Original Investigation | PACIFIC COAST SURGICAL ASSOCIATION

A Paradigm Shift in Trauma Resuscitation
Evaluation of Evolving Massive Transfusion Practices

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IMPORTANCE The evolution of damage control strategies has led to significant changes in the use of resuscitation after traumatic injury.

OBJECTIVE To evaluate changes in the administration of fluids and blood products, hypothesizing that a reduction in crystalloid volume and a reduced red blood cell (RBC) to fresh frozen plasma (FFP) ratio over the last 7 years would correlate with better resuscitation outcomes.

DESIGN Observational prospective cohort study.

SETTING Urban level I trauma center.

PARTICIPANTS A total of 174 trauma patients receiving a massive transfusion (>10 units of RBCs in 24 hours) or requiring the activation of the institutional massive transfusion protocol from February 2005 to June 2011.

EXPOSURE Patients had to either receive a massive transfusion or require the activation of the institutional massive transfusion protocol.

MAIN OUTCOMES AND MEASURES In-hospital mortality.

RESULTS The mean (SD) Injury Severity Score was 28.4 (16.2), the mean (SD) base deficit was −9.8 (6.3), and median international normalized ratio was 1.3 (interquartile range, 1.2-1.6); the mortality rate was 40.8%. Patients received a median of 6.1 L of crystalloid, 13 units of RBCs, 10 units of FFP, and 1 unit of platelets over 24 hours, with a mean RBC:FFP ratio of 1.58:1. The mean 24-hour crystalloid infusion volume and number of the total blood product units given in the first 24 hours decreased significantly over the study period ($P < .05$). The RBC:FFP ratio decreased from a peak of 1.84:1 in 2007 to 1.55:1 in 2011 ($P = .20$). Injury severity and mortality remained stable over the study period. When adjusted for age and injury characteristics using Cox regression, each decrease of 0.1 achieved in the massive transfusion protocol's RBC:FFP ratio was associated with a 5.6% reduction in mortality ($P = .005$).

CONCLUSIONS AND RELEVANCE There has been a shift toward a reduced crystalloid volume and the recreation of whole blood from component products in resuscitation. These changes are associated with markedly improved outcomes and a new paradigm in the resuscitation of severely injured patients.

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At least 10% of civilian deaths after traumatic injury are considered potentially preventable, and 15% of these are due to hemorrhage; many of these deaths occur within the first few hours of definitive care, with coagulopathy playing a major role.[1,2] In response to this realization, the last 10 years has seen a widespread paradigm shift in the resuscitation of critically injured patients. Early in this era, landmark studies identified iatrogenic and resuscitation-associated causes of coagulopathic bleeding after traumatic injury; hypothermia, metabolic acidosis, and dilutional coagulopathy were recognized as primary drivers of bleeding after trauma.[3] In response to this pioneering literature, rewarming efforts, early correction of acidosis, and the limitation of crystalloid became prime tenets of a trauma resuscitation strategy. This focus on early correction of physiological abnormalities, as opposed to definitive surgical repair, has prompted the era of "damage control" surgery.[4,5] As these major risk factors began to be appropriately managed or avoided altogether, a distinct additional biochemical coagulopathy has been unmasked in the setting of significant injury and hypoperfusion, occurring prior to the onset of the "vicious triad"; this has been termed *acute traumatic coagulopathy*.[6,7] Several candidate biochemical mechanisms for acute traumatic coagulopathy have been identified, including abnormalities in endogenous anticoagulant activation; however, definitively targeted therapy for this clinical entity remains elusive.[8,9]

Concurrent with the elucidation of acute traumatic coagulopathy, large retrospective military and civilian series suggested a survival benefit to transfusion strategies employing earlier and more frequent use of plasma, particularly among patients who received a massive transfusion (MT). Beginning with data from military casualties, multiple retrospective studies clearly demonstrated that lower ratios of red blood cells (RBCs) to fresh frozen plasma (FFP) were associated with improved survival.[10-13] However, the critical limitations of retrospective evidence, as well as concerns of survival bias, remain significant challenges to the evidence base of this practice,[14] and currently ongoing prospective randomized studies in this arena face significant challenges. Furthermore, whether the apparent survival benefit stems from earlier treatment and empirical avoidance of coagulopathy or is the result of still undescribed inflammomodulatory effects remains unclear.[15] Despite these limitations and a lack of both clinical and basic science evidence, plasma-based resuscitation has been overwhelmingly accepted by the trauma community.[16]

Given the widely acknowledged lack of a clear evidence base for many of the novel resuscitation strategies advanced during this dynamic time period, we sought to analyze a prospectively maintained database of 174 critically injured trauma patients who either received an MT or required the activation of the institutional MT protocol within 24 hours of admission, in order to evaluate changing trends in fluid and blood product administration at our institution over the last 7 years and to correlate these trends with overall outcomes.

Methods

From February 2005 to June 2011, data were prospectively collected from 174 trauma patients receiving an MT (>10 units of RBCs in 24 hours) or requiring the activation of the institutional MT protocol by a dedicated transfusion service coordinator. All patients meeting MT criteria or requiring MT protocol activation during the study period were eligible. Patients younger than 18 years of age, patients with more than 5% body surface area burns, patients who received more than 2 L of intravenous fluid prior to admission, patients transferred from another institution, and patients who had a nontraumatic mechanism of hemorrhage were prospectively excluded. Demographics and laboratory, resuscitation, and outcomes data were collected in parallel. Admission standard laboratory samples were collected via initial placement of a 16 g or larger peripheral intravenous line or direct arterial puncture. Our study was approved by the University of California Committee on Human Research.

An MT was defined as a transfusion of 10 units of RBCs or more within the first 24 hours of admission. To mitigate survivor bias by including patients who received a high-volume transfusion but did not survive to 24 hours, scaled transfusions of 5 units or more for patients who died before 12 hours or of 2.5 units or more for patients who died before 6 hours were also defined as MTs. The institutional MT protocol was adopted in 2003, prior to data collection for our study. Activation of the protocol was at the discretion of the attending trauma surgeon or anesthesiologist. Protocol activation prompts the serial delivery of "packs" of 6 units of RBCs/4 units of FFP when activated in the operating room and of 4 units of RBCs/4 units of FFP when activated elsewhere. After the transfusion of each "pack," the protocol prompts consideration of a pooled donor platelet "6 pack" for a platelet count of less than 100 000/mL and 2 units of pooled cryoprecipitate for a fibrinogen level of less than 100 mg/dL, both at the discretion of the treating clinician. A minimum of 4 units of thawed AB plasma and 6 units of type O blood are available in the blood bank at all times for immediate release. Adjunct hemostatic agents such as recombinant factor VIIa (NovoSeven RT; Novo Nordisk Inc) and prothrombin complex concentrate (Bebulin VH; Baxter) were administered purely at the discretion of the attending trauma surgeon or anesthesiologist. Injury was assessed by the Injury Severity Score.[17] Acute lung injury was based on the American-European consensus definition.[18]

All values are presented as mean (SD) values, median values (interquartile range), or percentages; univariate comparisons were made using the *t* test for normally distributed data, the Wilcoxon rank sum test for skewed data, and the Fisher exact test for proportions. Kaplan-Meier time-to-event analysis and log-rank testing were used to assess differences in mortality between groups. Cox proportional hazards regression was performed to identify adjusted predictors of survival. An α level of .05 was considered to be statistically significant. All data analysis was performed by the authors using Stata version 12 (StataCorp).

Results

For the 174 trauma patients evaluated, the mean (SD) Injury Severity Score was 28.4 (16.2), with 50.0% of patients having a penetrating injury and 50.7% of patients having a traumatic brain injury. The mean (SD) admission base deficit was

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Table 1. Overall Patient Demographics

Characteristic	Value
Age, mean (SD), y	39.1 (19.0)
Penetrating injury, %	50.0%
ISS, mean (SD)	28.4 (16.2)
TBI, %	50.7
GCS score, median (IQR)	13 (4-15)
Hemoglobin, mean (SD), g/dL	11.6 (2.3)
Hematocrit, mean (SD), %	34.8 (6.9)
Platelet count, mean (SD), $\times 10^3/\mu L$	244 (93)
INR, median (IQR)	1.3 (1.2-1.6)
Activated PTT, median (IQR), s	31.4 (26.6-39.8)
Base deficit, mean (SD)	−9.8 (6.3)
Duration, median (IQR), d	
Hospital stay	9 (2-30)
ICU stay	4 (1-15)
Ventilation-free	4 (0-25)
Acute lung injury, %	15.5
Mortality rate, %	40.8

Abbreviations: GCS, Glasgow Coma Scale; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; ISS, Injury Severity Score; PTT, partial thromboplastin time; TBI, traumatic brain injury.

SI conversion factors: To convert hemoglobin to grams per liter, multiply by 10; to convert hematocrit to proportion of 1.0, multiply by 0.01; and to convert platelet count to $\times 10^9$ per liter, multiply by 1.0.

Table 2. Resuscitation and Transfusion Characteristics

Characteristic	Value
Required activation of MT protocol, %	76.4
Time to activation, median (IQR), min	41 (20-104)
Received true MT, %	69.5
Activated in emergency department, %	48.1
Activated in operating room, %	45.9
Before MT	
Crystalloid volume, median (IQR), L	1.0 (0-2)
Packed RBCs, median (IQR), U	3 (1-4)
FFP, median (IQR), U	0 (0-0)
Platelets, median (IQR), U	0 (0-0)
RBC:FFP ratio, mean (SD)	1.71 (1.08)
MT protocol	
Crystalloid volume, median (IQR), L	2.0 (1-4)
Packed RBCs, median (IQR), U	8 (4-15)
FFP, median (IQR), U	7 (4-14)
Platelets, median (IQR), U	1 (0-2)
RBC:FFP ratio, mean (SD)	1.22 (0.70)
24-h Total	
Crystalloid volume, median (IQR), L	6.1 (3.4-10.2)
Packed RBCs, median (IQR), U	13 (8-22)
FFP, median (IQR), U	10 (6-18)
Platelets, median (IQR), U	1 (0-2)
RBC:FFP ratio, mean (SD)	1.58 (0.77)

Abbreviations: FFP, fresh frozen plasma; IQR, interquartile range; MT, massive transfusion (>10 U of RBCs in 24 hours); RBCs: red blood cell.

−9.8 (6.3), and the median admission international normalized ratio was 1.3 (interquartile range, 1.2-1.6); the incidence of acute lung injury was 15.5%, and the in-hospital mortality rate was 40.8% (**Table 1**). The institutional MT protocol was formally activated for 133 of the 174 patients (76.4%) in the study population: the median time to activation was 41 minutes, with 64 patients (48.1%) requiring activation in the emergency department, 61 patients (45.9%) requiring activation in the operating room, and 8 patients (6.0%) requiring activation in the radiology department. Overall, patients received a median of 6.1 L of crystalloid, 13 units of RBCs, 10 units of FFP, and 1 unit of platelets over 24 hours, with a mean RBC:FFP ratio of 1.58:1 within 24 hours of admission (**Table 2**). The RBC:FFP ratio sustained during protocolized MT was significantly lower than the RBC:FFP ratio of units administered before activation of the MT protocol ($P = .013$), as well as compared with the 24-hour overall ratio ($P < .001$). Of the 174 patients, 30 (17.2%) received recombinant factor VIIa, and 3 (1.7%) received prothrombin complex concentrate during the course of resuscitation.

We then examined trends in the conduct of resuscitation throughout the study period. The median number of total blood product units given in the first 24 hours decreased significantly over time, from a peak of 57 units in 2006 to 22 units in 2011 (**Figure 1**A; $P = .03$ for trend). The mean RBC:FFP ratio also decreased from a peak of 1.84:1 in 2007 to 1.55:1 in 2011, although this trend did not reach statistical significance (Figure 1B; $P = .20$ for trend). The median total 24-hour crystalloid volume also decreased over time, from a peak of 13 L in 2005 to 4 L in 2011 (Figure 1C; $P < .001$ for trend). There were significant trends toward earlier administration of both RBCs and FFP, as defined by the percentage of total blood product transfused within 6 hours. Specifically, the percentage of RBCs transfused within 6 hours increased from a nadir of 80.2% in 2005 to 87.6% in 2011 ($P = .04$ for trend), while the percentage of FFP transfused within 6 hours increased from a nadir of 74.3% in 2005 to 87.3% in 2011 ($P = .02$); there was no significant trend in the percentage of platelets administered within 6 hours ($P = .39$). Time to activation of the MT protocol, injury severity, and mortality remained stable over the study period ($P = .72$, $P = .24$, and $P = .88$ for individual trends, respectively).

We then examined the effect of all identified trends with $P < .200$ on overall survival throughout the entire study period. Univariate hazard ratios for mortality for each predictor are given in **Table 3**, where increasing transfusion requirements (hazard ratio, 1.01; $P = .001$) and increasing RBC:FFP ratio (hazard ratio, 1.91; $P < .001$) were found to significantly predict mortality in unadjusted analysis. We then used Cox proportional hazards regression to adjust for age, Injury Severity Score, Glasgow Coma Scale score at admission, and base deficit at admission to identify multivariate predictors of in-hospital mortality (Harrell C index of 0.808 for the adjustment model). When adjusted for age and injury characteristics using Cox regression, both the increasing 24-hour transfusion requirement (hazard ratio, 1.02; $P = .006$) and the increasing RBC:FFP ratio (hazard ratio, 1.71; $P = .006$) remained significant multivariate predictors of mortality (Table 3). The total 24-hour crystalloid volume and the percentages of RBCs and FFP transfused before 6 hours were not

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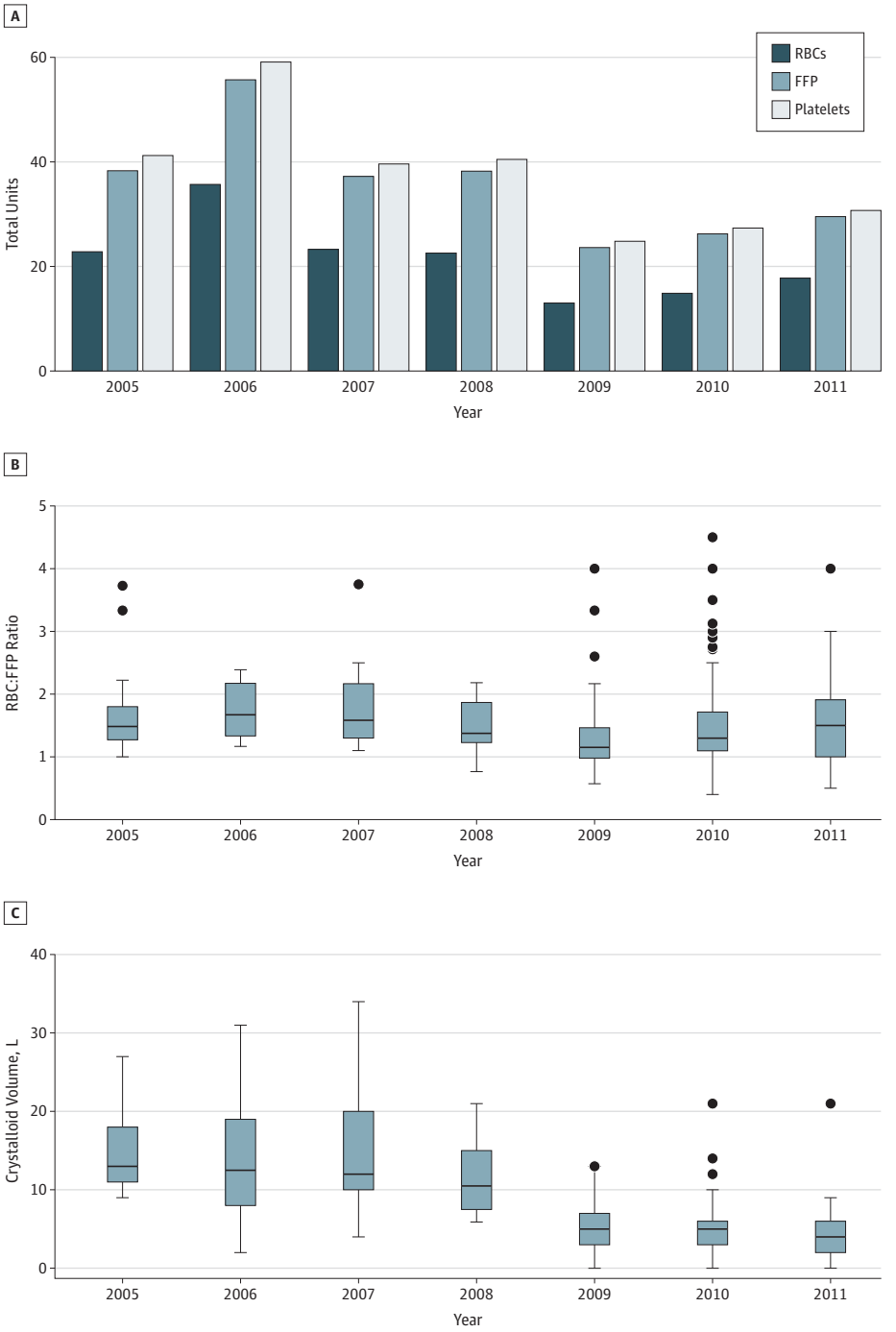
Figure 1. Trends in 24-Hour Blood Product and Crystalloid Administration Over Time



A, The mean combined numbers of red blood cells (RBCs), fresh frozen plasma (FFP), and pooled donor platelets given within 24 hours of admission, by year of study period, are shown. The bars represent the product breakdown ($P = .03$ by test for trend). B, The median ratios of RBCs to FFP transfused within 24 hours of admission, by year of study period ($P = .20$ by test for trend), are shown. C, The median volumes of intravenous crystalloid administered within 24 hours of admission, by year of study period ($P < .001$ by test for trend), are shown. The horizontal line in each box indicates the median, and the top and bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers above and below the box mark the 90th and 10th percentiles. The points beyond the whiskers are outliers beyond the 90th percentile.

significantly associated with mortality in either unadjusted or adjusted analysis (all $P > .100$). Unadjusted and adjusted survival curves for a high- vs low-ratio transfusion are shown in **Figure 2**. In particular, mortality was 1.71-fold more likely for patients transfused at an RBC:FFP ratio of 2:1 compared with those transfused at a 1:1 RBC:FFP ratio, while each decrement of 0.1 in RBC:FFP ratio was associated with a 5.2% reduction in risk for mortality, even when adjusted for patient and injury characteristics.

Discussion

Herein, we describe prospectively collected data on trends in MT practices during a changing era of trauma resuscitation, and we further identify univariate and multivariate associations of the effect of these trends on in-hospital mortality. We observed trends toward reduced overall transfusion practices, earlier empirical plasma transfusion, and more plasma-based RBC:

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Table 3. Unadjusted and Adjusted Predictors of Mortality[a]

Predictor	Unadjusted HR (95% CI)	Unadjusted *P* Value[b]	Adjusted HR (95% CI)	Adjusted *P* Value[b]
Total No. of transfused blood product units	1.01 (1.01-1.02)[c]	.001	1.02 (1.01-1.03)[c]	.006
RBC:FFP ratio	1.91 (1.47-2.48)[c]	<.001	1.71 (1.16-2.52)[c]	.006
Crystalloid volume	0.97 (0.93-1.01)	.18	0.96 (0.91-1.01)	.12
% of Packed RBCs transfused early	1.57 (0.45-5.47)	.48	2.40 (0.39-14.9)	.35
% of FFP transfused early	1.70 (0.57-5.05)	.34	2.10 (0.45-9.81)	.35

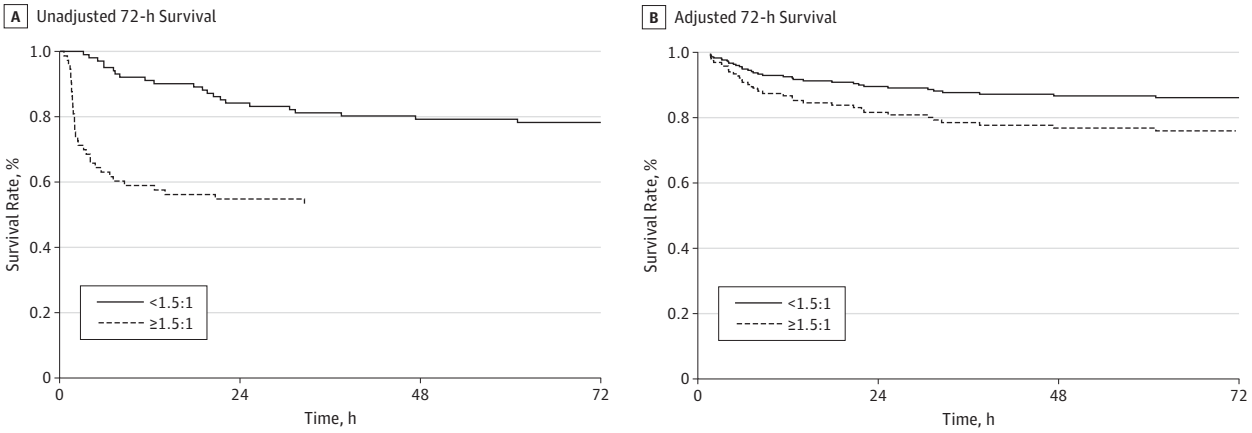
Abbreviations: FFP, fresh frozen plasma; HR, hazard ratio; RBC, red blood cell.

[a] Cox proportional hazards regression was used to generate both unadjusted univariate and adjusted multivariate HRs for in-hospital mortality. The multivariate model adjusted for Injury Severity Score, Glasgow Coma Scale score, and base deficit at admission (Harrell C index of 0.808 for adjustment model).

[b] Determined by the Wald test.

[c] $P < .05$ determined by the Wald test.

Figure 2. Unadjusted and Adjusted Survival Plots



Kaplan-Meier 72-hour survival plots based on the red blood cell (RBC) to fresh frozen plasma (FFP) ratio transfused within 24 hours of admission are shown for unadjusted survival ($P < .001$ determined by log-rank test) (A) and adjusted for age, Injury Severity Score, Glasgow Coma Scale score, and base deficit at admission using Cox proportional hazards regression (B). The Harrell C index was 0.808 for the adjustment model. By convention, the solid line indicates a plasma-based ratio (RBC:FFP ratio < 1.5:1), and the dashed line indicates an erythrocyte-based ratio (RBC:FFP ratio ≥ 1.5:1).

FFP transfusion ratios, in parallel with countrywide trends in MT. We further investigated the association of these trends with improved survival, finding a clinically and statistically significant association of lower RBC:FFP transfusion ratios with reductions in both unadjusted and injury-adjusted in-hospital mortality.

The complexity and the frequently conflicting conclusions of the rapidly changing trauma resuscitation literature over the study period has made it clear that best practices are elusive. As even the "gold standard" randomized clinical trials currently in progress to meaningfully address these topics are fraught with logistic, clinical, and ethical challenges, much of clinical practice in MT for traumatic hemorrhage remains based more on common sense than on clinical evidence. Therefore, we sought to describe the changing practices of clinicians during this dynamic period, with the broad aim of gauging whether promising but untested trends in the literature have gained acceptance on the ground despite the absence of level I evidence.

Paralleling results from a large multicenter study of transfusion practices,[16] we found that the median number of total blood product units administered decreased significantly, that the RBC:FFP transfusion ratio had a moderate trend toward a more plasma-based ratio, and that a higher percentage of total RBCs and FFP were being administered within 6 hours of admission. Despite clinically resonant retrospective data from large military and civilian series,[11-13,19] the utility of plasma-based resuscitation remains unknown; furthermore, the risks of inappropriate plasma administration are ominous, particularly for patients who undergo early plasma-based resuscitation but ultimately do not require an MT.[20] A frequent critique of landmark studies in this field is their clear susceptibility to survival bias. As pointed out in a recent systematic review of trauma resuscitation,[14] the conventional crystalloid- and RBC-based approach to trauma resuscitation (placing many patients who die early after admission in a "high" RBC:FFP ratio category and "reducing" the apparent mortality rate among patients who simply survive long enough to receive substan-

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tial plasma) biases toward the finding of a plasma-based survival benefit, whereas the exclusion of early deaths (thereby excluding patients who may stand the greatest chance of benefiting from early plasma therapy) subtly biases against a plasma-based survival benefit. Little agreement exists on the appropriate analytic techniques to account for this potential bias using currently available data. Snyder et al[21] concluded that adjustment for survival time using time-dependent covariate analysis eliminated the observed survival benefit of plasma-based resuscitation, whereas both Lustenberger et al[22] and Brown et al[23] came to the opposite conclusion using the same technique. Despite significant disagreement, the results presented herein suggest that clinicians have been migrating toward more plasma-based resuscitation strategies, even while the national and international conversation on its merits continues.

We also identify a clear trend toward restricted crystalloid use, with the median 24-hour crystalloid volumes decreasing more than 3-fold over the study period. Similarly to the transfusion ratio controversy, conflicting data exist regarding optimal crystalloid resuscitation as well. An early landmark prospective randomized study[24] began advocating for restricted crystalloid in the treatment of trauma patients nearly 20 years ago, and the theoretical clinical appeal of avoiding hypothermia, saline-associated metabolic acidosis, and dilutional coagulopathy is clear. However, no systematic review or randomized trial has identified an undisputed benefit to this strategy.[25] In fact, a large retrospective series using pooled data from 23 centers found that larger crystalloid volumes of at least 1 L per 1 unit of RBCs are associated with improved survival and fewer overall complications among patients receiving plasma-based resuscitation who either received or did not receive an MT.[26] Again, in the absence of a clear evidence base, clinicians trained under the current Advanced Trauma Life Support guideline paradigm (initial transfusion of 1-2 L of crystalloid, followed by transfusion of RBCs for nonresponders)[27] appear to be migrating away from classical teaching and toward crystalloid-restricted, more plasma-based transfusion practices.

Interestingly, although the trend toward plasma-based transfusion strategies was the weakest trend identified in our data, it was also the most robust predictor of improved survival in both univariate and multivariate analysis. Whether the apparent survival benefit of plasma-based resuscitation identified herein and elsewhere is the result of the empirical avoidance and early reversal of coagulopathy or is related to still poorly understood inflammomodulatory effects of plasma transfusion remains unclear. While the benefit of coagulation factor replacement is easily appreciated in the bleeding and coagulopathic patient, there is also intriguing clinical evidence that this benefit is independent of the presence of coagulopathy.[28] Both in vitro[29] and in vivo[30] studies identify potential direct endothelial modulatory effects of plasma that may serve as additional plausible mechanisms, suggesting that plasma transfusion may play a still unclear inflammomodulatory role above and beyond its function of replacing coagulation factors. Given the observed association of balanced resuscitation with better outcomes confirmed herein, the critical basic science and clinical work aimed at identifying the biochemical underpinnings of plasma-based resuscitation will hopefully provide the needed biological plausibility for available clinical evidence, facilitating more specifically targeted, goal-directed therapy for traumatic hemorrhage.

As with other single-center clinical studies, several limitations are important to the interpretation of the data, in addition to the potential for survival bias already noted. Although the prospective nature of data collection and the careful use of proportional hazards regression lend credence to the internal validity of these results, residual confounding cannot be convincingly minimized outside of the setting of a randomized trial. In terms of external validity, the single-center nature of our study may not allow one to generalize to other institutions with a different MT protocol or to different patient populations, such as patients with long transport times or those who have been transferred from a nontrauma center after acute stabilization. However, the trends toward reduction in median 24-hour RBC administration, more plasma-based resuscitation ratios, and earlier FFP administration seen herein parallel those seen in a large prospective multicenter database,[16] providing some basis for broad relevance of our single-center practice trends and their associations with outcomes.

Overall, the data presented herein provide both an informative exposition of trauma resuscitation trends, reflecting a sea change in the conduct of trauma resuscitation, and a clear statement that clinical equipoise exists and, in fact, demands well-designed multicenter clinical trials on the resuscitation of the critically injured. In the meantime, despite the unavailability of high-quality evidence, it appears that clinicians who care for injured patients are forging ahead, regardless of the controversies in clinical evidence, by migrating toward crystalloid-restricted, more plasma-based MT practices.

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Analysis and interpretation of data: Kutcher, Kornblith, Narayan, Cohen.
Drafting of the manuscript: Kutcher, Narayan, Curd, Fiebig, Cohen.
Critical revision of the manuscript for important intellectual content: Kutcher, Kornblith, Daley, Redick, Nelson, Cohen.
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