Revised international surveillance case definition of transfusion-associated circulatory overload: a classification agreement validation study

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Summary

Background **Transfusion-associated circulatory overload (TACO) is a major cause of transfusion-related morbidity and mortality in countries with well developed transfusion services. The International Society of Blood Transfusion, the International Haemovigilance Network, and AABB (formerly American Association of Blood Banks), have developed and validated a revised definition of TACO.**

Methods **International Haemovigilance Network-member haemovigilance systems (Australia, Austria, Denmark, Finland, Greece, India, Ireland, Italy, Japan, Malta, Netherlands, New Zealand, Norway, Slovenia, United Kingdom and United States) provided cases of respiratory complications categorised by their systems, including clinical parameters listed in the 2017 draft definition (part 1). Individual transfusion professionals were then invited to assess 24 case descriptions according to the draft definition (part 2). Positive and negative agreement and inter-rater agreement (κ) were calculated. Based on validation results, cases were reanalysed and slight adjustments made to yield the final 2018 TACO definition.**

Findings **In part 1, 16 (44%) of 36 haemovigilance systems provided 178 cases, including 126 TACO cases. By use of the 2018 definition, 96 (76%) of 126 cases of TACO were in positive agreement. 19 (37%) of 52 cases were recognised as non-TACO respiratory complications. In part 2 (47 experts from 20 countries), moderate all-case agreement (κ=0·43) and TACO-specific agreement (κ=0·54) were observed. Excluding cases missing some clinical information (eg, N terminal pro-brain natriuretic peptide, distinctive chest x-ray findings, and relationship with existing respiratory co-morbidities like pneumonia and chronic obstructive pulmonary disease) improved all-case agreement to κ=0·50 (moderate) and κ=0·65 (good) for TACO cases.**

Interpretation **The two-part validation exercise showed that the revised 2018 TACO surveillance case definition captures 76% of cases endorsed as TACO by participating haemovigilance systems. This definition can become the basis for internationally consistent surveillance reporting and contribute towards increased awareness and mitigation of TACO. Further research will require reporting more complete clinical information to haemovigilance systems and should focus on improved distinction between TACO and other transfusion respiratory complications.**

Funding **International Society of Blood Transfusion, International Haemovigilance Network, and AABB.**

Introduction

National haemovigilance systems have shown that transfusion-associated circulatory overload (TACO) is one of the most important causes of serious transfusion-associated morbidity and mortality in countries with well developed transfusion services.[1–4] The incidence of cases reported to haemovigilance systems is 10–29 per 100 000 blood components transfused, in which all levels of severity of reactions are collected, as is the case in Ireland, The Netherlands, Canada, and France.[3,5–7] A 100-fold higher incidence of TACO emerges using active surveillance than with systems with voluntary reporting (passive surveillance), with TACO in about 1–5% of patients who received transfusions.[8,9] TACO fatalities are reported to the US Food and Drug Administration annually at 0·11 per 100 000 blood components transfused whereas some haemovigilance systems report that about six patients die from TACO per 100 000 blood components transfused.[1,4]

Risk factors for TACO include cardiac, pulmonary ,or renal disease; older age (≥70 years); low bodyweight; and a pretransfusion positive fluid balance.[10–12] Many cases of TACO can be prevented through measures such as a slower infusion rate and pre-emptive diuretics,[10–12] although further research is needed to establish the best practices for different patient subgroups.

An internationally harmonised surveillance case definition can assist clinicians, hospitals, and haemovigilance systems to monitor the incidence of TACO, and to observe the effects of interventions to reduce its occurrence. Surveillance can make use of results of diagnostic testing and effects of instituted treatment. As with a diagnostic

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Research in context

Evidence before this study

In the past two decades, transfusion-associated circulatory overload (TACO) has emerged as an important cause of serious transfusion-related harm, and is the major cause of deaths associated with blood transfusions. It is characterised by respiratory deterioration during or up to 12 h after completion of blood transfusion, and is associated with hydrostatic pulmonary oedema. Typically, cardiovascular system changes occur, such as an increase of blood pressure, widened pulse pressure, and tachycardia. A positive fluid balance is common and patients show clinical improvement from diuresis, generally with intravenous loop diuretics (furosemide). Risk factors for developing TACO include poor cardiac pump function, a history of congestive cardiac failure, pulmonary or renal disease, a positive fluid balance, deep anaemia, and rapid infusion of large volumes of blood components. Although physicians are aware of the importance of fluid management, there is less recognition that transfusion constitutes a specific hazard, greater than that of a similar volume of non-sanguinous fluid. A TACO case surveillance definition, composed by international experts, for haemovigilance reporting was published in 2011, by the International Society of Blood Transfusion in collaboration with the International Haemovigilance Network, but was found inadequate because many cases diagnosed as TACO by clinicians and endorsed by haemovigilance systems did not meet the criteria. This has been an impediment to international collaboration in research and efforts to promote awareness and prevention of TACO.

Added value of this study

After developing a revised definition by an iterative process based on consensus and the literature, we subjected it to a validation exercise with the collaboration of multiple national haemovigilance systems and individual experts. The results show that the revised definition achieves a worthwhile improvement for use in haemovigilance settings, correctly recognising a higher percentage of cases previously designated as TACO by haemovigilance systems, than the old definition.

It can be difficult to clinically distinguish between transfusion-associated acute lung injury (TRALI) and TACO at the bedside and radiographic images might be inconclusive in patients with respiratory distress and pulmonary oedema during or soon after a transfusion (two of the core criteria). The 2018 TACO definition is accompanied by notes and a didactic table listing key features to assist in making the differential diagnosis. The definition underlines the need to collect and review all available information in detail to diagnose the patient correctly and obtain optimal surveillance classification. The distinction between the types of complications has therapeutic implications, because the management of TACO differs from that of TRALI.

Implications of all the available evidence

We recommend implementation of the 2018 revised TACO definition for surveillance by national haemovigilance systems. More research is needed to develop an evidence base for most effectively prescribing preventive measures for specific patient risk groups. In the meantime, the existing knowledge of the patient risk factors for TACO should guide clinicians in appropriately prescribing administration rates of transfusions or the use of pretransfusion diuretics, or both, so as to increase the safety of transfusion therapy. This newly revised definition will provide a focus for efforts to promote awareness of TACO as a hazard for hospitalised or day-case patients receiving transfusion.

test, the case definition should capture true cases (positive agreement), and exclude patients with an alternate cause for their symptoms (negative agreement).

We describe the collaborative effort by haemovigilance experts representing the International Society of Blood Transfusion (ISBT), the International Haemovigilance Network (IHN), and the AABB (formerly the American Association of Blood Banks), to develop and validate a revised definition for TACO for use in haemovigilance reporting.

Methods

International definition development

The ISBT haemovigilance working party, in collaboration with IHN, first published a surveillance definition for TACO in 2011 (table 1; appendix p 1);[13] however, users within haemovigilance systems noted that many cases diagnosed as TACO by clinical judgement did not meet the criteria of the 2011 definition.[2,5] These users identified that cases could be accompanied by hypotension instead of hypertension, tachycardia is a non-specific finding, and reporters might not provide pulse and blood pressure data. Additionally, cases could occur beyond 6 h after transfusion.[2,14]

See Online for appendix

The revision process was formally launched at the ISBT haemovigilance working party meeting in 2013. In accordance with ISBT's formal definition procedure,[15] a group from the ISBT and IHN revised the definition, using serial group conference calls. The revision group comprises members with clinical, laboratory, blood bank, and haemovigilance backgrounds from Europe, Canada, and the USA. The draft was circulated by email and posted on the ISBT website haemovigilance working party page for comment in December, 2014. A revised version was tested in 2015, by contributors from haemovigilance systems in several countries who applied it to their own cases, and also formally applied to cases reported to Serious Hazards of Transfusion (SHOT), the UK haemovigilance scheme, in 2014 and 2015.[16,17] The 2014 version gave marginally better agreement than the 2011

	US TACO definition, 2010–current	Former ISBT-IHN TACO definition, 2011	Draft revised definition (used in validation studies), 2017	Revised ISBT-IHN-AABB TACO case surveillance definition, 2018
Surveillance diagnosis criteria	New onset or exacerbation of three or more of the criteria below within 6 h of cessation of transfusion	TACO is characterised by any four of the following, occurring within 6 h of completion of transfusion	Patients classified with a TACO (surveillance diagnosis) should have acute or worsening respiratory compromise during or up to 12 h after transfusion and should exhibit two or more of the criteria below	Patients classified with a TACO (surveillance diagnosis) should exhibit at least one required criterion with onset during or up to 12 h after transfusion and a total of three or more criteria (required and additional)
Respiratory system	Acute respiratory distress (dyspnoea, orthopnoea, cough); radiographic evidence of pulmonary oedema	Acute respiratory distress; acute or worsening pulmonary oedema on frontal chest radiograph	Evidence of acute or worsening pulmonary oedema based on clinical physical examination, radiographic chest imaging, other non-invasive assessment of cardiac function, or a combination of these	Acute or worsening respiratory compromise;* or evidence of acute or worsening pulmonary oedema* based on clinical physical examination, radiographic chest imaging, other non-invasive assessment of cardiac function, or a combination of these
Cardiovascular system	Evidence of left heart failure	Tachycardia; increased blood pressure	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, peripheral oedema, or a combination of these	Development of cardiovascular system changes not explained by the patient's underlying medical condition,† including development of tachycardia, hypertension, jugular venous distension, enlarged cardiac silhouette, peripheral oedema, or a combination of these
Fluid	Evidence of positive fluid balance	Evidence of positive fluid balance	Evidence of fluid overload, including a positive fluid balance or clinical improvement following diuresis	Evidence of fluid overload,† including a positive fluid balance or clinical improvement following diuresis
Biomarkers	Elevated brain natriuretic peptide; elevated central venous pressure	An elevated brain natriuretic peptide is supportive of TACO (not a criterion but stated as a comment)	Elevation in B-type natriuretic peptide concentrations (eg, brain natriuretic peptide or N terminal-pro brain natriuretic peptide) to greater than 1·5 times the pretransfusion value.	Supportive result of a relevant biomarker†—eg, an increase of B-type natriuretic peptide concentrations (brain natriuretic peptide or N terminal-pro brain natriuretic peptide) above the age group-specific reference range and greater than 1·5 times the pretransfusion value

TACO=transfusion-associated circulatory overload. ISBT=International Society of Blood Transfusion. IHN=International Haemovigilance Network. AABB=Association representing individuals and institutions involved in transfusion medicine and cellular therapies, formally the American Association of Blood Banks. *Required criterion. †Additional criterion.

Table 1: **Evolution of TACO surveillance definition**

version; ie, more of the cases met the criteria; however the 2014 version was limited by the weight placed on enlargement of the cardiac silhouette and an increase of brain natriuretic peptide (BNP), both often not investigated or not reported to haemovigilance systems.

In a further round of revision with the same working method, the ISBT-IHN group was joined by representatives of the AABB Hemovigilance and Patient Safety Organisation Advisory committees. The next draft was posted on the ISBT website haemovigilance working party page for comment and yielded the April 2017 version (table 1; appendix p 1), which was subjected to the validation exercise described later.

Study design

The two-part study was done by use of an online questionnaire. Part 1 ran from May 17, to Aug 15, 2017, and assessed the agreement of the April 2017 draft of the revised TACO definition with cases previously reported and accepted as TACO by national haemovigilance systems. Part 2 ran from Oct 15, to Dec 15, 2017, and tested whether the revised definition enabled haemovigilance professionals to recognise TACO and distinguish between TACO and other acute pulmonary reactions. The objective was to document and optimise agreement with the criteria and maximise clarity of the definition.[18]

For part 1, representatives of established IHN-member haemovigilance systems were invited to participate through IHN, whereas part 2 was open to transfusion professionals worldwide, who were involved in the reporting and monitoring of complications of blood transfusion. These professionals were recruited through e-mail invitations to the ISBT haemovigilance working party members, official IHN contacts, and AABB Hemovigilance Committee and Patient Safety Organisation Advisory committee members. All participants were provided with the April 2017 draft TACO definition, the 2011 ISBT definitions for other types of transfusion reactions (appendix pp 2,3),[13] and the study protocol;[18] no additional training was provided.

Participants in part 1 were asked to classify existing cases reported to their national haemovigilance systems using the 2017 draft TACO definition. They provided data for such reactions, including ten cases of TACO, two cases of transfusion-associated acute lung injury (TRALI), two cases of transfusion-associated dyspnoea (TAD; if an accepted option within their haemovigilance systems), and an unclassified case with significant pulmonary features (other). The case information included the imputability assessment (ie, the likelihood that the observed reaction could be attributed to the transfusion). Cases were not critically reviewed by the authors but accepted on the basis of the endorsement of the haemovigilance systems. Not all haemovigilance systems capture cases of TAD; hence, they were asked how their system assessed cases of TAD.

In part 2, TACO, TRALI, TAD, and other transfusion reaction case reports were assembled from the

For more on the **online questionnaire** see www.qualtrics.com

	Version 1 (April 2017)	Version 2	Version 3	Version 4 (adopted as 2018 definition)	Version 5	Version 6	Version 7
Required criteria (onset during or up to 12 h after transfusion)	Evidence of acute or worsening respiratory distress	Evidence of acute or worsening pulmonary oedema	Equal weight given to all five criteria	Evidence of acute or worsening respiratory distress; evidence of acute or worsening pulmonary oedema; or both; total of three or more criteria, including additional criteria (below)	Evidence for cardiovascular system changes; evidence of acute or worsening pulmonary oedema; evidence of acute or worsening respiratory distress; the first should be combined with at least one other required criterion; total of three or more criteria, including additional criteria (below)	Evidence of fluid overload; evidence of acute or worsening pulmonary oedema; evidence of acute or worsening respiratory distress; the first should be combined with at least one other required criterion; total of three or more criteria, including additional criteria (below)	Elevation in B-type natriuretic peptide concentrations; evidence of acute or worsening pulmonary oedema; evidence of acute or worsening respiratory distress; the first should be combined with at least one other required criterion; total of three or more criteria, including additional criteria (below)
Additional criteria (onset during or up to 12 h after transfusion)	Plus two or more of: evidence of acute or worsening pulmonary oedema; evidence for cardiovascular system changes; evidence of fluid overload; or elevation in B-type natriuretic peptide concentrations	Plus two or more of: evidence of acute or worsening respiratory distress; evidence for cardiovascular system changes; evidence of fluid overload; or elevation in B-type natriuretic peptide concentrations	Three or more of: evidence of acute or worsening respiratory distress; evidence of acute or worsening pulmonary oedema; evidence for cardiovascular system changes; evidence of fluid overload; or elevation in B-type natriuretic peptide concentrations	Plus evidence for cardiovascular system changes; evidence of fluid overload; elevation in B-type natriuretic peptide concentrations; or a combination of these	Evidence of fluid overload; elevation in B-type natriuretic peptide concentrations; or both	Evidence for cardiovascular system changes; elevation in B-type natriuretic peptide concentrations; or both	Evidence for cardiovascular system changes; evidence of fluid overload; or both
Positive agreement*	93 (74%)	94 (75%)	96 (76%)	96 (76%)	81 (64%)	55 (44%)	24 (19%)
Negative agreement†	20 (38%)	19 (37%)	19 (37%)	19 (37%)	21 (40%)	42 (81%)	46 (88%)

Data are n (%). TACO=transfusion-associated circulatory overload. *Cases submitted as TACO (n=126) and classified as such under each version of the definition criteria. †Cases not submitted as TACO (22 transfusion-associated dyspnoea, 20 transfusion-associated acute lung injury, and ten other), which did not meet the TACO criteria (ie, were appropriately classified as not TACO) under each version.

Table 2: **Case classification permutations considered for April 2017 draft TACO definition on the basis of on results of part 1**

established haemovigilance systems with which the revision group was associated. Cases were reviewed independently by the members of the revision group to verify the diagnosis, and minimally edited for uniform terminology. The numbers of cases per type of reaction were specified in the protocol, based on proportions of the reactions in haemovigilance data.[1,19,20] The participants in part 2 were asked to assess 24 case reports using the provided definitions (appendix pp 2,3). Using the randomisation feature available on the online questionnaire tool, the cases were presented in a random order for each respondent (example cases are in the appendix p 4).

Statistical analysis

Calculations of frequencies of features of the reactions and positive and negative percentage agreement between case classification by participating haemovigilance systems and the definition were done in part 1. All imputabilities were included because case recognition is separate from assessment of the presence of contributory factors. The agreement among all participants in part 2 was measured by Fleiss' κ coefficient and category wise, with poor ($\kappa \leq 0 \cdot 20$), fair ($0 \cdot 20 < \kappa \leq 0 \cdot 40$), moderate ($0 \cdot 40 < \kappa \leq 0 \cdot 60$), good ($0 \cdot 60 < \kappa \leq 0 \cdot 80$), and very good ($\kappa > 0 \cdot 80$). All statistical analyses were done with R, version 3.3.1, and statistical significance was established for results with a p-value of less than 0·05.

Adjustments to the definition

Based on the part 1 and part 2 responses, the revision group considered modifications to the April 2017 draft definition. For the final definition, the part 1 cases were evaluated by use of six permutations of the April 2017 draft definition, each using different emphases on the same five core criteria (table 2). The validation outcome and this reprioritisation of the criteria were presented in meetings open to registrants of ISBT, IHN, and AABB in 2018; the features of the core criteria were not changed, and no subsequent revalidation was undertaken. For part 2, survey participants' free text comments were reviewed for cases with poor agreement, to assess the need for further clarification; this process resulted in minor modifications in the explanatory notes accompanying the core criteria.

Role of the funding source

This study was supported by ISBT, IHN, and AABB through provision of teleconferencing facilities and funding an expert meeting in 2017; AABB allowed staff time to work on the study. No additional funding was received. The supporting organisations had no influence on the study protocol, data collection, analysis, writing of the manuscript or decision to submit. The corresponding author had full access to all the data and the final responsibility to submit for publication.

Results

16 haemovigilance systems (Australia, Austria, Denmark, Finland, Greece, India, Ireland, Italy, Japan, Malta, Netherlands, New Zealand, Norway, Slovenia, UK, and USA) of 36 IHN members approached, participated in part 1, submitting 178 transfusion reaction cases (two to 15 per system; median 14, IQR 9–15). Of these, 126 cases were reported as TACO, 20 as TRALI, 22 as TAD, and ten as other; the non-TACO cases came from 11 of the participating haemovigilance systems. The other reactions were five reports of cardiogenic pulmonary oedema, three non-specific pulmonary reactions, and two other non-specific transfusion reactions. Cases varied in imputability (appendix p 5).

The findings associated with the transfusion reaction cases are shown in table 3. As a result of the types of case requested, nearly all submitted cases presented with respiratory distress (169 [95%] of 178). Evidence of acute or worsening pulmonary oedema based on radiographic chest imaging, or clinical physical examination or other non-invasive assessment of cardiac function, or both, was reported in 110 (87%) of 126 TACO cases, all 20 (100%) TRALI cases, 15 (68%) of 22 TAD cases, and nine (90%) of ten other cases. Among patients with diagnosed TACO, clinical findings included cyanosis or hypoxia in absence of other specific causes (57 [45%]) and crackles on lung auscultation (30 [24%]). Cardiovascular changes were reported in three-quarters of patients overall (130 [73%] of 178) and in patients with TACO (93 [74%] of 126). Tachycardia (57 [45%]), hypertension (53 [42%]) and increase in arterial blood pressure (45 [36%]), were the most frequently reported changes in TACO cases, whereas an enlarged cardiac silhouette at the time of reaction was reported in 19 (15%) TACO cases and in two (10%) patients with TRALI. In this cohort, evidence of fluid overload and elevated BNP concentrations were least commonly reported: only 56 (44%) TACO cases had documented fluid overload. In the majority of TACO cases (98 [78%]) no BNP determination was done or no information was given about BNP determinations; 25 (20%) TACO cases had documented elevated BNP concentrations. Among the TACO cases, 122 (97%) of 126 occurred within 12 h of the transfusion. Of TACO cases that met at least three of the criteria, nine (9%) occurred between 6 h and 12 h (appendix p 6).

After analysing all cases, the 2017 draft TACO definition (version 1; table 2) was adjusted, yielding the finalised 2018 TACO surveillance case definition (version 4), which showed a positive percentage agreement of 76%, capturing 96 of 126 cases recognised by the haemovigilance systems with a TACO diagnosis. The negative agreement was 19 (37%) of 52 cases, indicating the ability of the definition to classify non-TACO cases as such. The overall percentage agreement (96 TACO cases correctly included and 19 non-TACOs correctly excluded, of 178 total cases) of the definition was 65%. The estimated positive agreement increased to 96 (83%) of 115, when TACO cases with missing information (no information available for three or more items n=11) were removed from the analyses.

All participating haemovigilance systems responded to the question about their use of the diagnosis of TAD. The majority (12) stated that they used TAD when other causes were ruled out; two either did not or rarely used TAD, one used TAD when circumstances associated with the patient or transfusion reaction, or both, were

	TACO (n=126)	TRALI (n=20)	TAD (n=22)	Other (n=10)
Evidence of respiratory distress (new or worsened)	119 (94%)	19 (95%)	22 (100%)	9 (90%)
Manifested by (open-ended response)				
Dyspnoea	70 (56%)	12 (60%)	16 (73%)	4 (40%)
Wheezing	19 (15%)	0	1 (5%)	1 (10%)
Tachypnoea	18 (14%)	4 (20%)	4 (18%)	0
Shortness of breath	15 (12%)	2 (10%)	1 (5%)	0
Hypoxia	15 (12%)	4 (20%)	4 (18%)	1 (10%)
Evidence of pulmonary oedema	110 (87%)	20 (100%)	15 (68%)*	9 (90%)
Clinical examination (multiple choice)				
Cyanosis or hypoxia in absence of other specific causes†	57 (45%)	16 (84%)	12 (55%)	4 (40%)
Crackles on lung auscultation	30 (24%)	5 (25%)	3 (14%)	3 (30%)
Other‡	29 (23%)	5 (26%)	2 (9%)	1 (10%)
Orthopnoea or cough	17 (13%)	2 (11%)	1 (5%)	2 (20%)
None	26 (21%)	0	7 (32%)	3 (30%)
Pulmonary oedema on chest imaging				
Yes, new (if latest imaging showed no oedema or if no imaging done recently)	54 (43%)	13 (65%)	5 (23%)	7 (70%)
Yes, worsened	12 (10%)	1 (5%)	1 (5%)	0
No imaging done	18 (14%)	1 (5%)	2 (9%)	1 (10%)
None	9 (7%)	4 (20%)	6 (27%)	1 (10%)
Not recorded	33 (26%)	1 (5%)	8 (36%)	1 (10%)
Cardiovascular system changes	93 (74%)	17 (85%)	12 (55%)	8 (80%)
Enlarged cardiac silhouette at time of reaction				
Yes, larger than before in that patient	8 (6%)	0	0	0
Yes, larger than normal	11 (9%)	2 (10%)	0	3 (30%)
No imaging performed	21 (17%)	1 (5%)	4 (18%)	0 0
None	16 (13%)	7 (35%)	4 (18%)	1 (10%)
Not recorded	70 (56%)	10 (50%)	14 (64%)	6 (60%)
Other cardiovascular system changes unexplained by patient's condition (multiple choice)				
Tachycardia	57 (45%)	9 (45%)	6 (27%)	6 (60%)
Hypertension	53 (42%)	5 (25%)	5 (23%)	4 (40%)
Jugular venous distension	8 (6%)	0	1 (5%)	0
Peripheral oedema	10 (8%)	1 (5%)	0	0
Other	8 (6%)	5 (25%)	4 (18%)	0
Not reported	47 (37%)	4 (20%)	11 (50%)	3 (30%)
Increase in arterial blood pressure				
Yes (eg, ≥20 mm Hg)	45 (36%)	4 (20%)	5 (23%)	3 (30%)
Drop in blood pressure	7 (6%)	6 (30%)	2 (9%)	0
No clinically significant change	20 (16%)	2 (10%)	6 (27%)	0
No information	54 (43%)	8 (40%)	9 (41%)	7 (70%)

(Table 3 continues on next page)

	TACO (n=126)	TRALI (n=20)	TAD (n=22)	Other (n=10)
(Continued from previous page)				
Evidence of fluid overload	56 (44%)	4 (20%)	1 (5%)	5 (50%)
Fluid overload				
Positive fluid balance	17 (13%)	4 (20%)	0	4 (40%)
Diuretic response to treatment and clinical improvement	39 (31%)	0	1 (5%)	1 (10%)
None	5 (4%)	4 (20%)	7 (32%)	1 (10%)
Not applicable	3 (2%)	2 (10%)	0	1 (10%)
Not recorded	62 (49%)	10 (50%)	14 (64%)	3 (30%)
Weight change				
Increase from weight before transfusion	1 (1%)	0	0	0
Not recorded	125 (99%)	20 (100%)	22 (100%)	10 (100%)
Elevation in B-type natriuretic peptide concentrations	25 (20%)	1 (5%)	2 (9%)	3§ (30%)
Brain natriuretic peptide or N terminal-pro brain natriuretic peptide (at or soon after reaction)				
Above normal, no value for comparison	15 (12%)	0	1 (5%)	0
Rise 1·5 times concentration before transfusion	10 (8%)	1 (5%)	1 (5%)	3 (33%)
Not elevated	3 (2%)	2 (10%)	1 (5%)	2 (22%)
Not recorded	63 (50%)	10 (50%)	13 (59%)	3 (33%)
Not established	35 (28%)	7 (35%)	6 (27%)	2 (22%)

TACO=transfusion-associated circulatory overload. TRALI=transfusion-associated acute lung injury. TAD=transfusion-associated dyspnoea. *This question was answered for 19 of 22 TAD cases. †Cyanosis was inadvertently duplicated by being listed in this position in the validation form; it is (only) listed under the features of respiratory distress in the final 2018 version. ‡Open-ended response; responses included drop in oxygen saturation, tachypnoea, intubation required, wheeze, and bilateral crackles on auscultation. §This question was answered for nine of ten other cases.

Table 3: **Comparison of features in respiratory reaction cases reported in part 1 of the study using the April 2017 proposed TACO reporting criteria**

complicated, and one used TAD when multiple potential causes existed.

For each case, information on the number of blood units transfused (171 cases, 96%) or estimated volume transfused (114 cases, 64%), or both, was provided. This information is summarised in the appendix (p 7). The median total volume of blood components transfused in the reported TRALI cases (622 mL, IQR 349–2088; median 3 units, IQR 1–9) was approximately double the median volume for the TACO cases (305 mL, IQR 250–520; median 2 units, IQR 1–2; appendix p 7).

In part 2, 47 respondents who self-classified as blood-banking professionals (24, 51%), haematologists (nine, 19%), clinicians (six, 13%), and other health-care professionals (eight, 17%) from 20 countries participated. Nine (75%) of 12 TACO cases were classified as TACO by more than 50% of the respondents; their classifications are given in the appendix (p 8). Overall agreement was moderate, with κ 0·43. The category-wise κ statistics were 0·54 (moderate agreement) for TACO cases, 0·45 (moderate agreement) for TRALI cases, 0·36 (fair agreement) for TAD cases, and 0·35 (fair agreement) for other cases. All κ values represent statistically significant agreement above the null hypothesis of no agreement. Detailed review of the TACO cases showed that the absence of information in the case reports was the main reason for the low congruence. With exclusion of these (four) cases, the overall agreement among all respondents was good, with κ 0·50, and the category-wise estimate for TACO cases increased to κ 0·65.

Discussion

The two-part validation exercise showed that the revised 2018 TACO surveillance case definition (version 4; table 2) captures 76% of cases endorsed as TACO by participating haemovigilance systems. This percentage is an improvement on the 2011 ISBT-IHN definition, under which only slightly more than half of reported cases were assessed as highly likely or probably cases of TACO in the 2013–14 analyses by SHOT.[2,16] Capture of cases improved after the exclusion of cases that were missing essential data—a familiar problem in haemovigilance systems.

However, these revised criteria are not effective to distinguish between TACO and other complications of transfusion, which have a respiratory component. The poor negative agreement constitutes a limitation of the revised definition, and results from the emphasis on core criteria, of which respiratory compromise and pulmonary oedema (ie, two of the requisite three criteria) are present in cases of TRALI and generally manifest within 6 h. Moreover, patients with TRALI might also exhibit unanticipated cardiovascular changes. The same problem arises in the clinical setting, where sometimes only a detailed evaluation of clinical examination findings, imaging, and biochemical parameters, and the response to therapy enables the most probable diagnosis to be established. The 2018 TACO surveillance case definition incorporates explanatory notes on specific findings in vital parameters, physical examination, and imaging, which can support clinicians in differential diagnosis and guide haemovigilance assessors in classifying a case (table 4).

The basis of circulatory overload leading to pulmonary oedema is generally perceived to be a problem of relative volume overload, with increased hydrostatic pressure leading to fluid transudates in the lung. However, recent work suggests that an inflammatory component might exist in some patients with TACO.[21,22] Investigation of this component is beyond the scope of our validation study; however, a context note in the definition states that some patients with TACO show an increase in body temperature, as reported by several haemovigilance systems.[1,23–25]

We are unable to draw conclusions from the volume data collected in this study (appendix p 7), which was focused on the definition; however, the finding that a patient might be tipped into TACO by a small volume of blood components is relevant and replicates earlier findings.[8,26] Learning points from SHOT include the warning that TACO can occur after transfusion of small

volumes of red blood cells, even one unit or less (2010);[26] the recommendation, "don't give two without review" (2013);[2] and the repeated finding that "lack of attention to appropriate red cell dose leads to TACO" (2017).[1]

Concurrently with this validation study, experts in anaesthesiology and intensive care have convened with blood bankers and haemovigilance professionals to develop a revised TRALI definition because of evidence and insights that have accrued since the 2004 Toronto Consensus Conference on TRALI.[27] Assessment of the applicability of the updated TRALI definition in clinical practice and haemovigilance will be essential.

A substantial change to the 2018 revised TACO definition (already present in the April 2017 draft) is the acceptance of cases arising up to 12 h after transfusion. This change was based on the SHOT analyses, and members of the revision group from other haemovigilance systems endorsed the finding that TACO might occasionally become apparent more than 6 h after transfusion. An extension to 24 h was discussed and rejected on the basis that exclusion of non-TACO cases (negative agreement) would become poorer.

One of the permutations of the parameters in the 2017 draft TACO case definition was based on any three out of five (version 3; table 2). The positive percentage agreement for capturing TACO cases was equivalent to other versions; however, this version was rejected by the revision group because it would allow a case with neither respiratory distress nor pulmonary oedema to be classified as TACO. The decision to require a pulmonary component was unanimous within the revision group, even though this constituted a small deviation from the US Centers for Disease Control and Prevention National Healthcare Safety Network Hemovigilance Module definition (table 1). From the international surveillance perspective, TACO has always been considered as a pulmonary complication of transfusion.[7,13] For surveillance purposes, the establishment of criteria to collect the most clear-cut cases is legitimate. As a consequence of this decision, our results cannot be generalised to transfusion reactions without respiratory features.

This study arises from within the field of haemovigilance, with the well recognised limitations that cases might be only partially investigated, have incomplete recording of examination findings, or absent fluid balance or bodyweight data. It is a practical difficulty for many haemovigilance systems that—particularly where hospital contacts are laboratory based—clinical details might be less accessible than laboratory information. The inclusion of cases with incomplete information in part 2 could be considered a limitation; however, the cases came from established haemovigilance systems and the full set was included in the main analyses.

Some features, such as presence of a positive fluid balance, are listed without stating a cutoff. In the absence of specific evidence, clinical judgement as to relevant values should be applied. The aim of this study was not to establish specific parameters or cutoffs. In future, with accruing evidence, a further update of the definition is likely to become necessary.

Other limitations are imposed by the insufficient knowledge of the true incidence of TACO in patients who received transfusions. Also, in the absence of a gold standard, it was not possible to state the sensitivity and

	TACO	TRALI	TAD*
Respiratory compromise	Yes	Yes	Yes
Risk factors	Cardiovascular, renal, pulmonary disease	Direct lung injury (aspiration, pneumonia, toxic inhalation, lung contusion, near drowning); indirect lung injury (severe sepsis, shock, multiple trauma, burn injury, acute pancreatitis, cardiopulmonary bypass, drug overdose); donor antibodies to HLA or HNA may be found (incompatible with recipient HLA or HNA)	Unknown
Pulmonary oedema	Yes	Yes	Unknown
Crackles on auscultation	Yes	Yes	Unknown
Wheezing	May occur	May occur	Unknown
Diagnosis clinically supported if	Orthopnoea; raised jugular venous pressure; frothy sputum in severe cases (may be pinkish)	Copious frothy sputum (typically pinkish)	Unknown
White lung fields on imaging	Yes	Yes	Unknown
Enlarged cardiac silhouette or widened vascular pedicle	Likely	No	Unknown
Diagnosis supported if	Kerley B lines, peribronchial cuffing; may be pleural fluid	Typically no pleural fluid	Unknown
Onset	During or up to 12 h	During or up to 6 h	During or up to 24 h
Positive fluid balance	Yes	No	No
Diuretic response	Yes (with clinical improvement)	No	No
Increase of natriuretic peptide concentration	Yes (may also be elevated before transfusion)	No or some elevation	Unknown
Weight change	Likely	Unlikely	Unlikely
Cardiovascular system changes	Yes	Possible	Unknown
Tachycardia	Yes	Yes	Unknown
Hypotension	Possible	Likely	Unknown
Hypertension	Likely	No	Unknown
Widened pulse pressure	Likely	No	Unknown
Transient white blood cell count decrease	Unknown	Possible	Unknown
Temperature increase	Possible	Possible	Unknown

TACO=transfusion-associated circulatory overload. TRALI=transfusion related acute lung injury. TAD=transfusion associated dyspnoea. HNA=human neutrophil antigens. *For a classification of TAD, TRALI and TACO must be excluded.

Table 4: **Comparison of characteristics of respiratory adverse transfusion events**

specificity. The calculated positive and negative agreement are similar in intent but had to be based on previous assessment by established haemovigilance systems.

It is a strength of the definition that a case could be reported as TACO even without imaging. This finding is relevant in high-income countries, where patients with suspected TACO are commonly diagnosed and treated without radiography, contributing to judicious use of resources and minimising exposure to radiation. Moreover, it extends the usefulness of the definition to clinical and haemovigilance settings in low-income and middle-income countries.

The availability of natriuretic peptide concentrations in the cases was so sporadic, that it was irrelevant at the current state of practice. Despite this, the revision group incorporated it as a non-obligatory feature, because of possible increased use in the future, and for highlighting its limitations and potential usefulness. There is support in the literature for the statements regarding a normal post-transfusion BNP and the 1·5-times increase in BNP.[28,29] In view of the likelihood of new evidence, the definition was reworded so that it refers to relevant changes in biomarkers.

One area was intentionally not addressed in the revision process: that of assessing the imputability or likelihood with which the observed reaction can be ascribed to the transfusion. All cases provided by the haemovigilance systems in part 1 were included in the main analyses because the imputability is not of importance for the definition. Imputability is distinct from the diagnostic certainty, and the imputability assessment takes place after deciding that a report meets the case definition. The ISBT provides generic imputability criteria applicable to all non-infectious transfusion reactions, whereas the US haemovigilance systems provides reaction-specific criteria for the imputability. At present, as far as we are aware, no evidence exists for increased uniformity of imputability assessment with specific imputability criteria.

With the present results, the 2018 revised TACO case surveillance definition has shown improved positive agreement and usability for classification of haemovigilance cases. The annual SHOT analyses (2013–17) of TACO cases document progressive improvement of agreement with the updated drafts and 89 (97%) of 92 of the 2017 cases met the criteria of the 2017 version.[1,2,14,16,17] An analysis from the USA, likewise showing improved agreement, was recently presented at the 2018 AABB annual meeting.[30]

The 2018 revised definition will be disseminated through newsletter articles, webpage updates, and advocacy for professionals to implement the revised TACO surveillance definition in national and international work. This revised definition will provide an international point of reference for haemovigilance, education, clinicians, and researchers in this area. Use of the revised definition by haemovigilance organisations, health-care institutions, and researchers will facilitate comparison and sharing of data, and will support research and the development of recommendations for the prevention and treatment of this transfusion complication.

Contributors

All authors participated in the definition revision process. JCW-O, BW, SG, KL, CA, and PB-M developed the validation protocol, for which the other authors provided comments and critical input. GP and SR developed the online validation questionnaires and GP did the analyses. JCW-O drafted the main text of the Article, and GP wrote the results section and prepared the tables and figures. All authors critically reviewed the data analyses and Article, contributed to improvement of the text and agreed to its submission. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

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