Transfusion-associated circulatory overload in ambulatory patients

Jock D. Simpson,1,2 Adam Hopkins,2 Adilah Amil,2 Bryony Ross1,2,3 and Anoop K. Enjeti1,2,3,4,5

1Haematology Department, Calvary Mater Newcastle, Waratah, NSW, Australia
2School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia
3NSW Health Pathology - Hunter, New Lambton Heights, NSW, Australia
4Hunter Medical Research Institute, New Lambton, NSW, Australia
5Hunter Cancer Research Alliance, Callaghan, NSW, Australia

Background and Objectives Transfusion-associated circulatory overload is a leading cause of transfusion-related adverse events. The frequency and risks for transfusion-associated circulatory overload in ambulatory haematology patients are not known.

Materials and Methods A retrospective cohort analysis of ambulatory patients transfused in a tertiary haematology centre, using medical records and an electronic transfusion database, was undertaken between January and December 2014. Variables studied included age, gender, diagnosis, heart failure, kidney disease and details of transfusions. Transfusion-associated circulatory overload was defined according to proposed International Society of Blood Transfusion criteria. Patients with clinical evidence of hypervolaemia, not meeting the TACO definition and/or who were prescribed otherwise unscheduled diuretic agent, were collectively deemed to be at ‘risk of clinically significant hypervolaemia’ (ROCSH).

Results In the study period, 93 ambulatory patients (male = 49, female = 44, mean age = 75.89 ± 11.37 years) attended 715 transfusion encounters, totalling 1536 packed red cell units. No cases of TACO occurred whilst ‘ROCSH’ events occurred in 57/715 (8%) of transfusion encounters. In a univariate model, age was significantly associated with ‘ROCSH’, odds ratio = 1.05 (P = 0.017 95%, CI 1.01–1.09) and no factors were significant on multivariate analysis.

Conclusions Transfusion-associated circulatory overload occurs infrequently in ambulatory haematology patients receiving ambulatory blood transfusions. To our knowledge, this is the first study to report on occurrence and risk factors for circulatory overload in ambulatory transfusions. This study provides vital baseline data for future prospective studies on this important aspect of haemovigilance.

Key words: ambulatory transfusions, haemovigilance, hypervolaemia, TACO.

Introduction

Transfusion-associated circulatory overload (TACO) is a major source of morbidity and mortality, as reported in the UK-based Serious Hazards of Transfusion (SHOT) haemovigilance programme [1]. TACO was also identified as a leading cause of transfusion-associated mortality in a recently published analysis of The International Haemovigilance Network’s adverse reaction and event database [2]. In the United States, TACO is the second most common cause of transfusion-related mortality reported to the Food and Drug Administration [3]. It is often regarded as a preventable event, with excessive transfusion being a modifiable risk factor [4]. Risk factors for
circulatory overload also include coexisting cardiac and/or renal impairment, increasing age, severe anaemia, and pre-existing positive fluid balance [5–8].

The International Society of Blood Transfusion (ISBT) defines TACO as the development of any four of the following within 6 hours of blood transfusion: acute respiratory distress, tachycardia, increased blood pressure, acute or worsening pulmonary oedema on frontal chest radiograph, evidence of positive fluid balance and an elevated Brain Natriuretic Peptide (BNP) [9]. A draft revision of these criteria is currently available for public comment with notable changes including a requirement for respiratory distress, and an extension of the interval between transfusion and symptoms to 12 h [10]. These definitions have evolved from experience in predominantly unwell hospitalized patients but no specific guidance exists for ambulatory patients.

Estimates of TACO incidence in published literature range from 1% to 8% [11–15]. These estimates are from peri-operative cohorts, medical emergency units, inpatients at tertiary care facilities and haemovigilance registries. The reported incidence varies depending on whether active or passive surveillance techniques are employed, with active surveillance resulting in higher estimates [8, 16].

Currently, there is a dearth of evidence for frequency and risk factors for TACO in an exclusively ambulatory care setting. We hypothesize that the frequency of circulatory overload in outpatients is likely to be different from inpatients. Several factors which directly influence risk such as age, comorbidities including coexisting renal and heart failure, volume and rate of red cell transfusion, and lack of additional parenteral therapies in ambulatory patients compared to hospital inpatients.

We undertook a retrospective analysis which included cohort with active clinical surveillance. This study aimed to evaluate the frequency and risk factors for circulatory overload in ambulatory transfusion dependent patients.

Materials and Methods

A retrospective cohort analysis of ambulatory patients transfused in a tertiary haematology centre (Calvary Mater Newcastle, New South Wales, Australia) was undertaken in a 12-month period between January and December 2014. Patients were included if they had a packed red blood cells (PRBC) transfusion in the haematology ambulatory care unit within the study period. Any emergency and inpatient admission transfusion episodes that occurred within this period were excluded. Electronic medical records, electronic transfusion database and patient medical file were reviewed for transfusion-related information. All blood products administered were universally leucodepleted and sourced from the Australian Red Cross Blood Service.

Patients had a planned active clinical surveillance within 30 minutes of completion of the PRBC transfusion. This included routine vital sign assessment and a mandatory medical review completed for clinical signs or symptoms of circulatory overload. These assessments were performed as routine clinical practice within the unit. Diuretic therapy if necessary was based on clinical findings, guided by clinical symptoms. Our retrospective analysis evaluated the patient records specifically for documented evidence of dyspnoea, abnormal vital signs, peripheral oedema, elevated jugular venous pulse and auscultation of the cardiovascular system for evidence of pulmonary oedema. Where there was any evidence of circulatory overload post-transfusion, cases were further evaluated to determine whether subsequent diuretic therapy, investigations and/or inpatient management were required, in consultation with a senior haematology registrar and/or consultant. The outcome of TACO was assessed according to the current International Society of Blood Transfusion (ISBT)-TACO diagnostic criteria, specifically, any four of the following: acute respiratory distress, tachycardia, increased blood pressure, acute or worsening pulmonary oedema on frontal chest radiograph, evidence of positive fluid balance, occurring within 6 h of transfusion an elevated Brain Natriuretic Peptide (BNP) as being supportive of TACO [9]. Patients meeting some but not all ISBT diagnostic criteria for TACO, and/or those who were prescribed otherwise unplanned diuretic therapy after medical review were identified as a cohort at ‘risk of clinically significant hypovolaemia’ (ROCSH). Any subsequent investigations such as X-ray and/or BNP level, if undertaken, were also evaluated. All patients who were readmitted within 24 h after a planned ambulatory transfusion were also assessed for evidence of TACO during that re-admission.

Variables evaluated included age, gender, haematological diagnosis, documented chronic heart failure (CHF) or chronic kidney disease (CKD) (CHF or CKD considered as present if documented as a comorbidity in clinical notes), estimated Glomerular Filtration Rate (eGFR), units of PRBC received and post-transfusion medical review. The transfusion episode data were obtained from the electronic transfusion database and the electronic discharge summary for each encounter. If the transfusion database and discharge summary were discordant, the transfusion chart in the medical file was reviewed to resolve the discrepancy. Data were independently collected and collated by two of the authors (AH and AA). Discrepancies were resolved by third author (JS), and cases identified as potential TACO or ROSCH were further evaluated by two
senior authors, both haematologists with transfusion expertise (JS and AKE).

Statistical analyses were programmed using Stata v13.0 (StataCorp Ltd, College Station, TX). Logistic regression adjusted for multiple encounters of each patient (cluster) were used to measure associations between the outcome (ROSCH) and patient covariates. Continuous variables were tested and observed to be linear to the logit. Variables were selected for entry into the statistical models based on a review of existing evidence for reported variables in literature.

This study was approved by the Hunter New England Local Health District Clinical Ethics Committee (Number: AU201705-11).

**Results**

During the study period, a total of 93 subjects were transfused a total of 1536 units of packed red blood cells (PRBC) across 715 transfusion encounters. The mean age of the cohort was 75.9 (±11.4) years and included 49 males and 44 females. The underlying haematological diagnoses included a range of bone marrow failures and/or transfusion dependent anaemias as shown in Figure 1. At baseline, 13 (14%) and 17 (18.3%) of subjects had a documented history of CHF and CKD, respectively. The baseline demographics are summarized in Table 1.

The median number of PRBC transfused was 2 per encounter (range 1–4). The median cumulative number of transfusions received per patient was 7 (range 1–58). As no cases of TACO were identified, further TACO-associated risk factor assessment was not undertaken. Of the patients readmitted within 24 h of an ambulatory transfusion, none were deemed to have TACO.

At total of 57 episodes (in 32 patients) were identified as ROCSh. There were 19 patients with a single episode and 13 with multiple episodes. No statistically significant differences in baseline demographic data were observed between patients who had a ROCSh event, and those that did not (Table 1). A univariate analysis for association of ROCSh with age, gender, CHF, CKD, PRBCs received per encounter and cumulative units received was undertaken (Table 2). This showed that age was significantly associated with having an episode of ROCSh, odds ratio = 1.05 \(P = 0.017, 95\% \text{ CI } 1.01–1.09\). A multivariate analysis adjusting for both units RPBC per encounter and cumulative PRBC units did not show any significance for any of the variables (data not shown). In addition, CHF, CKD, units received and cumulative units received were not statistically significant predictors in either univariate or multivariate analyses.

**Discussion**

This is the first report of frequency and risks factors for TACO in ambulatory transfusions. No episodes of TACO occurred in 93 patients receiving 1536 packed red cell units on 715 occasions over a 12 month period. However, ROCSh occurred in 57 (8%) of transfusion episodes in the ambulatory patients.

The absence of post-transfusion hypervolemia as per the prevailing ISBT-TACO diagnostic criteria is the major finding. Existing estimates of TACO incidence range from 1% to 8% of transfusions. However, these are derived from patient cohorts in markedly different clinical contexts to ambulatory haematology care such as peri-operative care, medical emergency units, inpatients at tertiary care facilities and haemovigilance registries [11–15].

![Figure 1 Underlying haematological disorder in the study patients](https://wileyonlinelibrary.com)
Despite the absence of TACO, post-transfusion clinical review resulted in patients receiving otherwise unplanned diuretic therapy at a frequency of 8% of transfusion encounters. Such patients were felt to be at risk of clinically significant hypervolaemia, and consequently received diuretics to prevent fluid overload. We coined the term ‘ROSCH’ to recognize that in real-world transfusion practice, there are patients at risk, who do not meet all criteria for TACO but nonetheless deemed to have some risk of circulatory overload based on bedside clinical assessment. It is acknowledged that there is an inherent risk of bias in such active clinical surveillance in post-transfusion patients, particularly in those with a past history of CKD and CHF or previous diuretic therapy. On the other hand, it does provide an insight into real-world practice, where a surveillance clinical review may minimize progression of ROSCH to TACO.

The UK Shot analysis observed that 57% of TACO cases occurred over the age of 70 years of age [4]. In our analysis, for each additional year of age, the odds of a ROSCH event increased by a factor of 1.05 (5%). Advancing age has been shown to be a risk factor for TACO by several investigators [17, 18]. Interestingly, a case–control study evaluating cases of severe TACO found an inverse association between age and TACO risk, an unanticipated finding, which prompted authors to hypothesize that a more conservative transfusion practice in elderly patients could explain this observation [8]. In our study, the mean patient age was 75.9 (range 25–96) years, which is reflective of patients routinely encountered in ambulatory transfusion practice. The absence of TACO events, despite the inclusion of elderly patients, is thus, a notable finding. We observed age to be significantly associated with having an episode of ROCSH, odds ratio $= 1.05$ ($P = 0.017$, 95% CI 1.01–1.09) in a univariate model; however, the significance was not seen in the multivariate model.

Important risk factors for TACO in the inpatient setting include CKD and CHF. Whilst CKD is widely regarded as a risk factor for TACO, and biologically plausible, the association is not consistently demonstrated. Although one case–control study found an association, a prospective cohort

<table>
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<tr>
<th>Risk of clinically significant hypervolemia (ROSCH)</th>
<th>No</th>
<th>Yes</th>
<th>Total</th>
<th>$P$-value</th>
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<tr>
<td>n = 62 (%)</td>
<td>n = 31 (%)</td>
<td>n = 93 (%)</td>
<td></td>
<td></td>
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<td>Age</td>
<td>79.7 (10.17)</td>
<td>73.98 (11.53)</td>
<td>75.89 (11.37)</td>
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<td>Median (min, max)</td>
<td>82 (54, 96)</td>
<td>75 (25, 93)</td>
<td>78 (25, 96)</td>
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<tr>
<td>Gender</td>
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<td></td>
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<tr>
<td>Male</td>
<td>30 (48.4%)</td>
<td>19 (61.3%)</td>
<td>49 (52.7%)</td>
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<tr>
<td>Female</td>
<td>32 (51.6%)</td>
<td>12 (38.7%)</td>
<td>44 (47.3%)</td>
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<td>13 (14%)</td>
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<tr>
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<td>4 (4.3%)</td>
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<tr>
<td>Chronic kidney disease</td>
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<td></td>
<td></td>
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<td>25 (80.6%)</td>
<td>72 (77.4%)</td>
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<tr>
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<td>6 (19.4%)</td>
<td>17 (18.3%)</td>
<td></td>
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<td>4 (6.5%)</td>
<td>4 (4.3%)</td>
<td></td>
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<tr>
<td>eGFR</td>
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<td></td>
<td></td>
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<td>31–90</td>
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<td>4 (12.9%)</td>
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<td>Number of ROCSH episodes</td>
<td></td>
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<td>0</td>
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<td>1 (3.2%)</td>
<td>1 (1.1%)</td>
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</table>

*eGFR = estimated glomerular filtration rate, PRBC = packed red blood cells.*
study in a medical intensive care unit found this association was not statistically significant [8, 19]. In our series, the rate of CKD was comparable to or lower than published TACO cohorts [7, 8]. CHF is regarded as an important risk factor for TACO as multiple groups have demonstrated the association between CHF and TACO [8, 19]. The frequency of CHF in our cohort, both overall and in patients with ROCSh events, was lower compared to other published cohorts of TACO [7, 19]. This analysis failed to identify pre-existing CHF or CKD as being positively associated with ROCSh events. This may be due to the fact that the outpatients are generally more stable compared to inpatients. The transfusion volume, in the former is generally limited to 1–2 PRBC units per day and it is uncommon for outpatients to be receiving additional intravenous therapies in the same encounter.

Mandatory active clinical surveillance with medical review post-transfusion was a key clinical practise that was uniformly practised during the duration of this study. This was undertaken in all ambulatory transfusions irrespective of age or clinical risk factors and potentially influenced the results of this study. In the subset of patients who had signs of positive fluid balance and/or were prescribed diuretics, whether a few may have subsequently developed TACO, without the medical review for fluid overload, is uncertain. We propose to prospectively follow a cohort of patients with and without medical review to ascertain the role of the medical review in post-ambulatory transfusions in preventing ROCSh or TACO.

Our cohort had an even gender balance, an average age of 75.9 years, a CHF rate of 14% and CKD rate of 18.3%. As our cohort included all patients transfused on our service, it is reflective of the real-world ambulatory haematology population. Therefore, the findings of this study are generalizable to other ambulatory haematology units. Thus, the absence of TACO in this population is an important observation.

The limitations of this study include a small sample size and a single centre retrospective design. Nonetheless, based on our findings, it can be surmised that transfusions in the ambulatory context carry a lower risk of TACO than suggested by existing estimates in other clinical contexts.

Active post-transfusion surveillance is not routine clinical practice in most ambulatory centres. The lack of pre-transfusion medical review, apart from measurement of vital signs at baseline, as well as inter-individual medical officer variation in post-transfusion medical surveillance review might contribute to measurement error and/or bias. Some of the parameters such as JVP have inter-observer variability; however, this was used in conjunction with other clinical findings such as auscultation [20]. In the absence of any existing estimate of TACO in ambulatory patients, this study provides a valuable starting point for prospective efforts using standardized assessment tools.

The ISBT-TACO definition and criteria are not specific for the outpatient setting [9, 10]. TACO, by definition is a severe medical event, and thus our review of readmissions post-transfusion will have captured any patients who presented beyond 6 h. The time window of 6–12 h, as mentioned in this definition, exceeds the usual post-transfusion observation periods in most ambulatory care units. BNP and chest radiography are not routinely assessed post-transfusion in the outpatient setting unless TACO is clinically suspected.

The ISBT-TACO criteria, both current and proposed, have evolved from experience and observations in predominantly unwell hospitalized patients. It does not provide specific guidance for ambulatory patients. It is also likely to be less sensitive for identification of mild to moderate volume status changes that is observed in ambulatory transfusions. The proposed new criteria with the requirement for respiratory distress will enable easier the categorization of post-transfusion hypervolaemia, as ROSCH without any additional criteria or as TACO. Haemovigilance organizations may wish to consider an entity such as ROSCH, so that moderate volume status changes which are clinically important are not overlooked in ambulatory transfusion medicine.

Directions for future research include incorporating TACO surveillance into larger, multi-site ambulatory care-based haemovigilance activities. This would allow a more definitive evaluation of the incidence TACO in this important, highly transfused, population including evaluation of specific populations at risk (such as CKD and
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Conflicts of interest

There are no conflicts of interest to declare for any of the Authors.

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