VoxSanguinis
The International Journal of Transfusion Medicine

ISBT International Society of Blood Transfusion

Vox Sanguinis (2018) **113**, 386–392

DOI: 10.1111/vox.12647

ORIGINAL PAPER

Transfusion-associated circulatory overload prevention: a retrospective observational study of diuretic use

Y. Lin,[1,2,3] R. Cohen,[1,3,4] C. Armali,[1,3,4] J. Callum,[1,2,3] C. Cserti-Gazdewich,[2,3,4] L. Lieberman[2,3,4] & J. Pendergrast[2,3,4]

[1]*Department of Clinical Pathology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*
[2]*Department of Laboratory Medicine & Pathobiology, University of Toronto, Toronto, ON, Canada*
[3]*University of Toronto QUEST Research Program, Toronto, ON, Canada*
[4]*Laboratory Medicine Program, University Health Network, Toronto, ON, Canada*

Vox Sanguinis

Received: 29 December 2017, revised 8 February 2018, accepted 13 February 2018, published online 8 March 2018

Background and Objectives Approaches to preventing transfusion-associated circulatory overload (TACO) include the use of diuretics. The purpose of this study was to determine how commonly diuretics are prescribed in patients receiving a red-blood-cell (RBC) transfusion.

Materials and Methods This was a retrospective study of 200 adult inpatient RBC transfusion orders, 50 consecutive at each of four academic institutions. Only the first transfusion order for each patient was included. Only 1 or 2 unit orders were included. The primary outcome was the percentage of patients receiving furosemide peri-transfusion. Secondary objectives included the dose, route, and timing of furosemide and the association of clinical factors with ordering furosemide.

Results The median age was 62·5 years (IQR 53, 73), and 52% were female. Peri-transfusion furosemide was ordered in 16% (95% CI 11–21%). The most common dose was 20 mg (55%), the route intravenous (90%) and timing post-transfusion (74%). At least one risk factor for TACO was present in 55% of patients: renal dysfunction (33%), older than 70 years (28%), history of congestive heart failure (18%), ejection fraction <60% (16%) and diastolic dysfunction (5%). Low haemoglobin as an indication for transfusion (OR 4·2; 95% CI 1·4–12·8) and diuretics on admission (OR 3·5; 95% CI 1·5–8·0) were associated with ordering furosemide peri-transfusion.

Conclusions Furosemide is not routinely ordered for RBC transfusion, even in patients with risk factors for TACO. Studies assessing the safety, efficacy, optimal dose, and timing of furosemide in preventing TACO are justified.

Key words: furosemide, prevention, transfusion-associated circulatory overload.

Introduction

Transfusion-associated circulatory overload (TACO) is one of the leading causes of transfusion-associated mortality [1–3]. Its prevalence varies depending on the type of reporting and the patient population, with estimates ranging from 1 in 5932 components transfused to 1 in 28 873 components issued in passive haemovigilance systems [4, 5] to 1–11% of transfused patients with active reporting [6–8]. Significant morbidity has been described with up to 18% requiring transfer to intensive care [9]. Thus, finding mitigating strategies is key to improving transfusion safety.

Unlike other risks of transfusion such as infectious risks or transfusion-related acute lung injury where mitigating interventions have focused on the blood supply, risk factors for TACO appear to be inherent to the recipient or the transfusion order. These risk factors include older age, positive fluid balance, increased number of

Correspondence: Yulia Lin, Department of Clinical Pathology, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Room B2-04, Toronto, ON M4N 3M5, Canada
E-mail: yulia.lin@sunnybrook.ca

units transfused, left ventricular systolic or diastolic dysfunction, history of congestive heart failure and chronic kidney disease [9–11]. Because the recipient risk factors are often non-modifiable, focusing on avoiding unnecessary transfusion and how the transfusion is administered are key. However, even if a clinician identifies a patient at high risk for TACO, no studies have been completed to date to determine which interventions will help reduce the incidence and severity of TACO in these patients [12]. Several approaches to preventing TACO have been suggested [13] and include decreasing the volume of transfusion, slowing the rate of infusion and prescribing diuretics, namely furosemide. In this report, we aim to determine how often patients are prescribed furosemide concomitantly with red-blood-cell (RBC) transfusion so as to understand current practices in planning for future studies of furosemide therapy for TACO prevention.

Materials and methods

This study was a retrospective audit of 200 adult inpatient RBC transfusion orders consisting of 50 consecutive orders at each of four academic institutions starting July 1, 2016. Only the first transfusion order for each patient was included. Transfusion orders for more than 2 units at a time were excluded. Consecutive transfusions were identified retrospectively through the blood bank laboratory information system, and then, the hospital electronic medical record and chart were reviewed. Data collected included patient demographics and risk factors (age, gender, admitting diagnoses, comorbidities, history of heart failure, left ventricular systolic or diastolic dysfunction, renal dysfunction, blood components transfused in the preceding 24 h, fluid balance if available), clinician demographics (specialty) and order details (indication, number of units, infusion rate, furosemide prescription, dose, timing and route of administration). A history of heart failure was deemed to be present if this was documented in the medical chart. Systolic dysfunction was defined as an echocardiogram or multigated acquisition (MUGA) scan showing ejection fraction <60%. Diastolic dysfunction was defined if noted on the echocardiogram report. Renal dysfunction was defined as a glomerular filtration rate of <60 ml/min or a creatinine above the normal range of the hospital site. Blood components transfused in the preceding 24 h included other RBC units, platelets, plasma and cryoprecipitate (intravenous immunoglobulin and albumin were not included). Fluid balance for the preceding 24 h was documented based on chart documentation and was considered not available if the patient had been in hospital for less than 24 h. Indications for transfusion were categorized as follows: low haemoglobin without symptoms, active bleeding, symptomatic anaemia, preoperative transfusion (within 48 h prior to the operation), intraoperative transfusion and postoperative transfusion (within 48 h after the operation). For the indication of low haemoglobin without symptoms, no specific haemoglobin level was defined; this was assumed to be the indication when no symptoms, bleeding or operation were noted in the chart. More than one indication could be chosen for a transfusion. The ordered infusion rate was based on the physician's transfusion order. In cases where the order was written as over 2–3 h, the average time was taken (i.e. 2·5 h). The actual infusion rate was determined by the documented start and stop time of the transfusion. Where two units were administered, the average of the first and second unit infusion rates was calculated. In addition, information was collected on whether the patient was on daily diuretics (loop, thiazide or potassium-sparing diuretics) prior to admission and whether it was discontinued in the 48 h prior to the index transfusion. For the timing of furosemide, pre-transfusion furosemide was defined as furosemide given within 2 h prior to transfusion (and not part of a daily furosemide order); and post-transfusion furosemide was defined as furosemide given within 2 h following transfusion. The post-transfusion furosemide was assumed to be prophylactic if no specific respiratory symptoms were reported.

At Site A, a pre-printed transfusion order set was mandatory for all non-urgent transfusions (exceptions included: trauma and the operating room) and included an option to select pre-transfusion furosemide. The order set was used in all transfusions included for Site A. Site A also had prospective screening by the medical laboratory technologist for compliance with transfusion guidelines promoting single unit transfusions for non-urgent transfusions. Sites B to D had the same transfusion guidelines as Site A, but no pre-printed transfusion order sets or prospective transfusion order screening for red blood cells was in place.

The primary objective was to determine the percentage of patients receiving furosemide peri-RBC transfusion. Secondary objectives included the dose, route and timing of furosemide administration and the association of clinical factors with ordering furosemide. Univariate analysis was performed to determine whether patient age, presence of risk factors for TACO, single unit (vs. 2 unit) transfusions, indication (low haemoglobin, symptomatic anaemia or bleeding), site or use of the pre-printed transfusion order set were associated with ordering of furosemide for RBC transfusion.

Descriptive variables were calculated using means with standard deviation for continuous variables (medians and interquartile ranges for non-normally distributed variables) and count and percentages for categorical variables. We used a sample size of 50 transfusion orders per

site which we had previously validated to be representative of appropriateness of transfusion orders [14]. Association of patient characteristics with the presence or absence of furosemide peri-transfusion was calculated using *t*-tests for continuous variables (or Wilcoxon rank sum tests for those with a non-normal distribution) and chi-square tests for categorical variables (or Fisher's exact tests in the case of low expected cell counts). A *P*-value <0·05 was used to denote statistical significance. Logistic regression was performed to assess the magnitude and strength of factors associated with ordering furosemide peri-transfusion. Based on the frequency distribution across the outcome (patients receiving furosemide peri-transfusion), only three factors could be selected for the logistic regression model. All analyses were run using SAS Version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

In July 2016, data on 200 RBC transfusion orders were collected, 50 from each site (Table 1). The median age was 62·5 years (IQR 53, 73) and 52% were female. The admitting diagnoses varied and differences among the sites reflected differences in each site's patient populations. Overall, at least one risk factor for TACO was present in 55% of patients (ranging from 32% to 76% at the four sites) (Table 2). The most frequent risk factors were the presence of renal dysfunction (33%), age older than 70 years (28%) and a history of CHF (18%). An echocardiogram or MUGA scan was performed in 99 (50%) patients, of whom 31 (31%) had an EF less than 60% and 10 (10%) had diastolic dysfunction. Fluid balance was only documented in 48 (24%) patients of whom 32 (67%) were positive. Twenty-three per cent of patients were on regular diuretics at the time of admission.

Transfusion order

Details of the transfusion are shown in Table 3. The most common indication was for low haemoglobin (66%), followed by active bleeding (17%) and symptomatic anaemia (12%). The median pre-transfusion haemoglobin was 70 g/l (IQR 67, 75). Eighty-two per cent of orders were single unit transfusion orders. The average infusion rate ordered was 1 unit over 1·9 h (0·5 units/h). The average actual infusion rate was 1 unit over 1·7 h (0·6 units/h). Site A with the use of the pre-printed transfusion order set had an average faster-ordered rate of 1 unit over 1·5 h compared to other sites at 1 unit over 2·4 h ($P = 0·02$). Site A also had an average faster actual infusion rate of 1 unit over 1 h compared to other sites at 1 unit over 2·3 h ($P < 0·0001$). The most common ordering specialties were oncology (26%), internal medicine (9%), critical care medicine (8%) and emergency (8%). No transfusion reactions, including TACO, were reported for any of the patients.

Use of furosemide

Peri-transfusion furosemide was ordered in 16% of cases (range 8–28% at four sites; 95% CI 11–21%). The most

Table 1 Patient demographics

	All *N* = 200	Site A *N* = 50	Site B *N* = 50	Site C *N* = 50	Site D *N* = 50
Median age (IQR)	62·5 (53, 73)	66·5 (57, 75)	59·0 (53, 69)	59·5 (49, 70)	64·0 (55, 79)
Female (%)	104 (52)	30 (60)	29 (58)	22 (44)	23 (46)
Admitting diagnoses (%)					
Cardiac	10 (5)	1 (2)	0 (0)	8 (16)	1 (2)
Cardiac surgery	15 (8)	4 (8)	0 (0)	11 (22)	0 (0)
Cerebrovascular	9 (5)	0 (0)	0 (0)	1 (2)	8 (16)
Gastrointestinal	19 (10)	7 (14)	0 (0)	3 (6)	9 (18)
Haematologic	6 (3)	2 (4)	1 (2)	0 (0)	3 (6)
Heme-oncologic	51 (26)	3 (6)	42 (84)	4 (8)	2 (4)
Non-cardiac surgery	32 (16)	6 (12)	0 (0)	15 (30)	11 (22)
Obstetrics	2 (1)	0 (0)	0 (0)	2 (4)	0 (0)
Oncology	23 (12)	6 (12)	7 (14)	8 (16)	2 (4)
Orthopaedic	14 (7)	3 (6)	0 (0)	0 (0)	11 (22)
Renal/Urologic	4 (2)	3 (6)	0 (0)	1 (2)	0 (0)
Respiratory	8 (4)	0 (0)	0 (0)	7 (14)	1 (2)
Trauma	10 (5)	10 (20)	0 (0)	0 (0)	0 (0)

IQR, interquartile range.

Table 2 Patient risk factors for TACO

	All *N* = 200	Site A *N* = 50	Site B *N* = 50	Site C *N* = 50	Site D *N* = 50
At least one risk factor for TACO (%)	110 (55)	26 (52)	16 (32)	38 (76)	30 (60)
Renal dysfunction (%)	65 (33)	16 (32)	8 (16)	22 (44)	19 (38)
Age >70 (%)	56 (28)	18 (36)	6 (12)	12 (24)	20 (40)
History of CHF (%)	35 (18)	6 (12)	2 (4)	15 (30)	12 (24)
Echo or MUGA performed (%)	99 (50)	15 (30)	32 (64)	33 (66)	17 (38)
Ejection fraction <60%	31 (16)	2 (4)	5 (10)	14 (28)	10 (20)
Diastolic dysfunction	10 (5)	1 (2)	0 (0)	5 (10)	4 (8)
Other blood products transfused in past 24 h (%)	37 (19)	7 (14)	16 (32)	11 (22)	3 (6)
Fluid balance documented (%)	48 (24)	16 (32)	14 (28)	12 (24)	6 (12)
Fluid balance positive (%)	32 (16)	13 (26)	7 (14)	7 (14)	5 (10)
Regular diuretics prior to admission (%)	46 (23)	10 (20)	6 (12)	14 (28)	16 (32)
Diuretics discontinued in 48 h prior to transfusion (%)	26 (13)	6 (12)	2 (4)	7 (14)	11 (22)

CHF, congestive heart failure; MUGA, multigated acquisition scan; TACO, transfusion-associated circulatory overload.

Table 3 Transfusion details

	All *N* = 200	Site A *N* = 50	Site B *N* = 50	Site C *N* = 50	Site D *N* = 50
Indication for transfusion (%)[a]					
Low Hb	132 (66)	24 (48)	48 (96)	33 (66)	27 (54)
Active bleeding	34 (17)	11 (22)	1 (2)	6 (12)	16 (32)
Symptomatic anaemia	23 (12)	13 (26)	1 (2)	4 (8)	5 (10)
Intraoperative transfusion	17 (9)	7 (14)	0 (2)	3 (6)	7 (14)
Postoperative transfusion	11 (6)	1 (2)	1 (2)	7 (14)	2 (4)
Median pre-transfusion Hb (g/l) (IQR)	70 (67, 75)	69 (67, 76)	72 (70, 74)	69 (67, 75)	68 (62, 75)
Pre-transfusion Hb <80 g/l (%)	170 (85)	40 (80)	48 (96)	42 (84)	40 (80)
Number of single unit transfusions (%)	164 (82)	41 (82)	48 (96)	40 (80)	35 (70)
Number of orders with infusion rate (%)	87 (44)	37 (74)	13 (26)	17 (34)	20 (40)
Infusion rate ordered (units/h) (SD)	0·5 (0·4)	0·6 (0·6)	0·4 (0·1)	0·4 (0·1)	0·4 (0·2)
Actual infusion rate documented (%)	109 (55)	29 (58)	17 (34)	27 (54)	36 (72)
Actual infusion rate (units/h) (SD)	0·6 (0·7)	1·0 (1·2)	0·4 (0·1)	0·5 (0·3)	0·4 (0·2)
Furosemide ordered, *N* (%)	31 (16)	6 (12)	14 (28)	4 (8)	7 (14)

Hb, haemoglobin; IQR, interquartile range; SD, standard deviation.
[a]Patients could have more than one reason for indication.

common dose was 20 mg (55%), the route was intravenous (90%), and timing was post-transfusion (74%) (Table 4). Univariate analysis for association of patient characteristics with furosemide ordering is presented in Table 5. Patients where furosemide was ordered tended to be older and have a history of CHF in the chart although these associations were not statistically significant. Being on a diuretic on admission (45% vs. 19%; $P = 0{\cdot}001$) and a low haemoglobin indication for transfusion (87% vs. 62%; $P = 0{\cdot}006$) were associated with furosemide ordering, whereas active bleeding as an indication for transfusion was associated with no furosemide order (3% vs. 20%, $P = 0{\cdot}03$). As there was only one patient with active bleeding in the furosemide group, active bleeding was not included in the logistic regression model. Thus, the logistic regression was conducted with two factors: diuretics on admission and indication for transfusion of low haemoglobin. Low haemoglobin as an indication for transfusion (OR 4·2; 95% CI 1·4–12·8) and diuretics on admission (OR 3·5; 95% CI 1·5–8·0) were associated with ordering furosemide peri-transfusion. Although the preprinted transfusion order set did not increase the use of furosemide, patients receiving furosemide at site A were more likely to receive furosemide pre-transfusion than at other sites (four of six patients (67%) at site A vs. three of 25 patients (12%) at other sites; $P = 0{\cdot}01$).

Table 4 Furosemide order details

	All	Site A	Site B	Site C	Site D
Furosemide ordered, *N*	31	6	14	4	7
Dose (%)					
10 mg	6 (19)	1 (17)	2 (14)	1 (25)	2 (29)
20 mg	17 (55)	4 (67)	8 (57)	2 (50)	3 (43)
40 mg	5 (16)	1 (17)	2 (14)	0 (0)	2 (29)
Other	3 (10)	0 (0)	2 (14)	1 (25)	0 (0)
Route (%)					
Oral	2 (6)	2 (33)	0 (0)	0 (0)	0 (0)
Intravenous	28 (90)	4 (67)	13 (93)	4 (100)	7 (100)
Unknown	1 (3)	0 (0)	1 (7)	0 (0)	0 (0)
Timing (%)[a]					
Pre-transfusion	7 (23)	4 (67)	0 (0)	1 (25)	2 (29)
Between	3 (10)	0 (0)	1 (7)	0 (0)	2 (29)
Post-transfusion	23 (74)	2 (33)	13 (93)	3 (75)	5 (71)

[a]Two patients at Site D received furosemide at two time-points.

Discussion

In this study of 200 consecutive patients at four academic sites, furosemide was ordered for RBC transfusion in 16% of cases. When ordered, the most common prescription was 20 mg given intravenously post-transfusion.

This study characterizes the real-world use of furosemide peri-transfusion for TACO prevention at four academic institutions with a high percentage of single unit transfusions and slow infusion rates as suggested by the AABB guidance document [13]. Overall, the use was low with a range from 8% to 28% (95% CI of 11–21%). This low use may have been due to the inclusion of consecutive adult RBC transfusion orders (as opposed to restricting orders to older patients or high-risk patients for TACO), but we did this intentionally so as to understand the current use of furosemide in routine transfusion practice. Including consecutive RBC transfusion orders also allowed us to hypothesize whether patient risk factors for TACO were associated with the decision to order furosemide. Based on the limited data, being on diuretics on admission and low haemoglobin as an indication for transfusion were associated with whether or not furosemide was ordered. Age and a history of CHF in chart may have an impact but were not statistically significant.

Our findings are consistent with other published work although there is a large variation in the use of diuretics depending on the population being studied. Fry *et al.* [15] examined transfusion premedication practices and found that only two (0·6%) of 324 patients were treated with furosemide before transfusion although it was not reported how many received furosemide during or after a transfusion. Lieberman *et al.* [9] reported on 100 consecutive TACO events and found that the rate of furosemide use was 29%, with the most common practice being 20 mg intravenous midway or at the end of transfusion. This rate was likely higher than what we observed as these were selected cases of TACO where providers may have anticipated a higher risk of TACO. Tseng *et al.* [16] were able to increase the use of diuretics in general internal medicine patients at high risk for TACO from 37% to 64% with the aid of a physician pre-transfusion checklist that specifically addressed risk factors for TACO in

Table 5 Comparison of patients receiving furosemide vs. no furosemide

	Furosemide ordered *N* = 31	No furosemide ordered *N* = 169	*P*-value
Age (median, IQR)	70 (60, 76)	62 (51, 72)	0·07
Female (%)	17 (55)	87 (51)	0·73
At least one risk factor for TACO (%)	17 (55)	93 (55)	0·98
Renal dysfunction (%)	8 (26)	57 (34)	0·39
History of CHF in chart (%)	9 (29)	26 (15)	0·07
Ejection fraction <60% (%)	7 (23)	24 (14)	0·56
Diastolic dysfunction (%)	1 (3)	9 (5)	0·68
Other blood products transfused in past 24 h (%)	5 (16)	32 (19)	0·71
Fluid balance positive (%)	5 (16)	27 (16)	0·62
Diuretics on admission (%)	14 (45)	32 (19)	0·001
Diuretics discontinued in 48 h prior to transfusion (%)	4 (13)	22 (13)	0·98
Number of single unit transfusions (%)	27 (87)	137 (81)	0·42
Indication for transfusion (%)			
Low haemoglobin	27 (87)	105 (62)	0·006
Active bleeding	1 (3)	33 (20)	0·03
Pre-transfusion haemoglobin (median, IQR)	69 (66, 73)	70 (67, 76)	0·34
Use of pre-printed transfusion order set (%)	6 (19)	44 (26)	0·43

CHF, congestive heart failure; IQR, interquartile range; TACO, transfusion-associated circulatory overload.

addition to a pre-printed transfusion order set that recommended pre-transfusion intravenous furosemide if risk factors were present. Furosemide use may also be higher in paediatric populations with one report of 40 patients where 43% received furosemide [17].

The question of whether or for which patients furosemide peri-transfusion is required remains unanswered. The use of furosemide to prevent TACO is a rational suggestion. Gupta *et al*. [18] first demonstrated in a study of 20 patients that furosemide 40 mg intravenously pre-transfusion prevented an increase in pulmonary capillary wedge pressure that occurred with transfusion when no furosemide was administered. Furosemide is a routine treatment for fluid overload and congestive heart failure. The side-effects of furosemide even given intravenously are small. In a pharmacovigilance study of 585 medical inpatients treated with a combination of oral and intravenous furosemide, the risk of hyponatremia and hypokalemia was only 1·0% and 3·6%, respectively [19]. Among patients treated with a dose less than or equal to 40 mg of furosemide, the incidence of hypokalemia was only 1·7% and would likely be considerably lower in patients also receiving RBC transfusion support, as the blood product itself may provide a small degree of potassium supplementation [20]. In Tseng *et al*. [16], no cases of hypokalemia or acute kidney injury attributable to furosemide were seen. On the other hand, it is not clear what the added benefit of furosemide would be in the setting of optimal transfusion practice, that is single unit transfusions given restrictively and with a slow infusion rate. This is the basis of the TACO-BEL pilot randomized study which has recently been completed [21]. In this current report, we did not observe any TACO events, although we did not specifically collect changes in vital signs during the audit. We also hypothesize that the lack of TACO events may have been related to the high rate of single unit transfusions and not restricting orders to those with risk factors for TACO. There may also have been underreporting of transfusion reactions with current rates of reaction reporting at our institutions in 2016 ranging from one report in 128–206 components (including RBC, platelet, plasma and cryoprecipitate units) transfused (personal communication, Ana Lima, Sunnybrook Health Sciences Centre and Christine Cserti-Gazdewich, University Health Network, 15 December 2017).

One of the sites had a mandatory pre-printed order for non-urgent transfusions. We noted that the pre-printed order alone did not increase the use of furosemide. However, use of the pre-printed order did increase the timing of furosemide as pre-transfusion because 'prior to transfusion' was the default choice for timing of furosemide. The transfusion rate was also more frequently documented with the pre-printed order although we noted that the actual infusion rate administered by the nurse was often faster than the documented transfusion order. It is also curious why the most common timing of furosemide is post-transfusion. Could clinicians be concerned about the vasodilatory effects of furosemide and possible hypotension from furosemide? Could this just be a residual practice from the days of 2 unit transfusions when furosemide was given in between transfusions?

Limitations of this study include its small sample size; however, the confidence interval around the point estimate of 16% (95% CI 11–21%) suggests that furosemide is not a routine practice. Our study occurred in academic centres where trainees often prescribe transfusion and so may not be generalizable to other practice settings. In order to look at whether this practice is generalizable, our group is planning on doing a larger multicentre audit to look at the frequency of furosemide use. Finally, because this study was retrospective, some risk factors such as echo results and fluid balance were not well documented. In fact, we noted that fluid balance was so poorly documented outside of intensive care units that its inclusion as a criterion for the diagnosis of TACO may not be useful in the daily practice setting.

In conclusion, furosemide is not routinely ordered peri-transfusion, even in patients with risk factors for TACO. Questions remain about who should receive furosemide and about what the optimal dose and timing should be. This study supports further investigation of the role of peri-transfusion furosemide in clinical trials as an intervention to help mitigate the risk and severity of TACO.

Acknowledgements

This work was funded in part by the Alexandra Yeo Chair Grant in Benign Hematology and Canadian Blood Services Small Projects Fund. We acknowledge Nagina Parmar for her assistance with data collection and Alex Kiss for his statistical expertise. All authors made substantial contributions to research design, or the acquisition, analysis or interpretation of data; YL drafted the study; all authors revised it critically and approved the submitted and final version of the manuscript. YL has received research support from Novartis and Octapharma; consultant fees from Amgen, Boehringer-Ingelheim, Genzyme, Pfizer; travel honorarium from Pfizer, and unrestricted education grant funding from CSL Behring and Grifols. JC has received research support from Octapharma and Canadian Blood services. LL has received research support from Octapharma. RC, CA, CC and JP have no competing interests.

Funding

Alexandra Yeo Chair Grant in Benign Hematology and Canadian Blood Services Small Projects Fund.

References

1 U.S. Food and Drug Administration: Fatalities reported to FDA following blood collection and transfusion: annual summary for fiscal year 2015. http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM518148.pdf, 2015 [Last accessed 14 October 2016]

2 Public Health Agency of Canada: Health Canada transfusion transmitted injuries surveillance system, 2006 – 2012 report. http://www.phac-aspc.gc.ca/hcai-iamss/ttiss-ssit/index-eng.php, 2014 [Last accessed 15 January 2016]

3 Bolton-Maggs PH: Conference report: the 2015 SHOT symposium and report – what's new? *Transfus Med* 2015; **25**:295–298

4 Bolton-Maggs PE, Poles D, On behalf of the Serious Hazards of Transfusion (SHOT) Steering Group, *et al.*: The 2016 annual SHOT report. Manchester, 2017. https://www.shotuk.org/wp-content/uploads/SHOT-Report-2016_web_11th-July.pdf [Last accessed 15 December 2017]

5 McMaster Transfusion Research Program: *Ontario Transfusion Transmitted Injuries Surveillance System (TTISS) Program Report: 2012 -2016*. Hamilton, ON: McMaster University, 2017

6 Clifford L, Jia Q, Yadav H, *et al.*: Characterizing the epidemiology of perioperative transfusion-associated circulatory overload. *Anesthesiology* 2015; **122**:21–28

7 Rana R, Fernandez-Perez ER, Khan SA, *et al.*: Transfusion-related acute lung injury and pulmonary edema in critically ill patients: a retrospective study. *Transfusion* 2006; **46**:1478–1483

8 Roubinian NH, Hendrickson JE, Triulzi DJ, *et al.*: Incidence and clinical characteristics of transfusion-associated circulatory overload using an active surveillance algorithm. *Vox Sang* 2017; **112**:56–63

9 Lieberman L, Maskens C, Cserti-Gazdewich C, *et al.*: A retrospective review of patient factors, transfusion practices, and outcomes in patients with transfusion-associated circulatory overload. *Transfus Med Rev* 2013; **27**:206–212

10 Alam A, Lin Y, Lima A, *et al.*: The prevention of transfusion-associated circulatory overload. *Transfus Med Rev* 2013; **27**:105–112

11 Murphy EL, Kwaan N, Looney MR, *et al.*: Risk factors and outcomes in transfusion-associated circulatory overload. *Am J Med* 2013; **126**:e29–e38

12 Sarai M, Tejani AM: Loop diuretics for patients receiving blood transfusions. *Cochrane Database Syst Rev* 2015; (2): CD010138

13 AABB: Association bulletin #15-02: transfusion associated circulatory overload, 2015. http://www.aabb.org/programs/publications/bulletins/Docs/ab15-02.pdf [Last accessed 29 December 2017]

14 Spradbrow J, Cohen R, Lin Y, *et al.*: Evaluating appropriate red blood cell transfusions: a quality audit at 10 Ontario hospitals to determine the optimal measure for assessing appropriateness. *Transfusion* 2016; **56**:2466–2476

15 Fry JL, Arnold DM, Clase CM, *et al.*: Transfusion premedication to prevent acute transfusion reactions: a retrospective observational study to assess current practices. *Transfusion* 2010; **50**:1722–1730

16 Tseng E, Spradbrow J, Cao X, *et al.*: An order set and checklist improve physician transfusion ordering practices to mitigate the risk of transfusion-associated circulatory overload. *Transfus Med* 2016; **26**:104–110

17 Agrawal AK, Hsu E, Quirolo K, *et al.*: Red blood cell transfusion in pediatric patients with severe chronic anemia: how slow is necessary? *Pediatr Blood Cancer* 2012; **58**:466–468

18 Gupta SP, Nand N, Gupta MS, *et al.*: Haemodynamic changes following blood transfusion in cases of chronic severe anemia: increased safety with simultaneous furosemide administration. *Angiology* 1983; **34**:699–704

19 Lowe J, Gray J, Henry DA, *et al.*: Adverse reactions to frusemide in hospital inpatients. *BMJ* 1979; **2**:360–362

20 Vraets A, Lin Y, Callum JL: Transfusion-associated hyperkalemia. *Transfus Med Rev* 2011; **25**:184–196

21 Callum J: Pre-transfusion furosemide in patients at high risk of transfusion-associated circulatory overload - the Transfusion-Associated Circulatory Overload Best Eliminated With Lasix (TACO-BEL) study: a pilot randomized controlled trial. 2017. https://www.clinicaltrials.gov/ct2/show/NCT02802696?cond=TACO&trank=1 [Last accessed 29 December 2017]