

Pulmonary Complications of Transfusion: Non-TACO n=33

18b

Authors: Tom Latham and Oliver Firth

Definition:

Cases where there is a respiratory deterioration within 24 hours of transfusion which does not meet ISBT TACO criteria, and which is not explained by the recipient's underlying condition.

Abbreviations used in this chapter

ARDS	Acute respiratory distress	ICU	Intensive care unit
CRP	C reactive protein	IRC	International Revised Consensus (TRALI definition)
CT	Computed tomography	RR	Respiratory rate
CXR	Chest X-ray	SaO₂	Oxygen saturation
FFP	Fresh frozen plasma	SD-FFP	Solvent detergent FFP
FiO₂	Inhaled oxygen fraction	TACO	Transfusion-associated circulatory overload
Hb	Haemoglobin	TAD	Transfusion-associated dyspnoea
HLA	Human leucocyte antigen	TRALI	Transfusion-related acute lung injury
HNA	Human neutrophil antigen		
HR	Heart rate		

Key SHOT messages

- Pulmonary complications are often multifactorial
- Fluid overload is often suspected as a contributing factor even if cases do not meet TACO criteria
- Classification of a case as TRALI using international criteria does not imply or depend on the presence of leucocyte antibodies in the blood donor
- The risk-benefit balance of transfusion should be carefully considered particularly in patients with multiple risk factors for fluid overload and/or acute lung injury

Recommendation

- A structured TACO investigation tool should be used for all pulmonary complications

Action: All staff involved in investigating transfusion reactions

Introduction

In 2023, a total of 33 cases were included in the non-TACO category. Fifty-five cases were originally submitted or transferred from other categories. Of these, 11 were withdrawn as they were either of insufficient severity or due to the underlying condition, 10 cases were transferred to TACO and 1 was deferred pending investigation results. For more details, see the supplementary data tables and information on the SHOT website (<https://www.shotuk.org/shot-reports/report-summary-and-supplement-2023/>).

Cases were classified using the IRC definitions of TRALI (Table 18b.1). Cases satisfying both TRALI and TACO criteria (Wiersum-Osselton, et al., 2019) were categorised as 'TRALI-TACO' and cases satisfying neither as 'TAD'. The TAD category is subclassified into TAD-IC (cases which could not be classified because of incomplete information reported) and TAD-C (cases where there was sufficient information to judge that the case did not meet either TACO or TRALI criteria).

The final classification of cases with imputability is presented in Table 18b.2 and major morbidity and mortality in Table 18b.3.

Table 18b.1:
International
revised consensus
classification of
TRALI (Vlaar, et al.,
2019)

TRALI type I - Patients who have no risk factors for ARDS and meet the following criteria:	
a.	i. Acute onset
	ii. Hypoxemia (P/F \leq 300 or SpO ₂ < 90% on room air)
	iii. Clear evidence of bilateral pulmonary edema on imaging (e.g. chest radiograph, chest CT, or ultrasound)
	iv. No evidence of left atrial hypertension (LAH), or, if LAH is present, it is judged to not be the main contributor to the hypoxemia
b.	Onset during or within 6 hours of transfusion
c.	No temporal relationship to an alternative risk factor for ARDS
TRALI type II - Patients who have risk factors for ARDS (but who have not been diagnosed with ARDS) or who have existing mild ARDS (P/F of 200-300), but whose respiratory status deteriorates and is judged to be due to transfusion based on:	
a.	Findings as described in categories a and b of TRALI type I and
b.	Stable respiratory status in the 12 hours before transfusion

Table 18b.2: Final
classification of
non-TACO cases

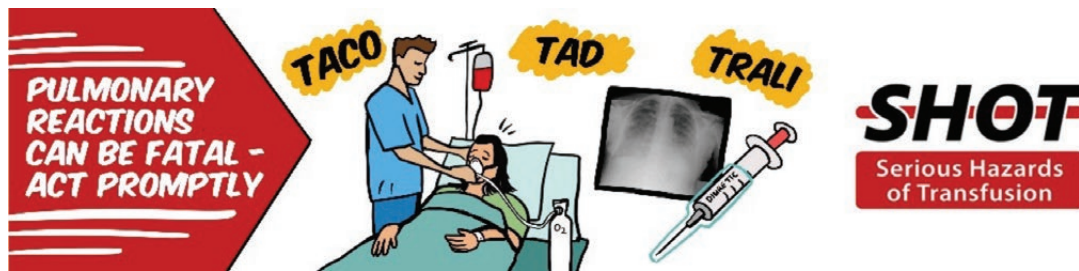
		Imputability			
		1-possible	2-probable	3-definite	Total
Category	TAD-C	7	8	1	16
	TAD-IC	7	4	0	11
	TRALI-TACO	0	0	1	1
	TRALI type II	4	1	0	5
Total		18	13	2	33

Table 18b.3:
Non-TACO major
morbidity and
mortality

		Major morbidity and mortality		
		Major morbidity	Death	Total
Category	TAD-C	6	2	8
	TAD-IC	0	3	3
	TRALI type II	4	0	4
Total		10	5	15

Deaths related to transfusion n=5

There were 5 deaths reported, all in the TAD category. All patients were severely unwell prior to transfusion. Death was possibly (imputability 1) related to TAD in 3 cases and probably related (imputability 2) in 2 cases. In both imputability 2 cases, extensive investigation was not considered appropriate because the patient was terminally ill. Fluid overload was clinically thought to have contributed to the deterioration in all 5 cases, but they did not satisfy sufficient criteria to be classified as TACO. For more details and a narrative summary of the deaths, see the supplementary information on the SHOT website (<https://www.shotuk.org/shot-reports/report-summary-and-supplement-2023/>).



Major morbidity n=10

There were 10 cases of major morbidity (defined as requiring ventilation or ICU admission). Six were classified as TAD-C and 4 as TRALI type II.

Case 18b.1: TAD-C - High suspicion of fluid overload not satisfying TACO criteria

A patient with decompensated liver disease, impaired left ventricular function, aortic stenosis, and low albumin, was receiving diuretics for fluid overload. They developed respiratory distress and crepitations during a two-unit FFP transfusion given to correct clotting abnormalities during an endoscopy for bleeding varices. The CXR showed increased consolidation in the left lower lobe. The risk of fluid overload was noted prior to transfusion. There was no immediate response to diuretic at the time of the reaction, but the patient was given further diuretics in ICU. The patient was ventilated overnight and improved by morning.

This case is included as it is emblematic of the challenges of transfusing unwell patients and of classifying reactions in such cases. The patient was identified as being at high risk of tolerating fluid poorly but there were also high risks of leaving clotting uncorrected during major bleeding. Appropriate treatment was rapidly provided. The case was classified as TAD-C since insufficient criteria were present to classify as TACO; the TACO criteria do not take account of pre-existing risk.

FFP transfusion to correct clotting in patients already fluid overloaded is a recurrent feature in cases reported to SHOT; the balance of risk and benefit must be carefully considered. The use of alternatives such as prothrombin complex concentrate is not recommended for routine correction of coagulation abnormalities in liver disease but could have a favourable risk/benefit ratio in this situation.

TRALI and leucocyte antibody cases

Cases have been classified as TRALI using the IRC definition. The presence of leucocyte antibodies plays no part in this definition. Antibodies however remain an established cause of TRALI, and one which is potentially preventable. Cases which were positive for antibodies (HLA or HNA) are therefore presented in parallel.

Cases meeting TRALI criteria n=6

Of the cases which met TRALI criteria, 5 were classified as TRALI type II. One case was classified as 'TRALI and TACO cannot be distinguished' and was positive for leucocyte antibodies, see Case 18b.3. Most patients were unwell prior to transfusion and the transfusion reactions were of low imputability. A summary of all cases meeting TRALI criteria is given in the supplementary data, Table 18b.5 (<https://www.shotuk.org/shot-reports/report-summary-and-supplement-2023/>).

Case 18b.2: TRALI type II - Recurrent pulmonary reactions with SD-FFP

A patient was undergoing plasma exchange for suspected thrombotic thrombocytopenic purpura (eventually confirmed as haemolytic uraemic syndrome). Respiratory deterioration occurred on three successive occasions during exchange. CXR showed worsening bilateral changes and there was a rising CRP, but the patient was not thought to have pneumonia. Renal function was normal and there was a negative fluid balance and no features of fluid overload.

The case meets criteria for TRALI and the recurrent deterioration during successive procedures does suggest a causative role for the transfusion. Investigation of the product for leucocyte antibodies is not within the scope of the Blood Services and would have to be arranged by the manufacturer. SD-FFP is a pooled product and pooling is generally considered to reduce the risk of antibody-mediated TRALI through dilution of antibodies from any given donor (Sachs, et al., 2005). Product information does include respiratory adverse events following SD-FFP, though acknowledges the difficulty in assigning imputability. A recent study from the Netherlands suggested the incidence of cases meeting TRALI criteria was reduced in critical care patients after changing to routine use of SD-FFP, although the difference was not statistically significant (Klandermann, et al., 2022). SD-FFP is regulated as a medicine not a blood component and is reported to the MHRA via the Yellow Card system but SHOT will accept cases for review.

Cases with leucocyte antibodies n=1

Case 18b.3: TRALI/TACO with HLA class I antibody

A patient with pre-eclampsia but normotensive, low albumin, and peripheral oedema was transfused one unit of red cells for postpartum haemorrhage following caesarean section. Dyspnoea developed 2-6 hours after transfusion, and oxygen saturation was 95% on oxygen (FiO2 not recorded). CXR showed upper lobe diversion and a CT scan the following day confirmed pulmonary oedema. There was no response to diuretic or haemodynamic change. Donor antibody testing showed HLA B45 antibodies cognate with the recipient. The patient made a complete recovery.

The case has been classified as TRALI/TACO since the case satisfies both TRALI and TACO criteria. The finding of cognate antibody in the sole donor supports the idea that antibody has caused or contributed to the reaction, although the association of HLA class I antibodies with TRALI is less strong than for class II or granulocyte specificities.

Clinical features of reactions

Many recipients had pre-existing factors which could cause acute lung injury or difficulty tolerating additional fluid ('risk factors' Figure 18b.1a) or had features reported at the time of transfusion indicating fluid overload or cardiorespiratory strain ('state factors' Figure 18b.1b). Notably, over half of cases had pre-existing risk factors for fluid overload and inflammatory conditions. Multiple risk factors were present in many cases, with a median of 4 risk factors per case (Table 18b.4). It is not possible to investigate whether individual risk factors entail a higher risk of pulmonary complications from this data in the absence of a control group. Figure 18b.2 however shows that certain pairs of risk factors occurred more commonly than expected statistically, suggesting the coexistence of multiple risk factors may have a more than additive risk of transfusion reaction. Liver disease and inflammation particularly appear to interact with other risk factors, consistent with an observation that sepsis and alcohol abuse were noted as risk factors for acute lung injury in transfused critical care patients in a prospective study (Gajic, et al., 2007).



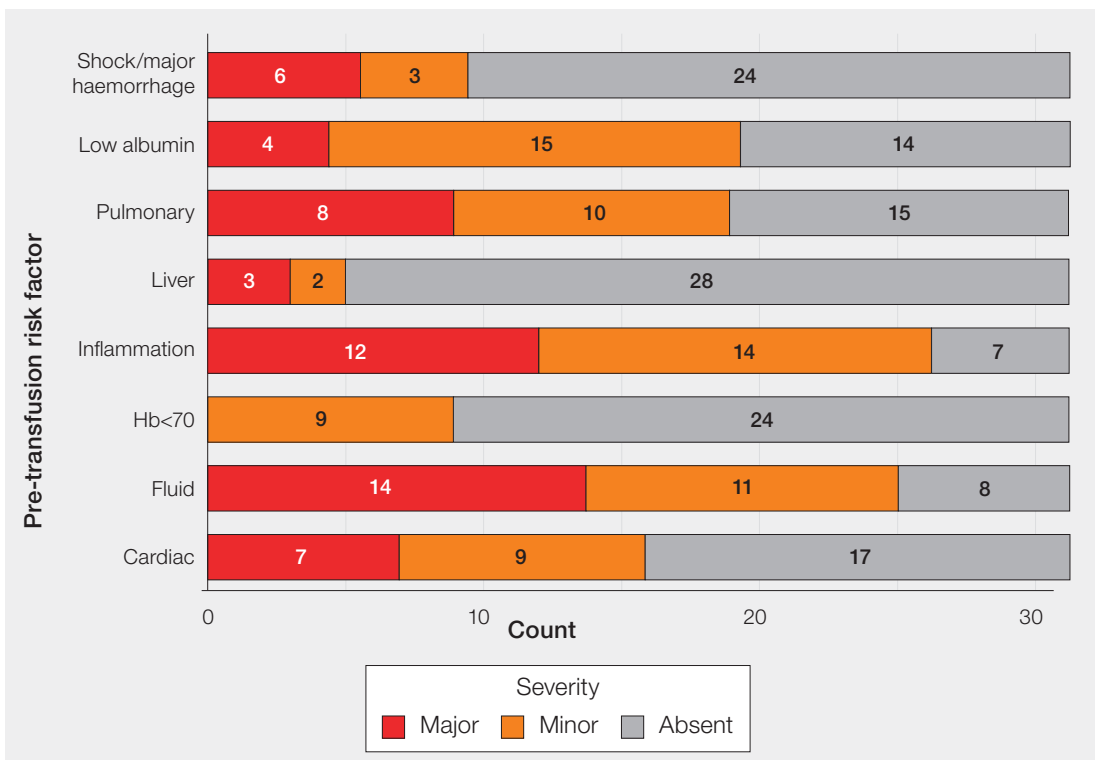


Figure 18b.1: Pre-transfusion features of pulmonary cases

Figure 18b.1a: Risk factors

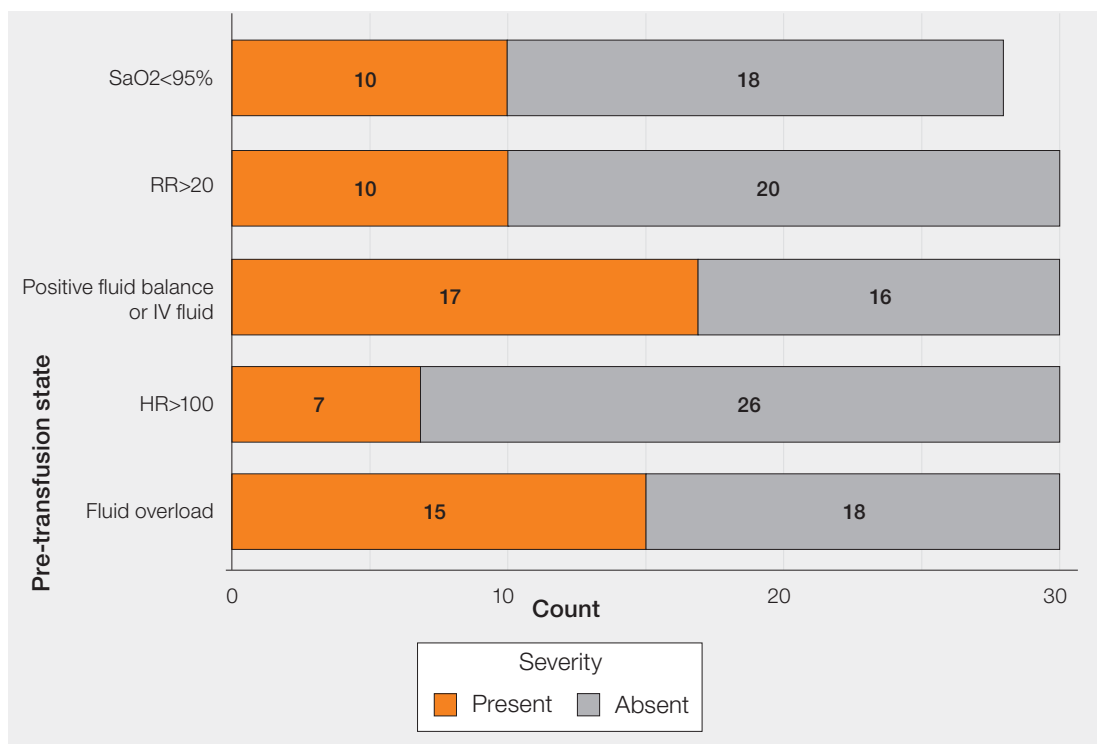
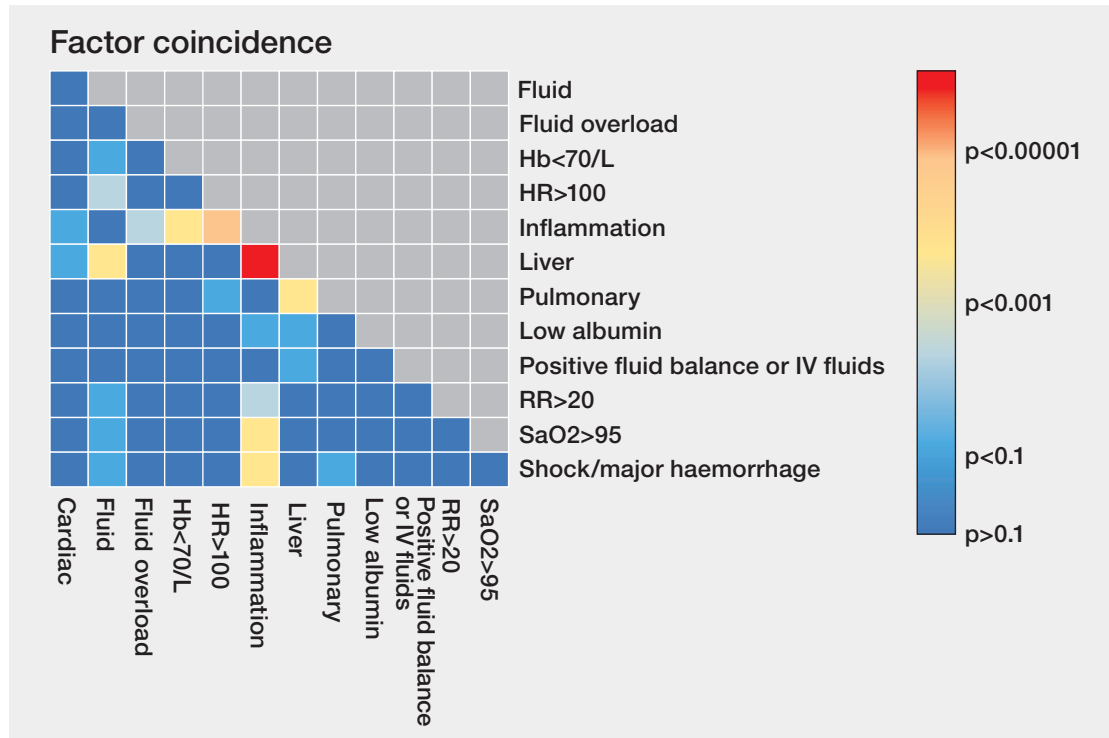


Figure 18b.1b: State factors

Number of pre-transfusion state factors present						
Number of pre-transfusion risk factors present	0	1	2	3	4	Total
1	0	1	1	0	0	2
2	1	2	0	2	0	5
3	1	1	1	1	1	5
4	1	4	2	2	0	9
5	1	3	1	1	2	8
6	0	1	2	1	0	4
Total	4	12	7	7	3	33

Table 18b.4: Number of factors present per pulmonary case

Figure 18b.2:
Statistical
significance of
factor coincidence
(Fisher exact
test with multiple
testing correction)



Hb=haemoglobin; HR=heart rate; RR=respiratory rate; SaO2=oxygen saturation

Data completeness and concordance with SHOT recommendations

The proportion of cases classified as TAD-IC because there was insufficient information to apply the TACO or TRALI criteria remains unsatisfying. This is not meant as a criticism of reporters or treating clinicians, but an observation that the data needed to classify reactions using formal international criteria seem to be challenging to provide in practice. This has been illustrated in the supplementary chapter. More generally, only about 2/3 of reports were able to supply a full set of the recommended transfusion observations and 9% were not able to supply any observations. These are long-established observations. Only about a third of submissions reported the use of a TACO pre-transfusion risk assessment or a structured investigation, as has been recommended by SHOT for several years. These figures are similar to the 2022 Annual SHOT Report (Narayan, et al., 2023).

Conclusion

As in previous years, transfusion recipients suffering pulmonary complications are often complex with multiple comorbidities across all reporting categories, with little to distinguish cases in different categories. Antibody-associated cases and cases where the transfusion appears the sole contributor are rare. Fluid overload is suspected as a contributory factor even in cases which do not meet TACO criteria; it is important to remember that TRALI and TACO are haemovigilance reporting categories not pathological diagnoses and examine all possibly preventable factors regardless of classification. The suggestion that comorbidities, particularly liver disease, and inflammation, may interact synergistically to create increased risk of tolerating transfusion poorly is worthy of further study.

Avoiding fluid overload and minimising transfusion remain the only approaches available to clinicians to prevent pulmonary complications. The risk/benefit balance of transfusion should be carefully considered in unwell patients, particularly those with multiple comorbidities.

Recommended resources

TACO Incident Investigation Guidance Tool

TACO Checklist: in risk assessment/checklist alternative format for incorporation into clinical documents

<https://www.shotuk.org/resources/current-resources/>

SHOT Video: TACO

<https://www.shotuk.org/resources/current-resources/videos/>

SHOT Bite No. 11: Respiratory Symptoms During Transfusion

<https://www.shotuk.org/resources/current-resources/shot-bites/>



References

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