TRALI.

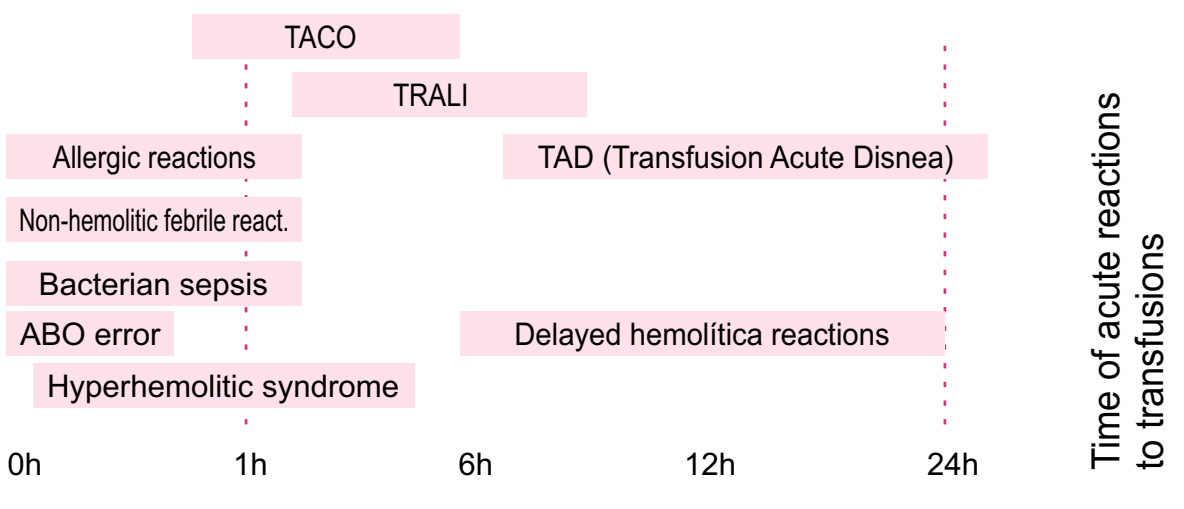
The International Haemovigilance Network Database (ISTARE) reports that TACO and TRALI cases account for 8.3% of all adverse reactions to transfusion, 20.1% of severe adverse events, and 52.2% of transfusion-related deaths.

The SHOT Report (UK) affirms that TACO is the most preventable reaction to transfusion, through practice improvement and monitoring.

In the year 2020, the Swiss series reports 0.15% of TRALI and 88 cases of TACO, 27 of which were life-threatening or even led to death.

In Italy, the 2021 register reports 3.7% of TAD, 0,1% of TRALI, and 1,7% of TACO. The Australian series presents 7.9% of TACO and 0.7% of TRALI.

France reports 10% of TACO, 0.4% of TAD, and 0.3% of TRALI.



At the Puerta de Hierro Hospital, a post-transfusion quarantine surveillance has been established, given that most serious reactions tend to happen several hours later, and frequently the physician in charge is no longer present (HEMACUA program, 24-hour quarantine active hemovigilance). With this post-transfusion surveillance, many more TRALI and TACO events are diagnosed.

Several therapeutic tools have been suggested, including ascorbic acid, although there are no specific treatments.

In conclusion, TACO and TRALI are acute distress syndromes emerging within the first hours after the transfusion, and they the main cause of transfusion-related mortality, with no specific therapy, hard to diagnose and to tell apart, with a complex not fully known pathophysiology. The current hemovigilance records suggest that TACO is the most severe transfusion reaction and that TRALI has a low incidence.

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2. SAFETY OF PREHOSPITAL TRANSFUSION

Cristophe Martinaud

Trauma is the main cause for loss of years of life in Western countries, and also the main cause for pre-hospital transfusions. There is a wide variety in terms of pre-hospital transfusion practice in different countries.

In order to **guarantee a safe transfusion in the pre-hospital setting**, it is important to **comply with the following premises:**

1 ADHERENCE TO THE REGULATION IN FORCE

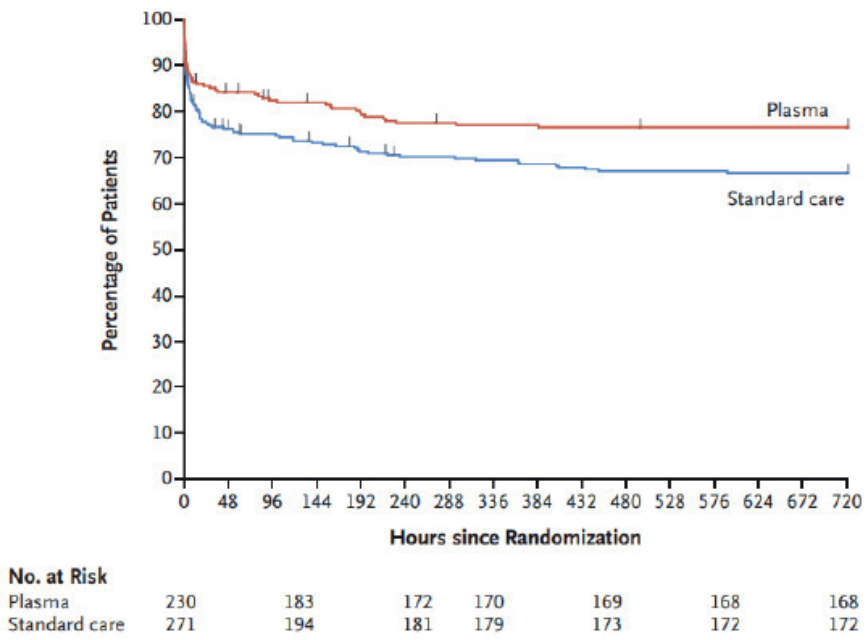
- Immunohematology samples before the transfusion
- Medical prescription
- On-site assessment
- Traceability
- Nurse training
- Patient follow-up

2 NO ALTERING THE PRODUCT DURING TRANSPORT

- Temperature variations
- Mechanical restrictions due to the means of transport
- Time without temperature control
- Systems to optimally preserve blood cells

3 EVIDENCE-BASED DECISIÓN-MAKING

- Two randomized clinical trials have shown benefits from pre-hospital transfusion in more severe patients, and European guides recommend its use.



Sperry et al. N Engl J Med, 2018[13]

	RBC N=223	RBC+P N=391	RCP N=295
	N (%), unless otherwise stated		
Mortality†			
Died on scene	65 (29.1%)	96 (25.2%)	77 (26.5%)
24-h mortality	106 (47.5%)	139 (36.1%)*	117 (40.2%)**
30-day mortality	120 (53.8%)	191 (49.1%)	148 (50.1%)

Sperry et al. N Engl J Med, 2018[13]

4 USING SCORES TO PREDICT THE NEED FOR PRE-HOSPITAL TRANSFUSION

- Making the best choice is a challenge in terms of striking a balance between its sensitivity and specificity.

5 CHOOSING THE RIGHT PRODUCT

- **Lyophilized plasma** ➡ only in the context of activating the massive transfusion protocol or when a time longer than 20 minutes to move to the closest hospital is estimated
- **Red blood cells** ➡ increase of survival and QALYs with red blood cells RhD+ ➡ is a beneficial strategy versus non-transfusion
- **Low-titer type O whole blood** ➡ safe and effective, but further randomized clinical trials are required to prove benefits in terms of survival.

Blood donation is valuable, and we must guarantee safety for donors, even preventing unnecessary expenses.

CSL Behring

Expert Comment

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Pre-hospital transfusion was first described in military scenarios (during World War 2), and subsequently in civil scenarios (emergency medicine, settings away from hospital care, such as sea cruises, or inter-hospital transport).

In trauma patients, the use of plasma instead of crystalloids outside of the hospital was associated to a 30% decrease in mortality.

Although extra-hospital transfusion practice is widespread in many European countries and beyond, the uneven implementation of this process raises questions.

In the United Kingdom, 91% of air ambulances are equipped for transfusion outside of hospitals. In France, this percentage reaches 72%.

Besides trauma bleeding, gastrointestinal and gyneco-obstetric bleedings are the main causes for pre-hospital transfusion. Up to 50% of pre-hospital transfusions are due to non-trauma causes.

In order to verify the safety of these transfusions, four conditions must be met

1. Adhering to the regulation in force: drawing immunohematology samples before the transfusion, medical prescription, bedside cross-matching, traceability, nurse training, and patient follow-up.
2. Ensuring optimal transport and storage of blood products: extreme temperatures for several hours and transport conditions have not shown significant changes in the morphology of red blood cells or hemolysis. Brunskill et al, (Transfus Med Rev 2012) could not find any negative impact in the quality of red blood cells or in bacterial contamination upon exposure to temperatures of 4+/- 2ºC, from 20 minutes to 42 days. There are various devices (electronic or otherwise) to preserve the right storage temperature
3. Following the current scientific evidence: only two randomized trials, PAMPER for PFC, and Tucker for CH7PFC, have proven the benefit of pre-hospital transfusion. The benefit is almost significant in most severe patients. European guides on trauma bleeding bring to light the lack of evidence of pre-hospital transfusion.
4. Transfusing the right product to the right patient: scores predicting the need for transfusion (TASH, ABC, Larson, PWH...) are essential, but they lack balance in terms of sensitivity and specificity.

Available products in the pre-hospital setting are lyophilized plasma, packed red blood cells, and whole blood for military settings.

Is pre-hospital transfusion safe? In various studies and records, adverse reactions to transfusion are reported in low percentages (0 to 3%) (Moore et al Lancet 2018, Rijnhout et al Injury Int J Care 2019, Angerman et al Prehospital Emergency Care 2022, Rapport Annuel d'Hemovigilance 2021).

Most commonly, type 0 negative blood is available for pre-hospital administration, but it has been reported that the damage from administering Rh positive is lower than not transfusing.

The use of antiA/antiB low-titer type 0 whole blood, with leukodepletion and administered through a platelet-saving filter, has promising results, even though no benefit has been proven in terms of mortality in randomized clinical trials.

The main drawback when using whole blood is the appearance of paroxysmal nocturnal hemoglobinuria.

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