

18 Pulmonary Complications n=205

Authors: Oliver Firth and Sharran Grey with input from other members of the Pulmonary Working Expert Group

Abbreviations used in this chapter

ISBT	International Society of Blood Transfusion	TACO	Transfusion-associated circulatory overload
IV	Intravenous		
MHRA	Medicines and Healthcare products Regulatory Agency		

Key SHOT messages

- Pulmonary complications of transfusion remain a leading cause of transfusion-related mortality and morbidity, contributing to 20/38 (52.6%) transfusion-related deaths reported to SHOT in 2023
- TACO-related deaths rarely occur in the absence of risk factors, with a median of four TACO risk-assessment criteria present in each case
- Management of TACO risk is hindered by underutilisation of the risk-assessment tool, low rates of risk identification, and frequent failure to translate risk assessments into proactive management plans
- Utilisation of the SHOT TACO incident investigation tool is high and steadily increasing

The recommendations from previous years continue to be relevant and specific recommendations are also covered in the individual chapters.

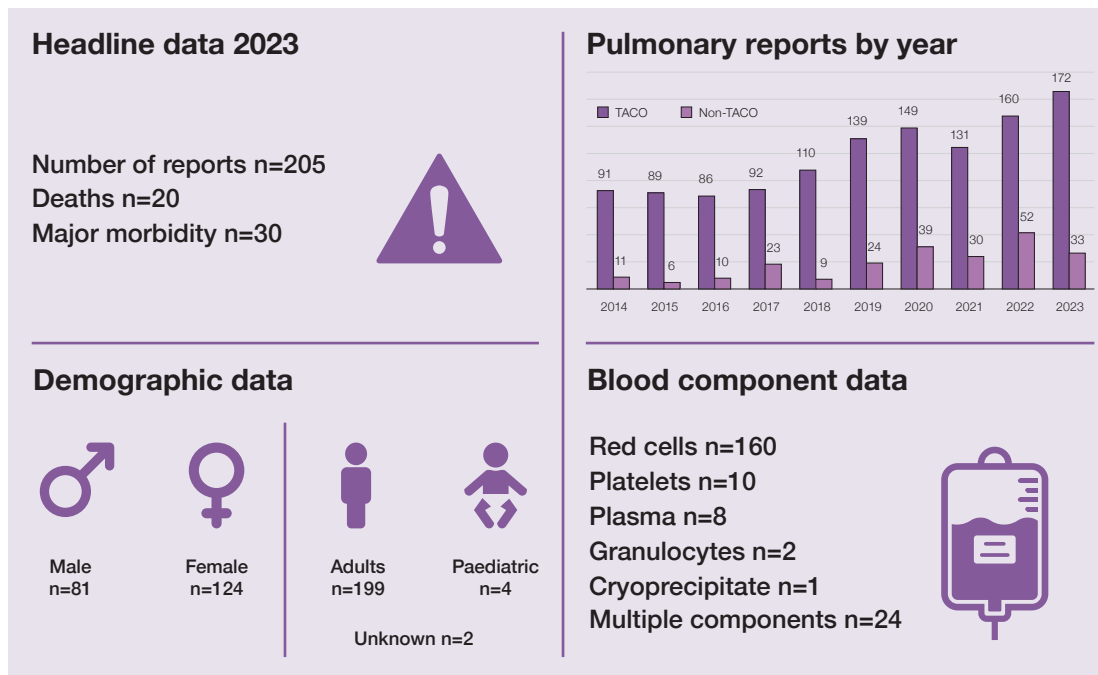
Recommendations

- All cases with pulmonary complications up to 24 hours post transfusion should be reported to SHOT with as much information as possible to ensure adequate inference and effective learning

Action: All SHOT reporters, national blood transfusion committees, hospital transfusion teams

- TACO risk assessment of all patients needing transfusions will help institute appropriate, timely mitigating actions to prevent or reduce the severity of pulmonary complications. Prompt recognition with appropriate investigations and accurate diagnosis will help improve morbidity and mortality
- A structured review and incident investigation should be undertaken for every case of TACO to optimise organisational and individual patient-safety measures

Action: All staff involved in transfusion

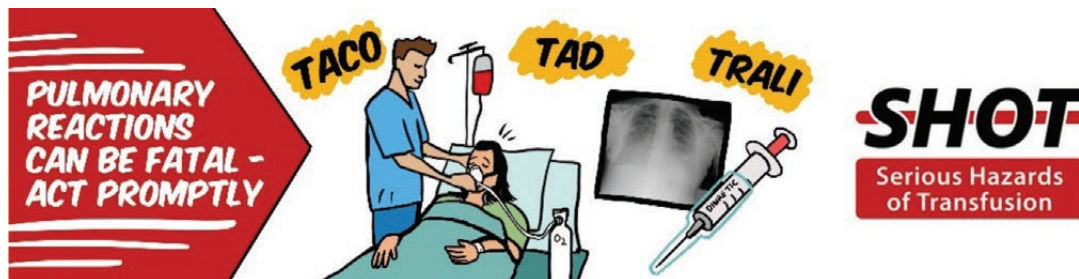


Introduction

Transfusion-related pulmonary complications contribute significantly to death and major morbidity. Patients with respiratory complications are often elderly with multiple comorbidities which could all contribute. Pulmonary complications present diagnostic and therapeutic challenges with mainly supportive measures available and paucity of specific therapies. Like in the recent years, the pulmonary cases which do not meet ISBT TACO criteria (Wiersum-Osselton, et al., 2019) have been consolidated into a single chapter. The approach acknowledges that multiple factors could have contributed to the reaction, and this has been explored further in the non-TACO chapter.

TACO is the leading cause of transfusion-related deaths over the past decade. In addition, SHOT data also suggests that fluid overload contributes to most pulmonary reactions which do not meet TACO criteria. A national patient safety alert to address the rising deaths from TACO has been released (MHRA and SHOT, 2024).

The analysis below evaluates 10 years of data from 2014-2023 provided to SHOT regarding TACO-related deaths. The data has been used to evaluate the presence of TACO risk factors, recognition of risk by clinicians, the use of TACO mitigation strategies, the use of risk assessment and incident investigation tools, and institutional learning following TACO-related deaths.



Prevalence of pre-transfusion TACO risk factors

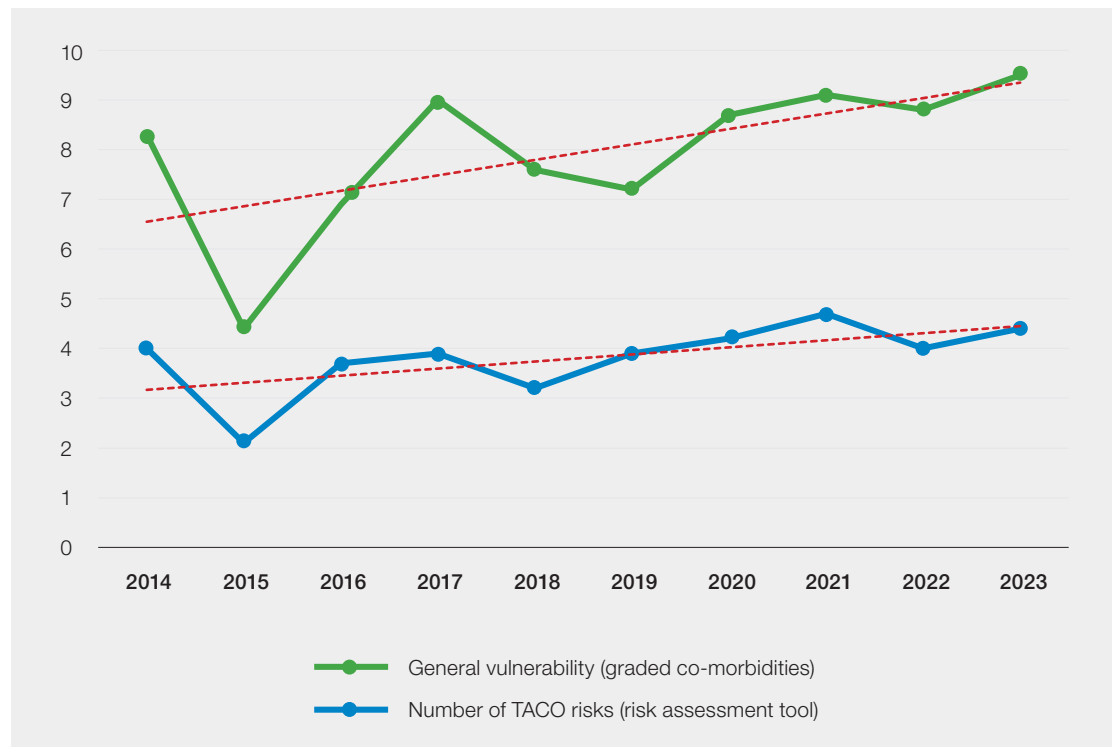
Retrospective application of the TACO risk assessment tool showed that 88/93 (94.6%) cases had identifiable TACO risk factors pre transfusion. Among the 5 cases where none could be identified, 2 lacked data, 2 likely had undocumented cardiac risk factors, leaving 1 case where no formal risk factors could be identified despite comprehensive data. Having a single TACO risk factor was uncommon and seen in only 8/93 (8.6%) of patients, with a median of four TACO risk factors present per patient. Table

18.1 illustrates the unadjusted prevalence of TACO risk factors. A scoring system was applied: where the risk factor was absent (0), present but incidental (1), or an active contributor to admission (2). This highlighted positive fluid balance as being both the most prevalent and clinically significant risk factor. Scoring made one further change to the overall ranking of the TACO risk factors, elevating severe anaemia in significance from 6th to 3rd. A yearly average of the number of TACO risks and comorbidities per patient, is shown in Figure 18.1, which demonstrates an increasing trend in general comorbidities and TACO risk over the period.

Table 18.1: The prevalence of each 'TACO risk' as outlined in the SHOT risk-assessment tool among TACO-related deaths over the past decade

SHOT TACO risk-assessment category	Frequency
IV fluids in the past 24 hours	59/93 – 63%
Clinically significant positive fluid balance	55/93 – 59%
Heart failure or related cardiac disease	42/93 – 45%
Renal impairment	39/93 – 42%
Hypoalbuminaemia	37/93 – 40%
Severe anaemia	36/93 – 39%
Peripheral oedema	30/93 – 32%
Regular diuretic use	29/93 – 31%
Undiagnosed respiratory symptoms	20/93 – 22%
Pre-existing pulmonary oedema	15/93 – 16%

Figure 18.1: The number of TACO risk factors and graded TACO vulnerability among TACO-related deaths reported to SHOT 2014-2023



TACO=transfusion-associated circulatory overload

Utilisation of the TACO risk-assessment tool

The TACO risk assessment was introduced in 2016, and data collected on its use since 2019. Analysis of the use of the TACO risk-assessment tool was possible in 54 of the 93 cases. Adoption of the risk assessment was initially slow, and rates of use have plateaued, with it being used in 35-40% of the most recent cases of TACO-related death (Figure 18.2). Where the tool was used, clinicians identified TACO risks in 11/20 (55.0%) patients, while retrospective application of the tool to these cases identified risks in 18/20 (90.0%). Reporting through the SHOT questionnaire on TACO risk factors has two questions, first whether the clinician identified TACO risks, and second which risks were identified. Due to a paucity

in data submission for this second question, it was not possible to assess the correlation between the risks identified through retrospective application of the risk assessment, and those recognised by the clinicians.

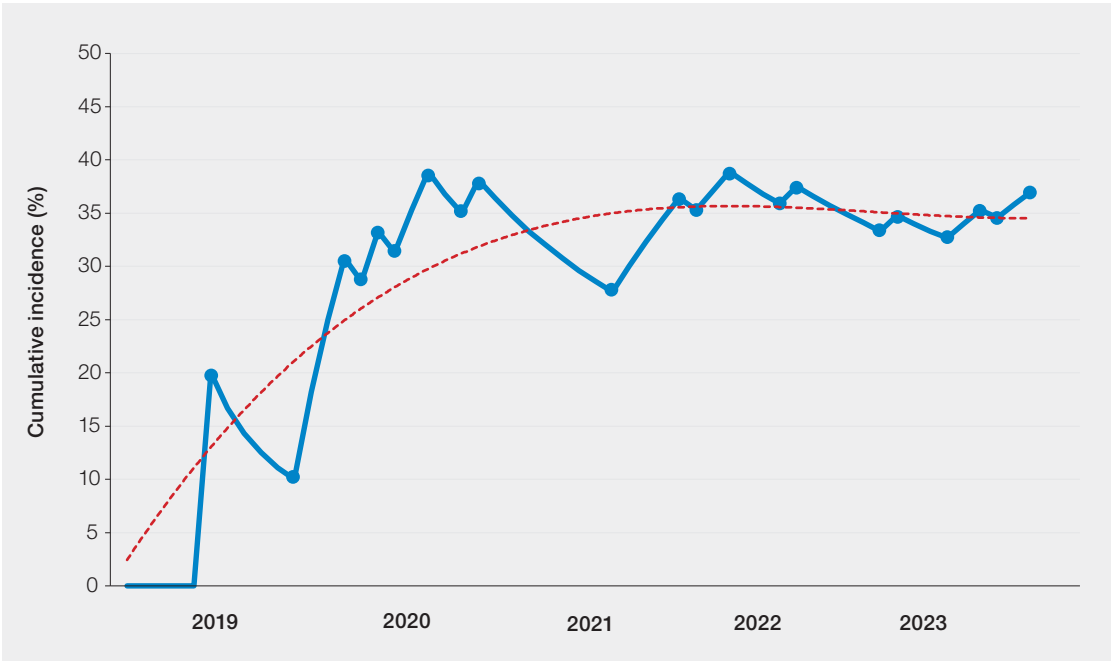


Figure 18.2: Cumulative incidence of usage of the SHOT TACO risk-assessment tool in TACO-related deaths 2019-2023

Preventability and TACO mitigation strategies

The data set was reviewed to assess potential preventability of TACO. In 84/93 (90.3%) cases potential mitigating actions were not undertaken, and in 64/84 (76.2%) cases there was more than one mitigation possible. Table 18.2 illustrates the frequency of the potential recommended mitigation strategies. Of the 9 cases where no additional mitigations could be recommended, 2 were transfusions in the context of major haemorrhage, where assigning mitigations is challenging, and 2 were transfusions in patients approaching the end of their life, where transfusion-related imputability was low. The final 5 cases consisted of four examples where use of the TACO risk assessment led to optimal mitigation strategies being employed, and 1 case with no reported TACO risk factors. While the data suggested a lower average preventability rating in cases where the TACO risk assessment had been used (1.15 versus 1.38), this did not reach statistical significance ($p=0.35$ by Welch's T-test).

Recommended unused mitigation	Frequency
Prophylactic diuretic	57/93 – 61%
Fluid balance measurement	53/93 – 57%
Single unit transfusion and review	36/93 – 39%
Body weight dosing	16/93 – 17%
Vital sign monitoring	13/93 – 14%
Other e.g., alternatives to transfusion	20/93 – 22%

Table 18.2: Frequency of unused TACO mitigation strategies in TACO-related deaths 2014-2023

Review and institutional learning

Over the 10-year period, 58/93 (62.4%) of TACO-related deaths were reviewed formally, 26/93 (27.9%) informally, and in 9/93 (9.7%) cases there was no evidence of review. The SHOT TACO incident investigation tool was introduced in 2021 to aid the review process by providing a framework from which

to work. Since its introduction there have been 20 TACO-related deaths. Initial uptake was slow, but its usage has increased, with 60% of recent case reviews utilising the SHOT TACO incident investigation tool to structure the review process (Figure 18.3). Institutional learning following review was demonstrated in 20/93 (21.5%) cases with the learning objectives presented in Table 18.3.

Figure 18.3:
Rolling cumulative
incidence of
use of the SHOT
TACO incident
investigation tool
for the previous 5
cases of TACO-
related deaths
2021-2023

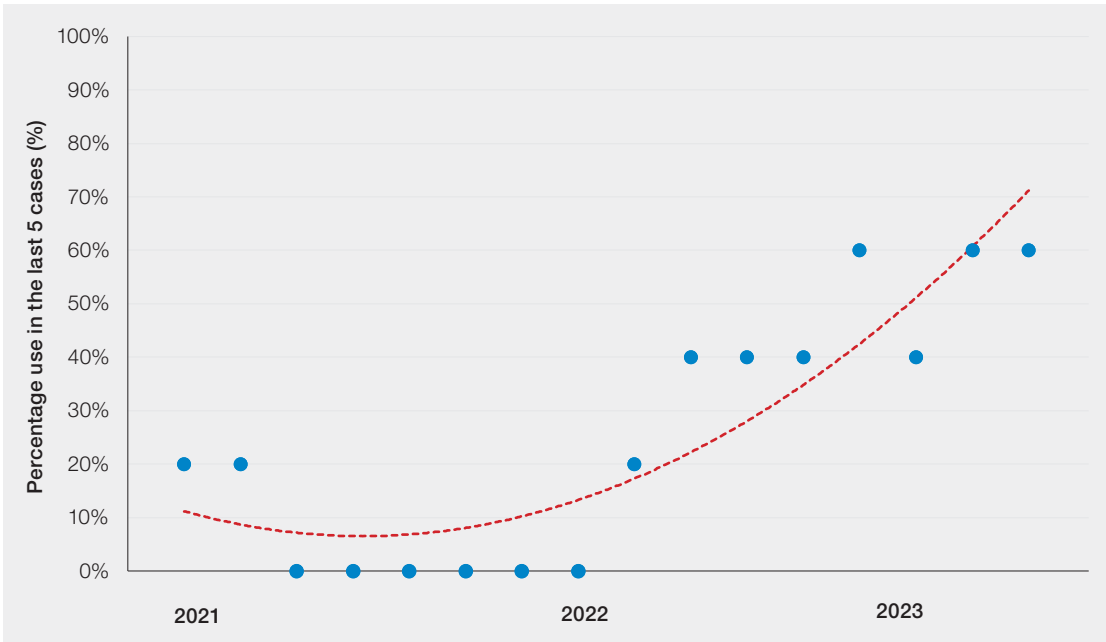
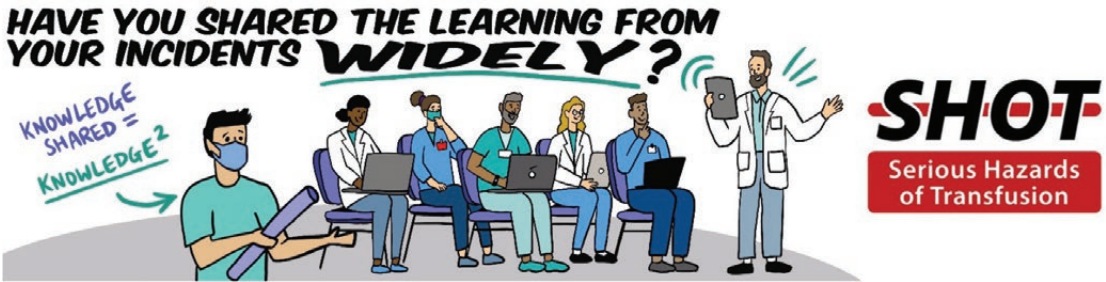


Table 18.3:
Reported
self-identified
institutional
learning objectives
following TACO-
related deaths

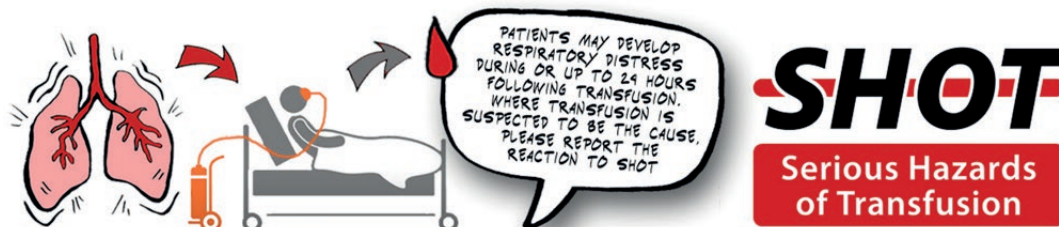
Category of improvement	Frequency
TACO pre-transfusion risk assessment related	11/20 – 55%
Education for prescribers	7/20 – 35%
Change in protocols/policies	6/20 – 30%



Conclusion

This data set supports current understanding that TACO seldom occurs in the absence of risk factors, and, in most instances multiple risk factors are present. Intravenous fluids, positive fluid balance, and congestive cardiac failure are the most prevalent risk factors, and therefore nearly every case of TACO-related death in the past 10 years had potential mitigation strategies that might have been suitable for application. Mitigation strategies appear to be underutilised, and while this is partly due to low use of the risk-assessment tool to guide practice, risks and potential mitigation strategies are commonly missed even when it is used. The rising number of TACO-related deaths raise concerns around our ability to recognise and manage patients at risk of TACO, but this data set may provide additional clarity. It shows that in cases of TACO-related death, patients in 2023 have more pre-transfusion risk factors and a higher vulnerability to TACO than 10 years ago. Possible explanations for this might include improvements in our reporting of patient risks, or that our ability to prevent TACO-related deaths in lower risk patients is improving. The increase in TACO-related deaths, therefore, may at least in part be due to increasing numbers of transfusions in patients with greater complexity and higher comorbidity burdens. A similar

pattern is seen in non-TACO pulmonary complications, and it is likely that wider adoption of TACO risk-reduction measures will also prevent or mitigate many of these. Positive practice was evident from the analysis, with a robust culture of review emerging, marked by increasing use of the SHOT TACO incident investigation tool. It was notable that conclusions drawn following formal review of TACO cases in hospitals mirror the deficiencies identified in this report, and the institutional learning it fosters appears to recommend suitable corrective measures.



References

Medicines & Healthcare products Regulatory Agency (MHRA) and Serious Hazards of Transfusion (SHOT), 2024. *Central Alerting System: Reducing risks for transfusion-associated circulatory overload*. [Online] Available at: <https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103249> (Accessed 08 April 2024).

Wiersum-Osselton, J. C. et al., 2019. Revised international surveillance case definition of transfusion-associated circulatory overload: a classification agreement validation study. *The Lancet*, 6(7), pp. e350-e358. doi: [https://doi.org/10.1016/s2352-3026\(19\)30080-8](https://doi.org/10.1016/s2352-3026(19)30080-8).

18a Transfusion-Associated Circulatory Overload (TACO) n=172

Author: Sharran Grey

Definition:

TACO is defined as acute or worsening respiratory compromise and/or acute or worsening pulmonary oedema during or up to 12 hours† after transfusion, with additional features including cardiovascular system changes not explained by the patient's underlying medical condition; evidence of fluid overload and a relevant biomarker‡.

† SHOT accepts cases up to 24 hours

‡ see Table 18a.1 for details of required and additional criteria for a surveillance diagnosis

Abbreviations used in this chapter

Hb	Haemoglobin	NBTC	National Blood Transfusion Committee
HFIT	Human factors investigation tool	NPSA	National Patient Safety Agency
ICU	Intensive care unit	NT-pro BNP	N-terminal-pro brain natriuretic peptide
IDA	Iron deficiency anaemia	TACO	Transfusion-associated circulatory overload

Key SHOT messages

- The number of TACO cases reported in 2023 is the highest to date. Although cases continue to increase, there is likely to be a level of under-reporting
- The continued adoption of the TACO risk assessment is encouraging although analysis of the data shows it is still under-used or used ineffectively
- TACO continues to be a major cause of transfusion-related mortality and morbidity
- Severe chronic anaemia (asymptomatic or minimally symptomatic) requires only minimal transfusion (usually a single unit) followed by pharmacological treatment where appropriate. Non-bleeding adult patients with severe chronic anaemia are particularly vulnerable to TACO even in the absence of comorbidities that predispose to TACO

Recommendation

- Perform a gap analysis and implement the recommendations of the NPSA alert on TACO (MHRA and SHOT, 2024). This incorporates ongoing SHOT recommendations and access to further guidance and supporting resources

Action: Hospital Trusts/Health Boards



Introduction

The TACO pre-transfusion risk assessment infographic (Figure 18a.1) was updated in the 2020 Annual SHOT Report to make it suitable for incorporation into clinical documents. Following feedback from reporters, a clarification has been added regarding the use of a prophylactic diuretic. The word 'checklist' has also been standardised to 'risk assessment'.

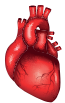


TACO Risk Assessment		YES	NO
	Does the patient have any of the following: diagnosis of 'heart failure', congestive cardiac failure (CCF), severe aortic stenosis, or moderate to severe left ventricular dysfunction?		
	Is the patient on a regular diuretic?		
	Does the patient have severe anaemia?		
	Is the patient known to have pulmonary oedema?		
	Does the patient have respiratory symptoms of undiagnosed cause?		
	Is the fluid balance clinically significantly positive?		
	Is the patient receiving intravenous fluids (or received them in the previous 24 hours)?		
	Is there any peripheral oedema?		
	Does the patient have hypoalbuminaemia?		
	Does the patient have significant renal impairment?		
If Risks Identified		YES	NO
Review the need for transfusion (do the benefits outweigh the risks)?			
Can the transfusion be safely deferred until the issue is investigated, treated or resolved?			
If Proceeding with Transfusion: Assign Actions			TICK
Body weight dosing for red cells			
Transfuse a single unit (red cells) and review symptoms			
Measure fluid balance			
Prophylactic diuretic prescribed (where appropriate/not contraindicated)			
Monitor vital signs closely, including oxygen saturation			
Name (PRINT):		<p>Due to the differences in adult and neonatal physiology, babies may have a different risk for TACO. Calculate the dose by weight and observe the notes above.</p>	
Role:			
Date:	Time (24hr):		
Signature:			

Figure 18a.1: TACO pre-transfusion risk assessment

TACO=transfusion-associated circulatory overload

Table 18a.1:
TACO surveillance
definition (adapted
from Wiersum-
Osselton, et al.,
2019)

TACO surveillance definition	
Patients classified with TACO (surveillance diagnosis) should exhibit at least one required criterion* with onset during or up to 12 hours after transfusion (SHOT continues to accept cases up to 24 hours), and a total of 3 or more criteria i.e., *A and/or B, and total of at least 3 (A to E)	
* Required criteria (A and/or B)	
<p>A. Acute or worsening respiratory compromise and/or</p> <p>B. Evidence of acute or worsening pulmonary oedema based on:</p> <ul style="list-style-type: none"> • clinical physical examination, and/or • radiographic chest imaging and/or other non-invasive assessment of cardiac function 	
Additional criteria	
<p>C. Evidence for cardiovascular system changes not explained by the patient's underlying medical condition, including development of tachycardia, hypertension, jugular venous distension, enlarged cardiac silhouette and/or peripheral oedema</p> <p>D. Evidence of fluid overload including any of the following: a positive fluid balance; clinical improvement following diuresis</p> <p>E. Supportive result of a relevant biomarker, e.g., an increase of BNP levels or NT-pro BNP to greater than 1.5 times the pre-transfusion value</p>	

The number of cases reported in 2023 is the highest to date and is an increase of 12 cases from 2022 (n=160). Although the pathophysiology of the pulmonary complications of transfusion is not fully understood, the evolving understanding of risk factors for TACO and the development of tools to mitigate risks has advanced significantly in recent years. This chapter describes the demographics of patients reported to have TACO, the adoption of risk-reduction strategies, and highlights areas for further focus based on signals from the data and ongoing trends.

Deaths related to transfusion n=15

There were 15 deaths related to TACO in 2023, 2 of which were probably related (imputability 2), and 13 were possibly related (imputability 1). In 2022 there was 1 case that was definitely related to transfusion (imputability 3). Although there are no cases that were evaluated as definitely related to transfusion reported in 2023, the number of deaths has almost doubled compared to 2022 when there were 8, which is a concerning signal in the data (Table 18a.2).

Major morbidity n=20

There were 20 cases of major morbidity in 2023 which is a slight reduction but broadly similar compared to recent years.

Table 18a.2:
Demographic
overview of TACO
cases in 2023

Demographic	Number of reports
Deaths (imputability 3)	0
Deaths (imputability 2)	2
Deaths (imputability 1)	13
Major morbidity	20
Age	Range: 2 months – 96 years (2 age under 18 years) Median: 75.5 years
Gender	104 female, 68 male
Body weight (adults)	Female (n=45): average 64.7kg (range 42-95.5kg) Male (n=36): average 71.1kg (range 50.9-122kg)
Top 4 medical specialties	Acute medicine=34, haematology=30, general medicine=14, emergency medicine=13
Bleeding patients (NBTC indication code R1 or 'massive bleeding' indicated) (NBTC, 2020)	21
Non-bleeding patients (other NBTC indication codes or not stated)	151

TACO is more commonly reported in elderly, non-bleeding patients but is seen across all age groups. These data are consistent with previous years. There were 2 cases in the under-18 age group (age 2 and 3 months). TACO was reported more frequently in female patients and appears to be a consistent characteristic compared to data from previous years. Weight was provided in 45 adult female cases, with an average of 64.7kg (42-95.5kg). Weight was provided in 36 adult male cases, with an average of 71.1kg (50.9-122kg). The apparent higher incidence of TACO in female patient may be attributed to the lower average weight of female patients compared to male, and increased risk of TACO in patients with lower body weight. This underlines the importance of weight-adjusted red cell dosing and single unit transfusion, particularly in patients with lower body weight. Adult medical specialties, including emergency medicine and haematology continue to be the most common specialties where TACO is reported. This should be considered when targeting TACO education and mitigation plans.

Case 18a.1: TACO risks failed to be identified leading to missed opportunities and death

A female patient weighing 52kg with a Hb level of 68g/L was prescribed two units of red cells. She had liver disease and sepsis with peripheral oedema. The cause of the anaemia was not clear, but she was not actively bleeding, and the NBTC indication code assigned to the transfusion was R2 (acute anaemia). A TACO pre-transfusion risk assessment was completed, and the clinician did not identify any risks, therefore no actions were assigned to mitigate TACO. The first unit of red cells was given without issue and the second unit was commenced 4 hours later without a clinical review. She became acutely unwell after the first hour, and an emergency call was made. She developed dyspnoea and tachypnoea with oxygen desaturation to 90% from a previously normal level and had tachycardia and systolic hypertension. The post-transfusion chest X-ray showed significant pulmonary oedema. The NT-pro BNP was significantly raised however there was no pre-transfusion value. An echocardiogram showed moderate left ventricular systolic dysfunction which had not been previously reported. A fluid balance was not reported but there had been a 5kg increase in weight post transfusion. Multiple doses of furosemide were given resulting in some diuresis, but respiratory symptoms remained unchanged. ICU admission was required, and continuous infusion of diuretic was administered, with morphine and antibiotics. The patient unfortunately died. Sepsis was clearly a major factor however the transfusion was assessed as contributory to the death.

A local structured review was performed in the form of an audit of the TACO pre-transfusion risk assessment completion, transfusions out-of-hours, and the single unit red cell policy.

Recommendations following the audit were broadly as follows:

- Education and training on single unit policy, transfusion triggers and Hb targets
- Review the operational use of the TACO risk-assessment tool
- Education on the TACO risk-assessment process
- Ensure the TACO risk assessment is applied to platelets and cryoprecipitate
- Additional education on stable patients with anaemia, overnight transfusion and adopting transfusion reaction e-learning



This is an example of the TACO risk assessment being completed incorrectly resulting in missed opportunities to prevent or mitigate TACO. The patient had peripheral oedema due to liver disease, sepsis, and hypoalbuminemia: therefore, there were clear signs of pre-transfusion fluid overload. The patient may have had previously undiagnosed heart failure which was uncovered by this episode of TACO. Had

this been correctly identified as a risk, several mitigation options could have been considered assuming deferral of the transfusion to manage the pre-transfusion overload was not clinically appropriate. A single unit policy or weight-adjusted red cell dosing would have prevented the transfusion of excessive and unnecessary volume of red cells. The patient had not developed signs of TACO after the first red cell unit. The patient was on a regular diuretic, and it may have been possible to give an additional prophylactic dose. Fluid balance monitoring was not in place, and it was only apparent after the transfusion that there was significant overload due to the increase in body weight when recorded post transfusion. The SHOT structured TACO incident investigation tool does not appear to have been used in this case, however actions concerning most of the preventable factors appear to have been identified.

Excessive red cell transfusion in non-bleeding adult patients with both chronic and acute anaemia continues to be a significant feature in TACO cases, particularly in patients with lower body weight. The team reporting this case should be commended for focussing education and training on transfusion triggers and the use of single unit transfusions. Organisations are encouraged to consider system changes such as embedding in electronic or other controlled processes to avoid the over-reliance on staff knowledge alone.

Potentially preventable factors in cases of mortality n=15

Table 18a.3 and Table 18a.4 below describe the use of the TACO risk assessment in 2023 and a review of potentially preventable factors following case review, with a summary of trends and themes which are similar findings compared to data from previous years.

Table 18a.3: Use of TACO risk assessment in TACO-related deaths in 2023

TACO risk assessment performed	9/15
Risk(s) identified on TACO risk assessment	8/9
Risk(s) NOT identified on TACO risk assessment when present on case review	1/9
Risks(s) identified on TACO risk assessment fully agree with risks present on case review	0/9
Instances of risks missed in the 6 cases where a TACO assessment was NOT performed:	Hypoalbuminaemia (2); renal impairment (2); fluids (3); cardiac impairment (1); peripheral oedema (2); positive fluid balance (1)
Instances of risks missed in the 9 cases where a TACO risk assessment WAS performed:	Positive fluid balance (3); fluids (2), pulmonary oedema (2); likely fluids involved (1); cardiac impairment (1); renal impairment (2); hypoalbuminaemia (3); peripheral oedema (1)
TACO mitigations assigned	7/15
Mitigation measures performed as assigned/planned	5/7

Key themes include:

- Failure to perform TACO risk assessment in a significant number of cases, and risks missed in all cases where the risk assessment was not performed. This is not limited to specific risks for TACO
- Risks not comprehensively identified in individual patients (additional risks were identified on case review). This is not limited to specific risks for TACO
- Missed opportunities to assign TACO mitigation measures
- Failure to perform TACO mitigation measures as assigned/planned

Transfusion NOT indicated	3/15 (includes 1 case of iron deficiency anaemia that could have been potentially treated with intravenous iron)
Indicated transfusions (n=12) that could have been deferred	1/12 (pre-transfusion overload with no clear urgency for transfusion)
Appropriate volume transfused	9/15 (clear evidence of overtransfusion in 2 cases)
Appropriate/close monitoring	14/15 (TACO not immediately recognised in 1 case)
Fluid balance monitoring	8/15
No prophylactic diuretic given	8/15
On regular diuretic (no additional prophylactic dose given)	4/15
Diuretic identified as required but unable to ascertain if given	1/15
No prophylactic diuretic and regular dose withheld	1/15
On regular diuretic and additional prophylactic dose given	1/15
Structured case review	6/15

Table 18a.4:
Preventable factors
for TACO-related
deaths in 2023

Key themes include:

- Some transfusions were inappropriate and could have been avoided altogether, including a case of IDA that could have been treated with iron replacement
- One case could potentially have been deferred to address the pre-transfusion overload
- Inappropriate volume of red cells transfused with clear cases of overtransfusion. Evidence for lack of application of weight-adjusted red cell dosing and single unit and review policy
- Fluid balance monitoring not performed in some cases. Unclear whether it was due to practical reasons or an oversight
- No prophylactic diuretic was administered in most cases. It is not possible to ascertain whether this was an oversight or that a diuretic was contraindicated. It is noted that there was some degree of renal impairment in 9/15 cases which may have influenced the decision not to give a prophylactic diuretic
- The transfusion contributed to death to some extent in all 15 cases. There was evidence of a structured review in only 6 cases, potentially leading to missed opportunities to improve practice and patient safety

A recent 10-year review of the TACO deaths, as reported to SHOT highlighted that TACO is rarely seen in the absence of risk factors identified on the pre-transfusion TACO risk assessment. This safety check appears to be under-utilised and often inaccurately completed, leading to inadequate mitigation strategies. Organisations are urged to implement SHOT recommendations to enhance patient safety (Firth, et al., 2024).

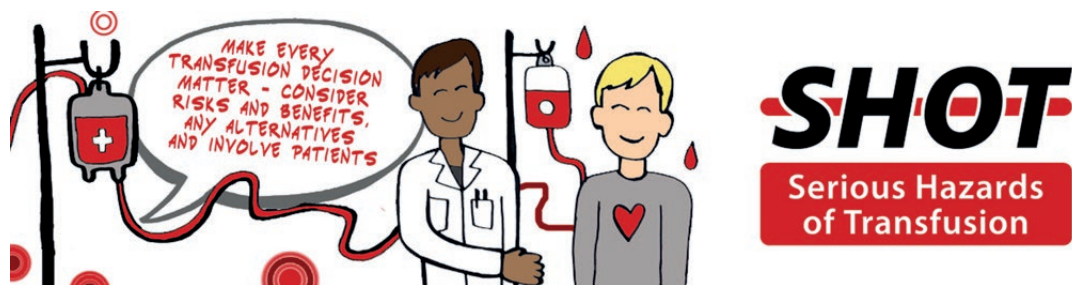


Transfusion management approach in non-bleeding adult patients: avoiding the risks of mismanagement in severe chronic anaemia

Accurate identification of the cause of anaemia is a critical step in safe and appropriate transfusion management. Acute anaemia is defined as anaemia of recent onset which is caused by bleeding, surgery, or critical illness in a haemodynamically stable patient. It corresponds to NBTC indication codes R2 and R3, the latter in the context of acute coronary syndrome. This contrasts with transfusion-dependent anaemia (R4) which may be caused by bone marrow failure or haemoglobinopathy, and severe chronic anaemia (e.g., caused by haematinic deficiency, or anaemia of chronic disease) (NBTC, 2020). There is no

universal Hb trigger or target for severe chronic anaemia. Physiological compensation means transfusion is not likely to be required if the Hb is $>70\text{g/L}$. The transfusion of a single unit may be indicated to alleviate symptoms in severe anaemia (Hb $<70\text{g/L}$) or prevent the acute complications of severe anaemia while the underlying cause is treated e.g., iron replacement in iron deficiency anaemia.

SHOT data have shown that severe anaemia is an independent risk factor for TACO (Narayan, et al., 2019) and these patients are vulnerable to overtransfusion leading to TACO-related deaths and major morbidity. It is important that clinicians authorising transfusion understand the rationale for different approaches to transfusion management, and the risks of not recognising acute versus chronic anaemia. The presence of acute coronary syndrome and cardiac ischaemia in acute and chronic anaemia present additional challenges and risks. The decision to transfuse further units to achieve a higher Hb target in a patient with acute coronary syndrome/cardiac ischaemia should be balanced against the increased risk of TACO and exacerbation of heart failure. Strategies that support this such as education, training and process-embedded guidelines are key components of safe decision-making in transfusion. Figure 18a.2 describes the transfusion management approach for non-bleeding adult patients and details the specific approach that should be adopted for patients with severe chronic anaemia.

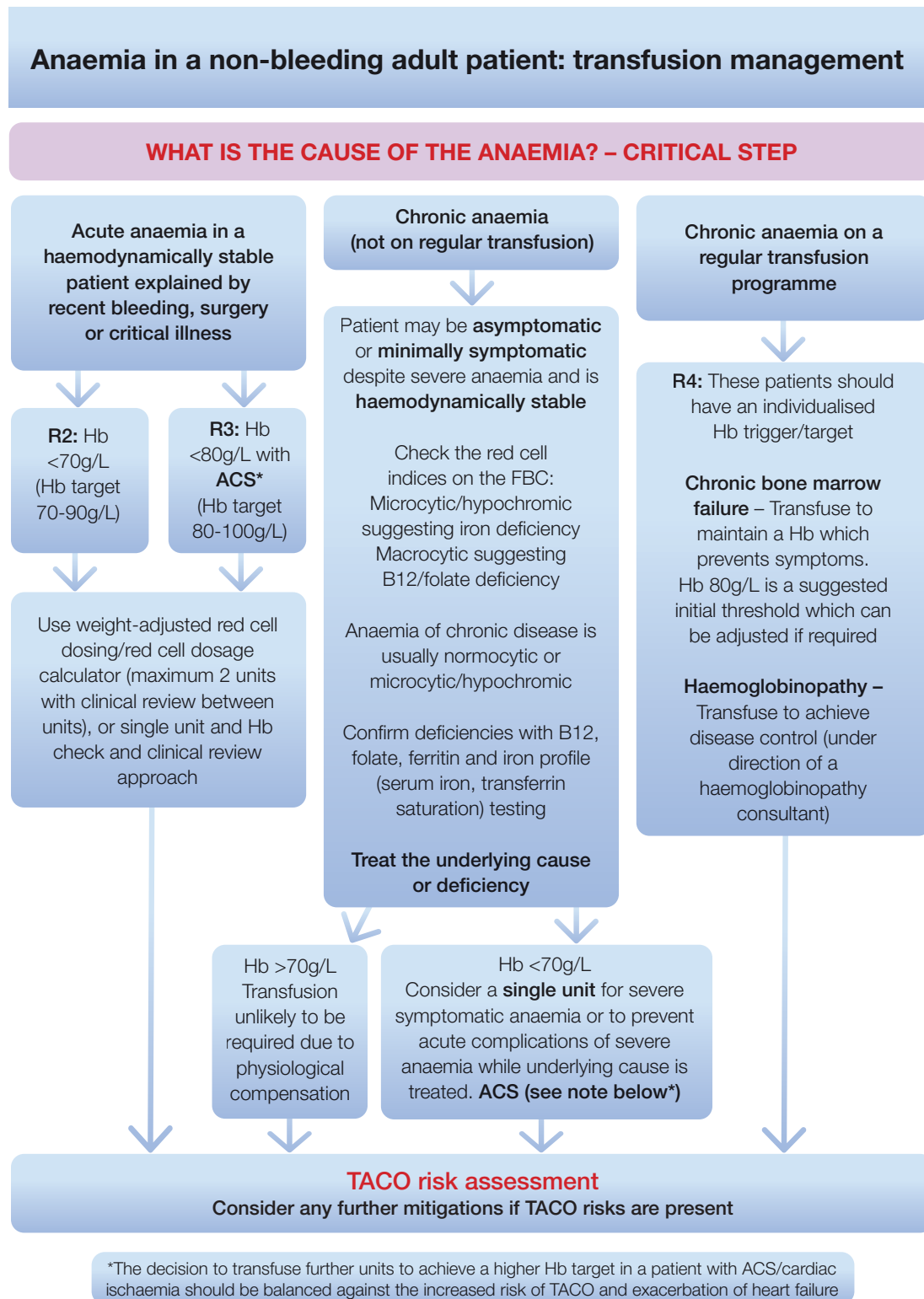


Conclusion

There has been slow adoption of the TACO pre-transfusion risk assessment tool since it was launched but this is increasing steadily. While encouraging, the analysis of the data shows it is still under-used or used ineffectively. Although there has been some uptake of the TACO structured incident investigation tool, there are still missed opportunities to enhance patient safety. The SHOT HFIT questions, and the analyses in the main chapter, are only included for reports in established error categories, but it can be demonstrated that some reaction cases may also be error-based. For the first time this year, a TACO case has been examined in the Human Factors and Ergonomics (HFE) supplementary information using the HFIT main headings to examine the significance of HFE involved (<https://www.shotuk.org/shot-reports/report-summary-and-supplement-2023/>).

Overtransfusion of red cells remains an issue which could be minimised by weight-adjusted or single unit transfusion in non-bleeding patients. The transfusion management of patients with severe chronic anaemia is concerning and continues to contribute to patient deaths due to excessive transfusion. There are several strategies available to mitigate the risk of TACO based on many years of haemovigilance data. Everyone involved in the transfusion process has a professional duty to protect patients from TACO wherever possible. With an increasing number of TACO cases reported to SHOT year-on-year, including instances of preventable deaths, a National Patient Safety Alert has been released UK-wide by SHOT through the MHRA (MHRA and SHOT, 2024). This is intended to support and provide a structure for organisations to implement measures to enhance safety and facilitate appropriate transfusion decisions. The NBTC indication codes are also being reviewed currently and an updated version is expected to be released in due course. Identifying risk-factors for TACO in vulnerable patients prior to transfusion helps initiate appropriate mitigating measures. TACO deaths are potentially preventable.

Figure 18a.2:
Transfusion
management
approach in
non-bleeding
adult patients



ACS=acute coronary syndrome; FBC=full blood count; Hb=haemoglobin; TACO=transfusion-associated circulatory overload



Recommended resources

Example of weight-adjusted red cell dosing implemented in clinical practice

NHS MHRA and UKCA Marked blood transfusion Red Cell Dosage Calculator Software App (rcdcalculator.co.uk)

TACO Incident Investigation Guidance Tool

TACO Risk assessment in alternative format for incorporation into clinical documents

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

SHOT Bite No. 11: Respiratory Symptoms During Transfusion

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

SHOT Video: TACO – Transfusion-Associated Circulatory Overload

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

NPSA Alert (2024): TACO

National Patient Safety Alert: Reducing risks for transfusion-associated circulatory overload (NatPSA/2024/004/MHRA) - GOV.UK (www.gov.uk)

Transfusion-Associated Circulatory Overload (TACO) Cumulative Data

<https://www.shotuk.org/resources/current-resources/data-drawers/transfusion-associated-circulatory-overload-taco-data-drawer/>

National Comparative Audit of TACO

<https://hospital.blood.co.uk/audits/national-comparative-audit/reports-grouped-by-year/transfusion-associated-circulatory-overload-audit-2017/>

References

Firth, O., Grey, S., Narayan, S. & Poles, D., 2024. Deaths attributable to transfusion-associated circulatory overload: 10-year review of serious hazards of transfusion (SHOT) data. *British Journal of Haematology*, 204(S1), pp. 63-64. doi: <https://doi.org/10.1111/bjh.19398>.

Medicines & Healthcare products Regulatory Agency (MHRA) and Serious Hazards of Transfusion (SHOT), 2024. *Central Alerting System: Reducing risks for transfusion-associated circulatory overload*. [Online] Available at: <https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103249> (Accessed 08 April 2024).

Narayan, S., Grey, S., Bolton-Maggs, P. & Poles, D., 2019. Is severe anaemia an independent risk factor for TACO? Case based discussions based on TACO reports to SHOT, the United Kingdom haemovigilance scheme (abstract). *Vox Sanguinis*, 114(S1), p. 231. doi: <https://doi.org/10.1111/vox.12792>.

National Blood Transfusion Committee (NBTC), 2020. *Indication Codes for Transfusion in Adults - An Audit Tool*, England: National Blood Transfusion Committee. Available at: <https://nationalbloodtransfusion.co.uk/sites/default/files/documents/2023-02/NBTC%20indication%20codes%20-%20Final%20-%20Jan%2020%20%28004%29.pdf> (Accessed 03 May 2024).

Wiersum-Osselton, J. C. et al., 2019. Revised international surveillance case definition of transfusion-associated circulatory overload: a classification agreement validation study. *The Lancet*, 6(7), pp. e350-e358. doi: [https://doi.org/10.1016/s2352-3026\(19\)30080-8](https://doi.org/10.1016/s2352-3026(19)30080-8).

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

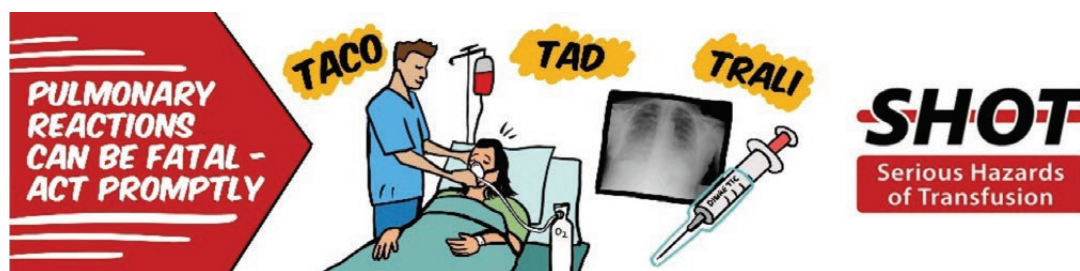
		Imputability			
		1-possible	2-probable	3-definite	Total
Category	TAD-C	7	8	1	16
	TAD-IC	7	4	0	11
	TRALI-TACO	0	0	1	1
	TRALI type II	4	1	0	5
Total		18	13	2	33

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).



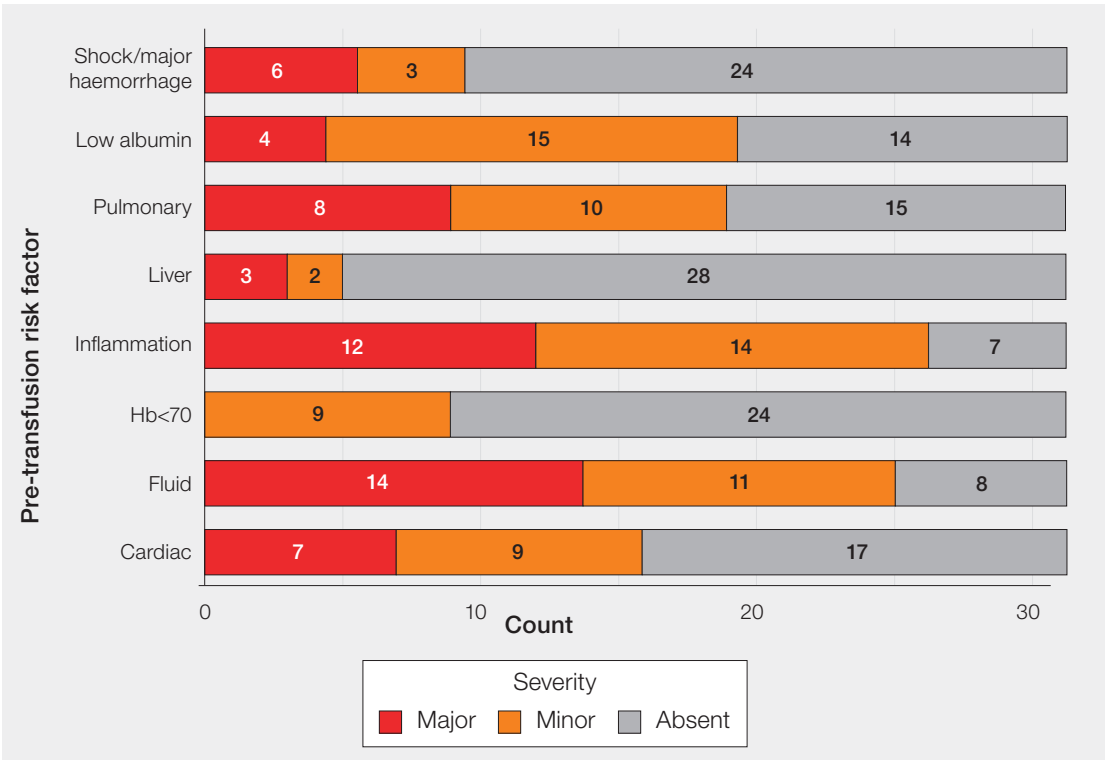


Figure 18b.1: Pre-transfusion features of pulmonary cases

Figure 18b.1a: Risk factors

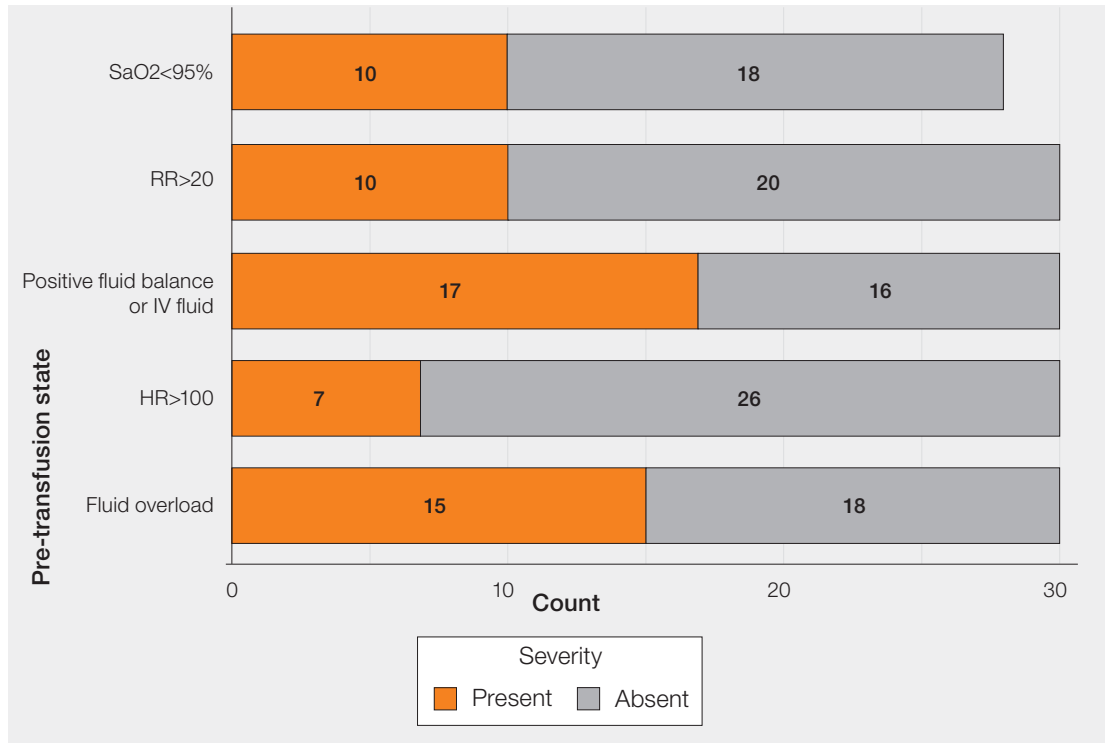
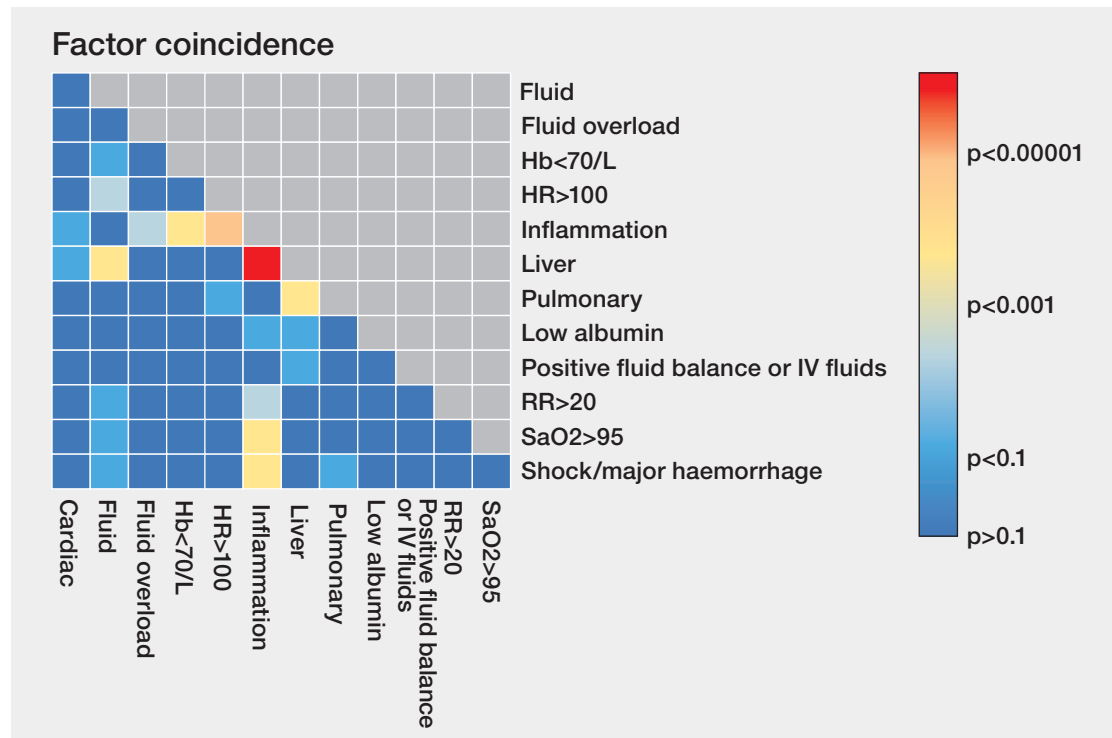


Figure 18b.1b: State factors

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

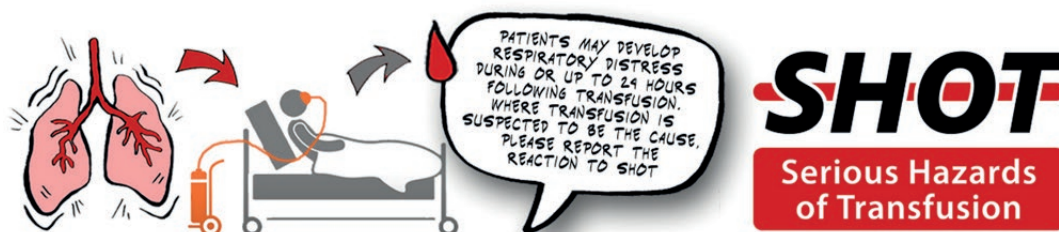
<https://www.shotuk.org/resources/current-resources/>

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

Gajic, O. et al., 2007. Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. *American Journal of Respiratory and Critical Care Medicine*, 176(9), pp. 886-891. doi: <https://doi.org/10.1164/rccm.200702-271oc>.

Klanderman, R. B. et al., 2022. Incidence of transfusion-related acute lung injury temporally associated with solvent/detergent plasma use in the ICU: A retrospective before and after implementation study. *Transfusion*, 62(9), pp. 1752-1762. doi: <https://doi.org/10.1111/trf.17049>.

Narayan, S. et al., 2023. *The 2022 Annual SHOT Report*, Manchester: Serious Hazards of Transfusion (SHOT) Steering Group. doi: <https://doi.org/10.57911/WZ85-3885>.

Sachs, U. J., Kauschat, D. & Bein, G., 2005. White blood cell-reactive antibodies are undetectable in solvent/detergent plasma. *Transfusion*, 45(10), pp. 1628-1631. doi: <https://doi.org/10.1111/j.1537-2995.2005.00587.x>.

Vlaar, A. P. et al., 2019. A consensus redefinition of transfusion-related acute lung injury. *Transfusion*, 59(7), pp. 2465-2476. doi: <https://doi.org/10.1111/trf.15311>.

Wiersum-Osselton, J. C. et al., 2019. Revised international surveillance case definition of transfusion-associated circulatory overload: a classification agreement validation study. *The Lancet*, 6(7), pp. e350-e358. doi: [https://doi.org/10.1016/s2352-3026\(19\)30080-8](https://doi.org/10.1016/s2352-3026(19)30080-8).

