

# Fluid overload is associated with increases in length of stay and hospital costs: pooled analysis of data from more than 600 US hospitals

Glenn Magee<sup>1</sup>  
Art Zbrozek<sup>2</sup>

<sup>1</sup>Premier Research Services, Charlotte, NC, USA; <sup>2</sup>CSL Behring, King of Prussia, PA, USA

**Background:** Fluid overload, including transfusion-associated circulatory overload (TACO), is a serious complication of fresh frozen plasma (FFP) transfusion. The incidence of fluid overload is underreported and its economic impact is unknown. An evaluation of fluid overload cases in US hospitals was performed to assess the impact of fluid overload on length and cost of hospital stay.

**Study design and methods:** Retrospective analysis was performed using a clinical and economic database covering >600 US hospitals. Data were collected for all inpatients discharged during 2010 who received  $\geq 1$  unit FFP during hospitalization. Incidence of fluid overload was determined through International Classification of Diagnosis (ICD-9) codes. Multivariate regression analysis was performed for primary outcome measures: hospital length of stay (LOS) and total hospital costs.

**Results:** Data were analyzed for 129,839 FFP-transfused patients, of whom 4,138 (3.2%) experienced fluid overload (including TACO). Multivariate analysis, adjusting for baseline characteristics, found that increased LOS and hospital costs were independently associated with fluid overload. Patients diagnosed with fluid overload had longer mean LOS (12.9 days versus 10.0 days;  $P < 0.001$ ) and higher mean hospital cost per visit (\$46,644 versus \$32,582;  $P < 0.001$ ) compared with patients without fluid overload.

**Conclusion:** For a population of US inpatients who received FFP during hospitalization, fluid overload was associated with a 29% increase in LOS and a \$14,062 increase in hospital costs per visit. These findings suggest that the incidence of fluid overload in the general population is greater than historically reported. A substantial economic burden may be associated with fluid overload in the US.

**Keywords:** fresh frozen plasma, fluid overload, hospital costs, hypervolemia, length of stay, transfusion-associated circulatory overload

## Introduction

Transfusion with allogeneic blood components is the standard of care for treatment of bleeding and coagulopathy in the United States (US) and as many as 27 million units of blood components are transfused each year.<sup>1</sup> However, although blood component transfusion can be potentially life-saving therapy, it also carries a risk of transfusion-related adverse events.<sup>2</sup>

Fluid overload, which includes transfusion-associated circulatory overload (TACO), is a serious transfusion-related complication that can occur when patients are transfused with a large volume in a short timeframe.<sup>3</sup> Symptoms of the resulting hypervolemia include acute respiratory distress, pulmonary edema, hypertension, and acute left ventricular failure. Management of fluid overload involves stopping

Correspondence: Glenn Magee  
13034 Ballantyne Corporate Place,  
Charlotte, NC, USA 28277  
Tel +1 704 816 4013  
Email glenn\_magee@premierInc.com

transfusion, administering diuretics and oxygen, and may require cardiac support or admission to the intensive-care unit (ICU), alongside standard medical treatment.<sup>4,5</sup>

TACO is associated with increased length of hospital stay<sup>4</sup> and is the leading cause of transfusion-related mortality in the US behind transfusion-related acute lung injury.<sup>6</sup> Despite its severity, TACO had received little attention in the literature until recently because its incidence had been underestimated by passive reporting methods.<sup>6</sup> Recent prospective reports suggest that the true incidence of TACO may be high, for example occurring following 1.5%–6% of transfusions in some settings.<sup>3,7</sup>

TACO has been reported following administration with as little as one unit of red blood cells,<sup>6</sup> although recently published reports have focused on its association with transfusion of fresh frozen plasma (FFP).<sup>3,7</sup> FFP has a broad range of indications encompassing treatment of bleeding and prophylaxis for congenital and acquired coagulation defects. However, recent systematic reviews have questioned the efficacy and safety of FFP,<sup>8,9</sup> suggesting that its therapeutic and prophylactic benefits are unproven in most settings, and may be limited to patients with intracranial hemorrhage or a need for massive transfusion.<sup>10</sup> In the US, warfarin reversal is one of, if not the major indication for FFP transfusion.<sup>11</sup> Although FFP is standard treatment for urgent warfarin reversal, it is also associated with the development of TACO.<sup>3</sup> This is likely due to patients on warfarin typically being >65 years old and having underlying cardiopulmonary conditions. With the US population continuing to age, the number of people at risk of fluid overload and TACO is increasing.

To assess the scale of the problem and its economic impact, we performed an evaluation of fluid overload cases, including TACO, in US hospitals using a large US clinical and economic database. Our dataset was compiled from the records of inpatients who received FFP across more than 600 hospitals in the year 2010. We aimed to measure the average length of stay (LOS) and the average additional cost incurred by a hospital when a patient develops fluid overload. In addition, we aimed to identify patient and hospital characteristics that are associated with the occurrence of fluid overload.

## Materials and methods

### The Premier Research database

The Premier Research database (Premier, Inc, Charlotte, NC, US) is the largest US hospital clinical and economic database. The database includes information on all inpatients and hospital-based outpatients from the year 2000 onwards in

more than 600 US hospitals; it is not a random sample – data are collected for all patients across all therapeutic areas. The database contains 2.5 billion patient daily service records and 45 million records are added each month. More than 5 million inpatient discharges were recorded in 2010. The analysis reported here includes patient data from 2010 (see below).

In addition to patient demographic and diagnosis codes, the database contains a date-stamped log of all billed items, including procedures, medications, and laboratory, diagnostic, and therapeutic services, at the individual patient level. Laboratory test results are not available in this study. Patients can be tracked across the inpatient and hospital outpatient settings, as well as across visits, using a unique person identifier. All procedures and diagnoses are captured for each patient, including all drugs received and devices used. Drug utilization and enteral nutrition information is available by day of stay, and includes dose quantity (number of doses given), dose strength (for each individual dose given), dosing regimen (total dose administered), and hospital-reported cost.

Based on the regulation defined in the 1996 Health Insurance Portability and Accountability Act (HIPAA), data deliverables must contain limited Protected Health Information (PHI). Therefore, the times of admission and discharge are provided as month and year. Day-of-service level details are reported, using chronological days (eg, Day 1, Day 2). For patients aged 85 years or over, age was recorded as 85 years.

### Patient identification and selection criteria

Patients selected for the analysis were both (1) discharged from an inpatient hospital stay in 2010, and (2) received at least one unit of FFP during their hospital stay. Those patients who received FFP, as well as those who received warfarin, were identified from the detailed patient billing data. Admission type was based on the Medical Severity Diagnosis Related Groups (MS-DRG), which is a system that classifies hospital cases into groups to help identify specific services that a hospital provides. Emergency department (ED) admittance was identified using the hospital admission source variable. Fluid overload and bleed status were determined through International Classification of Diagnosis (ICD-9) codes ICD-9 276.61 (TACO) and 276.69 (other fluid overload). Bleed status ICD-9 codes and descriptions included in this study are listed in Table S1. No outpatient anticoagulation data were available for any patient. Patients who developed TACO or fluid overload and those who did not were compared.

## Outcomes

The primary outcomes were hospital LOS and total hospital costs. Hospital costs were reported directly from hospital charge master files. Cost-to-charge ratio calculations were not used in this study.

## Statistics

Univariate descriptive statistics were calculated for all patient and hospital covariates. Univariate analyses used chi-squared tests for categorical data and Student's *t*-tests for continuous variables. Multivariate analysis of outcome measures was performed using generalized linear models. Because of the skewed nature of the LOS and cost data, these outcomes were analyzed using multivariate regression with a gamma distribution and log link. Variables used in the model included age, gender, race, bleed status (see Table S1), fluid overload status, ED admittance, major diagnostic category (defined by Center for Medicare and Medicaid Services and formed by dividing all possible principal diagnoses from International Classification of Diseases-Ninth revision-Clinical Modification into 25 mutually exclusive diagnosis areas), hospital capacity (number of beds), teaching status, provider region, and urban/rural status. Covariates included in the model were from the univariate comparisons as well as variables that were identified as being clinically relevant to the model. Modeling was performed using SAS 9.2 statistical software (SAS Institute Inc, Cary, NC, USA).

## Results

### Patient and hospital demographics

Patients who were discharged from an inpatient hospital stay in 2010 and who received at least one unit of FFP during their hospital stay were identified from the Premier Research database. The analyses included a total of 129,839 patients, of whom 4,138 (3.2%) experienced fluid overload (including TACO) and 125,701 (96.8%) who did not. Table 1 presents the demographic characteristics of patients with and without fluid overload.

Univariate analysis revealed statistically significant differences between the groups for each of the characteristics ( $P < 0.001$ ), except for gender and inpatient warfarin administration (Table 1). Despite some between-group differences in the race and age distributions, the majority (~70%) of patients in both groups were white and between 40 and 79 years old. The largest difference between the groups was seen in the admission type: the majority (63%) of fluid overload patients were admitted to hospital for surgical reasons, whereas the majority (55%) of patients without fluid overload were admitted for medical reasons. Although the minority of patients

**Table 1** Patient characteristics

Characteristic	Fluid overload (n = 4138)	No fluid overload (n = 125,701)	P-value
<b>Age</b>			
Mean (SD), years	64 (17.5)	65 (19.7)	0.002 <sup>a</sup>
<18, n (%)	99 (2.4%)	4415 (3.5%)	<0.001 <sup>b</sup>
18 to 39, n (%)	255 (6.2%)	8209 (6.5%)	
40 to 64, n (%)	1547 (37.4%)	40,398 (32.1%)	
65 to 79, n (%)	1536 (37.1%)	42,825 (34.1%)	
≥80, n (%)	701 (16.9%)	29,854 (23.8%)	
<b>Gender, n (%)</b>			0.918
Male	2260 (54.6%)	68,611 (54.6%)	
Female	1878 (45.4%)	57,090 (45.4%)	
<b>Race, n (%)</b>			<0.001 <sup>b</sup>
White	2963 (71.6%)	87,518 (69.6%)	
Other	638 (15.4%)	18,283 (14.5%)	
Black	425 (10.3%)	14,947 (11.9%)	
Hispanic	112 (2.7%)	4953 (3.9%)	
<b>Admission type, n (%)</b>			<0.001 <sup>b</sup>
Surgical	2606 (63.0%)	57,145 (45.5%)	
Medical	1532 (37.0%)	68,556 (54.5%)	
<b>Emergency department admit, n (%)</b>			<0.001 <sup>b</sup>
No	3086 (74.6%)	79,728 (63.4%)	
Yes	1052 (25.4%)	45,973 (36.6%)	
<b>Bleed status,<sup>c</sup> n (%)</b>			<0.001 <sup>b</sup>
No	3075 (74.3%)	77,729 (61.8%)	
Yes	1063 (25.7%)	47,972 (38.2%)	
<b>Inpatient warfarin use (≥1 days), n (%)</b>			0.814 <sup>b</sup>
No	3204 (77.4%)	97,133 (77.3%)	
Yes	934 (22.6%)	28,568 (22.7%)	
<b>Major diagnostic categories,<sup>d,e</sup> n (%)</b>			<0.001 <sup>b</sup>
Circulatory system	1650 (39.9%)	28,649 (22.8%)	
Digestive system	526 (12.7%)	22,964 (18.3%)	
Infectious and parasitic DDs	381 (9.2%)	11,171 (8.9%)	
Hepatobiliary system and pancreas	368 (8.9%)	10,419 (8.3%)	
Respiratory system	224 (5.4%)	8426 (6.7%)	
Musculoskeletal system and connective tissue	213 (5.1%)	9953 (7.9%)	
Kidney and urinary tract	169 (4.1%)	4631 (3.7%)	
Nervous system	142 (3.4%)	10,165 (8.1%)	
<b>Diuretic use (≥1 days),<sup>c</sup> n (%)</b>			<0.001 <sup>b</sup>
No	15.0%	39.3%	
Yes	85.0%	60.7%	

**Notes:** <sup>a</sup>Difference between mean values; <sup>b</sup>differences between categories; "yes" indicates patient is positive for gastrointestinal, intracranial, or other bleeding event; <sup>d</sup>diagnosis reported in ≥3% of patients in either group; <sup>e</sup>defined by CMS as 25 categories based upon a patient's DRG.

**Abbreviations:** CMS, Center for Medicare and Medicaid Services; DDs, diseases and disorders (major diagnostic category); DRG, diagnosis-related group; SD, standard deviation.

in both groups were admitted to hospital after attending the ED, a smaller percentage of fluid overload patients (25%) were admitted via the ED compared with non-fluid-overload patients (37%). In both groups, less than 40% of patients had uncontrolled bleeding as determined by ICD-9 code during their hospital stay. The largest diagnostic category reported in both groups was circulatory-system-related, occurring in 40% of fluid overload patients and 23% of patients without fluid overload. The only other major diagnostic category with a difference of more than five percentage points between the groups was digestive-system-related, with more frequent reporting in the non-fluid-overload group (18%) compared with the fluid overload group (13%).

A comparison of hospital demographics between the fluid overload and non-fluid-overload groups is shown in Table 2. In both groups, at least 90% of patients were treated at hospitals located in urban areas and >70% were treated at hospitals with at least 300 beds. Patients in both groups were mostly from hospitals in the South Atlantic region (~27%), with the minority (<2%) coming from hospitals in New England.

### Hospital LOS and cost analysis

Patients diagnosed with TACO or other fluid overload spent a mean of 3.4 days longer in hospital than patients without

fluid overload ( $P < 0.001$ ; Table 3), of which 1.4 additional days were in the ICU. On average, fluid overload patients cost \$19,649 more in total hospital costs than patients with no fluid overload ( $P < 0.001$ ; Table 3).

Multivariate regression analysis, adjusting for factors and differences noted in Tables 1 and 2, was performed to determine any differences in hospital LOS per visit and hospital costs per visit that were independently associated with fluid overload (Table 3). Patients diagnosed with fluid overload had a mean adjusted LOS of 12.9 days, which was 29% longer than the mean duration of 10.0 days for patients without fluid overload ( $P < 0.001$ ). The mean increase in ICU stay was 0.8 days ( $P < 0.001$ ). The adjusted total hospital cost per visit of treating patients with fluid overload was 43% higher than for patients without fluid overload ( $P < 0.001$ ). On average, the total hospital cost of treating a patient with fluid overload was \$14,062 higher per visit compared with patients without fluid overload.

### Discussion

Our analysis investigated fluid overload in a real-world, general population of US inpatients who received FFP transfusion. We found that fluid overload, which encompassed TACO and other diagnoses of fluid overload, occurred in 3.2% of all inpatients and was independently associated with a 29% increase in the LOS (mean 2.9 days total, 0.8 days in ICU) and a 43% increase in total hospital costs (\$14,062) per patient visit.

In 2008, 4.5 million units of plasma were transfused in the US, of which the vast majority were either FFP (54%; frozen within 8 hours of phlebotomy) or FP24 (39%; frozen within 24 hours).<sup>12</sup> According to the US Department of Health and Human Services, the mean volume of plasma administered in the US in 2008 was 363 mL (between one and two units),<sup>12</sup> suggesting that the ~2.4 million units of FFP transfused were administered to approximately 1.2 million patients. Based on the incidence of fluid overload established in our study (3.2% of patients administered FFP), around 38,400 of these 1.2 million patients could be predicted to experience some form of fluid overload. As we found that fluid overload increased overall hospital costs by \$14,062 per visit, our findings conservatively suggest the annual economic burden associated with fluid overload in the US to be around \$540 million US. However, FP24 also accounts for 39% (~1.8 million units) of transfused plasma in the US, so the economic burden of fluid overload may be closer to \$1 billion US, assuming that FP24 transfusion carries similar

**Table 2** Hospital characteristics

Characteristic, n (%)	Fluid overload (n = 4138)	No fluid overload (n = 125,701)	P-value
<b>Teaching status</b>			<0.001
Teaching	2348 (56.7%)	57,210 (45.5%)	
Non-teaching	1790 (43.3%)	68,491 (54.5%)	
<b>Urban/rural status</b>			<0.001
Urban	3839 (92.8%)	113,181 (90.0%)	
Rural	291 (7.0%)	12,008 (9.6%)	
Unknown	8 (0.2%)	512 (0.4%)	
<b>Number of beds</b>			<0.001
<100	40 (1.0%)	2873 (2.3%)	
100–299	799 (19.3%)	30,125 (24.0%)	
300–499	1297 (29.9%)	43,795 (34.8%)	
≥500	2002 (48.4%)	48,908 (38.9%)	
<b>Region</b>			<0.001
South Atlantic	1093 (26.4%)	35,100 (27.9%)	
East North Central	749 (18.1%)	17,619 (14.0%)	
Middle Atlantic	548 (13.2%)	16,591 (13.2%)	
Pacific	487 (11.8%)	16,799 (13.4%)	
Mountain	430 (10.4%)	10,264 (8.2%)	
West South Central	373 (9.0%)	14,351 (11.4%)	
West North Central	230 (5.6%)	5765 (4.6%)	
East South Central	163 (3.9%)	6837 (5.4%)	
New England	65 (1.6%)	2375 (1.9%)	

**Table 3** Mean (standard deviation) length of stay and hospital costs per visit\*

Outcome	Fluid overload (n = 4138)	No fluid overload (n = 125,701)	% increase	P-value
<b>Univariate analysis</b>				
Hospital LOS (days)	15.3 (15.1)	11.9 (18.2)	28.6%	<0.001
ICU LOS (days)	4.4 (7.9)	3.0 (7.2)	46.7%	<0.001
Total hospital cost (\$)	\$56,817 (\$59,195)	\$37,168 (\$53,795)	52.9%	<0.001
<b>Multivariate analysis</b>				
Hospital LOS* (days)	12.9 (0.9)	10.0 (0.7)	29.0%	<0.001
ICU LOS (days)	6.0 (0.8)	5.2 (0.7)	12.7%	<0.001
Total hospital cost <sup>†</sup> (\$)	\$46,644 (\$3433)	\$32,582 (\$2354)	43.2%	<0.001

**Notes:** \*Significant factors in the multivariate model (all significant  $P < 0.001$ , unless otherwise indicated): fluid overload, diuretic use; admission through ER ( $P = 0.01$ ); two or more units of FFP; hospital bed size smaller than 100 ( $P = 0.0032$ ); female ( $P = 0.0031$ ); black ( $P = 0.002$ ), Hispanic, or other ( $P = 0.003$ ) group than white; any region relative to West South Central except New England, West North Central, and Pacific (Mountain  $P = 0.0167$ ); urban versus rural; bleed status; <sup>†</sup>significant factors in the multivariate model (all significant  $P < 0.001$ , unless otherwise indicated): fluid overload, diuretic use; admission through ER; two or more units of FFP; hospital bed size smaller than 500; black, Hispanic, or other ( $P = 0.003$ ) group than white; any region relative to West South Central except East North Central or West North Central; bleed status.

**Abbreviations:** ER, emergency room; FFP, fresh frozen plasma; ICU, intensive-care unit; LOS, length of stay.

risks of fluid overload to FFP. This burden may be expected to increase as the age-driven, at-risk population grows.

Our findings in a general inpatient population are in line with previous reports that TACO increases length of hospital stay in orthopedic patients.<sup>4</sup> Previous studies have examined the costs associated specifically with FFP transfusion. In addition to the direct costs of acquiring FFP (approximately \$60–80 US per unit<sup>12,13</sup>), there are numerous costs associated with infrastructure and the management of transfusion reactions, which include but are not limited to: cost incurred to donors, cost of producing blood components for transfusion, cost of administering transfusions and post-transfusion monitoring, and costs of treating adverse transfusion reactions and transmitted diseases.<sup>14</sup> When these indirect costs are considered, the overall cost of FFP may be >\$1,400 US per unit transfused.<sup>14</sup> Reimbursement rates for FFP marginally exceed direct acquisition costs (by ~16%),<sup>12</sup> so reimbursement covers only a small fraction of indirect transfusion-associated costs. FFP transfusion therefore represents a substantial burden to health care systems.

To prevent fluid overload and minimize the substantial burden it places upon patients and health care systems, approaches to fluid management should be reviewed and standardized. FFP is not a benign treatment, and is associated with significant safety concerns.<sup>3,15–17</sup> Our analysis did not seek to explore a causal link between the FFP transfusions received by US patients and their development of fluid overload; investigating this link would require a randomized, controlled trial. In addition, we did not have sufficient data to control for certain variables, such as preexisting congestive heart failure. However, our analysis did make adjustments for some potentially confounding variables, strengthening

the reliability of the findings. While there are undoubtedly other contributing factors, numerous studies have established that FFP transfusion is a major risk factor for TACO.<sup>3,7</sup> When the goal is to restore sufficient circulating volume (normovolemia), colloids/crystalloids may be preferred for their favorable safety profile.<sup>16</sup>

When the goal is to correct a coagulation defect (coagulopathy), specific, targeted therapy with coagulation factor concentrates may be appropriate. FFP contains coagulation factors at normal physiological levels and large volume transfusions are therefore required to achieve any increment in the patient's plasma levels.<sup>18,19</sup> In contrast, coagulation factor concentrates enable supraphysiological doses of the required factors to be delivered rapidly and in low volumes,<sup>19–21</sup> thereby minimizing the risk of fluid overload. Coagulation factor concentrates have shown benefit over transfusions of allogeneic blood products in a number of clinical settings, such as cardiovascular surgery<sup>22–24</sup> and trauma,<sup>25</sup> and in systematic reviews.<sup>26,27</sup> However, higher-quality efficacy data and large safety studies are needed. At present in the US, coagulation factor concentrates are generally licensed for use only in patients with congenital clotting factor deficiencies.

Although FFP is the standard of care in the US for reversal of oral anticoagulation, it has questionable efficacy.<sup>8,9</sup> Prothrombin complex concentrate (PCC) can correct the international normalized ratio more rapidly and more completely than FFP, and with a much lower administration volume.<sup>18,28,29</sup> Consequently, recent UK and European guidelines recommend PCC in place of FFP as first-line therapy for urgent vitamin K-antagonist reversal,<sup>30,31</sup> though four-factor PCC is not yet licensed in the US.

Beyond fluid and coagulation management, our data also suggest factors whose presence might alert the treating physician to the risk of fluid overload. Rates of non-bleeding patients and patients admitted for surgical reasons or with circulatory-system-related diagnoses were all higher in the population that had fluid overload. So, for example, prophylactic FFP administration may be unnecessary and potentially harmful in a patient who presents with a circulatory disorder but no bleed and is admitted for surgery.

Our study generated some predictable findings concerning the ‘average’ profile of a patient with fluid overload in the US. That absence of bleeding, circulatory system diagnoses, and admission for surgical reasons were associated with fluid overload is logical; the circulation is more easily overloaded when it is normovolemic to begin with, and patients with cardiovascular disease typically receive large volume transfusions perioperatively.<sup>28</sup> Also, patients with fluid overload may subsequently develop hypertension and tachycardia, leading to circulatory problems and potentially congestive heart failure.<sup>32</sup>

Our study has some limitations. First, our analyses identified factors associated with fluid overload but could not establish cause and effect relationships, due to the study’s retrospective, observational nature. When data is collected retrospectively there are often variables for which information cannot be gathered; for example, details of outpatient anticoagulation were not available in this study. Thus we cannot rule out that factors besides fluid overload, that weren’t measured and corrected for, contributed to the increased cost observed. Next, previous research by the authors (unpublished), utilizing an outpatient database linked to a subset of patients in the Premier Research database, suggested that patients taking warfarin at home received warfarin after inpatient admission approximately 75% of the time for surgical admissions and only 40% of the time for medical admissions; so these variables were likely to have been significantly underestimated in this study. In one sense, the breadth of our study population could be perceived as a limitation, though the inclusion of all inpatients across all diagnostic categories is also a strength as it reflects real-world clinical practice. Additional studies will be required to collect data on the precise nature of the extra costs incurred when a patient develops fluid overload. In broad terms, we presume that these extra costs relate to managing the symptoms of fluid overload and treating underlying disease, as well as any transfusion-associated adverse events, over the extended duration of the patient’s hospital stay. Lastly, the cohort used patients with at least 1 day of warfarin prior to

hospital discharge. Patients who were on warfarin but had it held throughout their hospitalization were difficult to identify due, in part, to the absence of ambulatory (ie, pre-admission) pharmacy use. It is unclear whether this population would have different FFP use with or without different risks for fluid overload. A study of this population would require either a prospective effort or use of an observational database consisting of both ambulatory pharmacy and sufficiently detailed inpatient data.

In conclusion, patients who receive FFP and suffer fluid overload spend longer time in hospital and their treatment costs are substantially greater, compared with patients without fluid overload. As the US population ages and the incidence of fluid overload increases, better approaches to fluid and coagulation management, with improved efficacy, safety, and cost-effectiveness, are needed to prevent fluid overload and minimize the substantial burden it places on patients and health care systems.

## Acknowledgment

The authors would like to thank Dorothy Baumer, MS, Premier, Inc, for her expert technical assistance in this analysis.

## Disclosure

This work was funded by CSL Behring. Glenn Magee is an employee of Premier Research Services, which received funding from CSL Behring to conduct this analysis. Art Zbrozek is an employee of CSL Behring. Editorial assistance was provided by Meridian HealthComms, funded by CSL Behring. The authors report no other conflicts of interest in this work.

## References

- Wallis JP, Dzik S. Is fresh frozen plasma overtransfused in the United States? *Transfusion*. 2004;44(11):1674–1675.
- Eder AF, Chambers LA. Noninfectious complications of blood transfusion. *Arch Pathol Lab Med*. 2007;131(5):708–718.
- Li G, Rachmale S, Kojicic M, et al. Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. *Transfusion*. 2011;51(2):338–343.
- Popovsky MA, Audet AM, Andrzejewski C Jr. Transfusion-associated circulatory overload in orthopedic surgery patients: a multi-institutional study. *Immunohematology*. 1996;12(2):87–89.
- UK Blood Transfusion and Tissue Transplantation Services Transfusion Handbook: Acute complications of transfusion [webpage on the Internet]. UK Blood Transfusion and Tissue Transplantation Services. Available from: <http://www.transfusionguidelines.org.uk/?Publication=HTM&Section=9&pageid=1145>. Accessed Oct 2012.
- Pandey S, Vyas GN. Adverse effects of plasma transfusion. *Transfusion*. 2012;52 Suppl 1:65S–79S.
- Narick C, Triulzi DJ, Yazer MH. Transfusion-associated circulatory overload after plasma transfusion. *Transfusion*. 2012;52(1):160–165.

8. Murad MH, Stubbs JR, Gandhi MJ, et al. The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis. *Transfusion*. 2010;50(6):1370–1383.
9. Yang L, Stanworth S, Hopewell S, Doree C, Murphy M. Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials. *Transfusion*. 2012;52(8):1673–1686; quiz 1673.
10. Roback JD, Caldwell S, Carson J, et al; American Association for the Study of Liver; American Academy of Pediatrics; United States Army; American Society of Anesthesiology; American Society of Hematology. Evidence-based practice guidelines for plasma transfusion. *Transfusion*. 2010;50(6):1227–1239.
11. Ozgonenel B, O'Malley B, Krishen P, Eisenbrey AB. Warfarin reversal emerging as the major indication for fresh frozen plasma use at a tertiary care hospital. *Am J Hematol*. 2007;82(12):1091–1094.
12. US Department of Health and Human Services. The 2009 National Blood Collection and Utilization Survey Report. Washington, DC: US Department of Health and Human Services, Office of the Assistant Secretary for Health; 2011. Available from: <http://www.hhs.gov/ash/bloodsafety/2009nbcus.pdf>. Accessed Oct 2012.
13. Toner RW, Pizzi L, Leas B, Ballas SK, Quigley A, Goldfarb NI. Costs to hospitals of acquiring and processing blood in the US: a survey of hospital-based blood banks and transfusion services. *Appl Health Econ Health Policy*. 2011;9(1):29–37.
14. Shander A, Hofmann A, Gombotz H, Theusinger OM, Spahn DR. Estimating the cost of blood: past, present, and future directions. *Best Pract Res Clin Anaesthesiol*. 2007;21(2):271–289.
15. Bochicchio GV, Napolitano L, Joshi M, Bochicchio K, Meyer W, Scalea TM. Outcome analysis of blood product transfusion in trauma patients: a prospective, risk-adjusted study. *World J Surg*. 2008;32(10):2185–2189.
16. Etemadrezai H, Baharvahdat H, Shariati Z, Lari SM, Shakeri MT, Ganjeifar B. The effect of fresh frozen plasma in severe closed head injury. *Clin Neurol Neurosurg*. 2007;109(2):166–171.
17. Inaba K, Branco BC, Rhee P, et al. Impact of plasma transfusion in trauma patients who do not require massive transfusion. *J Am Coll Surg*. 2010;210(6):957–965.
18. Boullis NM, Bobek MP, Schmaier A, Hoff JT. Use of factor IX complex in warfarin-related intracranial hemorrhage. *Neurosurgery*. 1999;45(5):1113–1118; discussion 1118–1119.
19. Makris M. Optimisation of the prothrombin complex concentrate dose for warfarin reversal. *Thromb Res*. 2005;115(6):451–453.
20. Lorenz R, Kienast J, Otto U, et al. Efficacy and safety of a prothrombin complex concentrate with two virus-inactivation steps in patients with severe liver damage. *Eur J Gastroenterol Hepatol*. 2003;15(1):15–20.
21. Lorenz R, Kienast J, Otto U, et al. Successful emergency reversal of phenprocoumon anticoagulation with prothrombin complex concentrate: a prospective clinical study. *Blood Coagul Fibrinolysis*. 2007;18(6):565–570.
22. Gorlinger K, Dirkmann D, Hanke AA, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. *Anesthesiology*. 2011;115(6):1179–1191.
23. Gorlinger K, Fries D, Dirkmann D, Weber CF, Hanke AA, Schöchl H. Reduction of fresh frozen plasma requirements by perioperative point-of-care coagulation management with early calculated goal-directed therapy. *Transfus Med Hemother*. 2012;39(2):104–113.
24. Rahe-Meyer N, Solomon C, Hanke A, et al. Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. *Anesthesiology*. 2013;118(1):40–50.
25. Schöchl H, Nienaber U, Hofer G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care*. 2010;14(2):R55.
26. Kozek-Langenecker S, Sørensen B, Hess JR, Spahn DR. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review. *Crit Care*. 2011;15(5):R239.
27. Warmuth M, Mad P, Wild C. Systematic review of the efficacy and safety of fibrinogen concentrate substitution in adults. *Acta Anaesthesiol Scand*. 2012;56(5):539–548.
28. Demeyere R, Gillardin S, Arnout J, Strengers PF. Comparison of fresh frozen plasma and prothrombin complex concentrate for the reversal of oral anticoagulants in patients undergoing cardiopulmonary bypass surgery: a randomized study. *Vox Sang*. 2010;99(3):251–260.
29. Fredriksson K, Norrving B, Stromblad LG. Emergency reversal of anticoagulation after intracerebral hemorrhage. *Stroke*. 1992;23(7):972–977.
30. Keeling D, Baglin T, Tait C, et al; British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin – fourth edition. *Br J Haematol*. 2011;154(3):311–324.
31. Rossaint R, Bouillon B, Cerny V, et al; Task Force for Advanced Bleeding Care in Trauma. Management of bleeding following major trauma: an updated European guideline. *Crit Care*. 2010;14(2):R52.
32. Skeate RC, Eastlund T. Distinguishing between transfusion related acute lung injury and transfusion associated circulatory overload. *Curr Opin Hematol*. 2007;14(6):682–687.

## Supplementary table

**Table S1** Bleed status ICD-9 codes used in this study

ICD-9 code	Description	Category
(V58.61)	Aftcr, long-term use, anticoag	Anti-coag
(790.92)	Abnormal blood coagulation profile	Anti-coag
(E934.2)	Adverse effect, anticoagulants	Anti-coag
(285.1)	Anemia, acute posthemorrhagic	Other
(578.9)	Hemorrhage, gastrointestinal NOS	Gastro
(578.1)	Blood in stool	Gastro
(784.7)	Symptom, epistaxis	Other
(569.3)	Hemorrhage, rectal, and anal	Gastro
(599.71)	Gross hematuria	Other
(578.0)	Hematemesis	Gastro
(431)	Hemorrhage, intracerebral	Brain
(459.0)	Hemorrhage NOS	Other
(535.41)	Gastritis NEC w/hemorrhage	Gastro
(535.51)	Gastritis NOS w/hemorrhage	Gastro
(432.1)	Hemorrhage, subdural	Brain
(372.72)	Hemorrhage, conjunctival	Other
(530.82)	Hemorrhage, esophageal	Gastro
(430)	Hemorrhage, subarachnoid	Brain
(719.16)	Hemarthrosis, lower leg	Other
(530.21)	Ulcer, esophagus w/bleeding	Gastro
(432.9)	Hemorrhage, intracranial NOS	Brain
(599.72)	Microscopic hematuria	Other
(853.01)	Hem brain NEC w/o opn wnd no LOC	Brain
(287.9)	Hemorrhagic condition NOS	Other
(596.7)	Hemorrhage into bladder wall	Other
(535.11)	Gastritis, atrophic w/hemorrhage	Gastro

**Abbreviations:** Aftcr, aftercare; Anti-coag, anticoagulation; Gastro, gastrointestinal; Hem, hemorrhage; ICD-9, International Classification of Diagnosis; LOC, loss of consciousness; NEC, not elsewhere classified; NOS, not otherwise specified; opn, open; wnd, wound.

### ClinicoEconomics and Outcomes Research

Dovepress

### Publish your work in this journal

ClinicoEconomics & Outcomes Research is an international, peer-reviewed open-access journal focusing on Health Technology Assessment, Pharmacoeconomics and Outcomes Research in the areas of diagnosis, medical devices, and clinical, surgical and pharmacological intervention. The economic impact of health policy and health systems

organization also constitute important areas of coverage. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/clinicoeconomics-and-outcomes-research-journal>