

## Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock

J.L. Sperry, F.X. Guyette, J.B. Brown, M.H. Yazer, D.J. Triulzi, B.J. Early-Young, P.W. Adams, B.J. Daley, R.S. Miller, B.G. Harbrecht, J.A. Claridge, H.A. Phelan, W.R. Witham, A.T. Putnam, T.M. Duane, L.H. Alarcon, C.W. Callaway, B.S. Zuckerbraun, M.D. Neal, M.R. Rosengart, R.M. Forsythe, T.R. Billiar, D.M. Yealy, A.B. Peitzman, and M.S. Zenati, for the PAMPer Study Group\*

### ABSTRACT

#### BACKGROUND

After a person has been injured, prehospital administration of plasma in addition to the initiation of standard resuscitation procedures in the prehospital environment may reduce the risk of downstream complications from hemorrhage and shock. Data from large clinical trials are lacking to show either the efficacy or the risks associated with plasma transfusion in the prehospital setting.

#### METHODS

To determine the efficacy and safety of prehospital administration of thawed plasma in injured patients who are at risk for hemorrhagic shock, we conducted a pragmatic, multicenter, cluster-randomized, phase 3 superiority trial that compared the administration of thawed plasma with standard-care resuscitation during air medical transport. The primary outcome was mortality at 30 days.

#### RESULTS

A total of 501 patients were evaluated: 230 patients received plasma (plasma group) and 271 received standard-care resuscitation (standard-care group). Mortality at 30 days was significantly lower in the plasma group than in the standard-care group (23.2% vs. 33.0%; difference, -9.8 percentage points; 95% confidence interval, -18.6 to -1.0%;  $P=0.03$ ). A similar treatment effect was observed across nine prespecified subgroups (heterogeneity chi-square test, 12.21;  $P=0.79$ ). Kaplan-Meier curves showed an early separation of the two treatment groups that began 3 hours after randomization and persisted until 30 days after randomization (log-rank chi-square test, 5.70;  $P=0.02$ ). The median prothrombin-time ratio was lower in the plasma group than in the standard-care group (1.2 [interquartile range, 1.1 to 1.4] vs. 1.3 [interquartile range, 1.1 to 1.6],  $P<0.001$ ) after the patients' arrival at the trauma center. No significant differences between the two groups were noted with respect to multiorgan failure, acute lung injury-acute respiratory distress syndrome, nosocomial infections, or allergic or transfusion-related reactions.

#### CONCLUSIONS

In injured patients at risk for hemorrhagic shock, the prehospital administration of thawed plasma was safe and resulted in lower 30-day mortality and a lower median prothrombin-time ratio than standard-care resuscitation. (Funded by the U.S. Army Medical Research and Materiel Command; PAMPer ClinicalTrials.gov number, NCT01818427.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Sperry at the University of Pittsburgh, Department of Surgery and Critical Care Medicine, 200 Lothrop St., Pittsburgh, PA, 15213, or at [sperryjl@upmc.edu](mailto:sperryjl@upmc.edu).

\*A complete list of the members of the PAMPer Study Group is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

Drs. Sperry and Guyette contributed equally to this article.

*N Engl J Med* 2018;379:315-26.

DOI: 10.1056/NEJMo1802345

Copyright © 2018 Massachusetts Medical Society.

**T**HE ACUTE CARE OF SEVERELY INJURED patients with hemorrhage after their arrival at a trauma center has evolved over the past decade.<sup>1,2</sup> Current treatment priorities include prevention of coagulopathy through minimization of the use of crystalloid-based resuscitation in favor of early blood component–based resuscitation that includes plasma and platelets in equal ratios with packed red cells.<sup>3</sup> These in-hospital practices, termed “damage-control resuscitation,” are widely used for both battlefield and civilian resuscitation after traumatic injury.<sup>2-5</sup>

Initiation of the tenets of damage-control resuscitation in the prehospital environment has the potential to reduce downstream complications attributable to hemorrhage by intervening close to the time of injury, before the development of coagulopathy, irreversible shock, and the ensuing inflammatory response.<sup>6-9</sup> Plasma transfusion mitigates the coagulopathy that can complicate traumatic hemorrhage, alters the inflammatory response after injury, and reduces the permeability of endothelial cells after hemorrhagic shock.<sup>3,7,10-14</sup> Despite these potential benefits, the risks associated with plasma transfusion in the prehospital environment remain unknown. High-level evidence is lacking to show its efficacy and support its use in the prehospital setting.<sup>15-17</sup>

The Prehospital Air Medical Plasma (PAMPer) trial was designed to determine the efficacy and safety of prehospital plasma resuscitation as compared with standard-care resuscitation (not including plasma administration) in severely injured patients at risk for hemorrhagic shock. We hypothesized that prehospital administration of plasma would reduce 30-day mortality.

## METHODS

### TRIAL DESIGN

The PAMPer trial was a pragmatic, multicenter, cluster-randomized, phase 3 trial involving injured patients who were at risk for hemorrhagic shock during air medical transport to a trauma center; outcomes in patients who received 2 units of thawed plasma (either group AB or group A with a low anti-B antibody titer) (the plasma group) were compared with outcomes in those who received standard-care resuscitation (the standard-care group) in the prehospital setting.<sup>18</sup> Other than the administration of plasma, we did not alter any aspect of treatment either during

transport of the patients or after their arrival at the definitive trauma center. Prehospital administration of plasma was not part of standard care for any of the participating sites during the trial.

### TRIAL OVERSIGHT

The trial was designed by the authors, and the Food and Drug Administration, the Human Research Protection Office of the Department of Defense, and the institutional review boards at the participating sites approved the design. The institutional review board at each site approved an exception from informed consent requirements, after consultation with community members and after public notification regarding the trial took place. We notified enrolled participants or their legally authorized representatives and asked them to provide, as soon as feasible, consent to continue participation.<sup>19</sup> An external data and safety monitoring board performed regular safety surveillance. No commercial support was involved in the trial. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). No one who is not an author participated in the writing or review of the manuscript.

### PATIENT POPULATION

Patients who were transported from the scene of their injury to a participating trauma center or who were transferred from an outside referral emergency department to a participating trauma center were eligible for enrollment in the PAMPer trial if they had at least one episode of hypotension (systolic blood pressure <90 mm Hg) and tachycardia (defined in this trial as a heart rate >108 beats per minute) or if they had any severe hypotension (systolic blood pressure <70 mm Hg), either before the arrival of air medical transport or any time before arrival at the trauma center (Table S2 in the Supplementary Appendix, available at NEJM.org). Patients were excluded if they were older than 90 years of age or younger than 18 years of age, if intravenous or intraosseous access could not be established in them, if they had had an isolated fall from standing, if they had a documented cervical cord injury, if they were known to be a prisoner, if they were known to be pregnant, if they had a traumatic cardiac arrest that lasted longer than 5 minutes, if they had a penetrating brain injury, if their injury was

due to isolated drowning or hanging, if they had burns over more than 20% of their total body-surface area, if they were being admitted as an inpatient at an outside referral hospital, if they or a family member voiced an objection to participation in the trial at the scene of the injury, or if they were wearing an “opt-out” bracelet, indicating that they wished to opt out of the PAMPer trial.

#### RANDOMIZATION AND MASKING

We used a single-stage cluster randomization scheme because of the limited availability and short shelf life (5 days) of universal donor thawed plasma. Using computer-generated block randomization, we assigned air medical bases at each participating institution to the plasma group or the standard-care group for 1-month time intervals. Because of the cluster design of the trial, the treatment group to which eligible patients were assigned was based on the random assignment of the transporting base, irrespective of whether a patient received plasma or standard-care resuscitation at an outside hospital. The block scheme varied randomly among 2-month, 4-month, and 6-month block sizes during the period of enrollment. It was not possible for prehospital personnel and receiving physicians at the trial sites to be unaware of the treatment assignments because the trial intervention was a blood product, which requires full traceability. However, treatment assignments were concealed to personnel who assessed the trial outcomes.

#### INTERVENTION

Air medical bases that were randomly assigned to the plasma group for the month were provided 2 units of either group AB or group A with a low anti-B antibody titer (<1:100) thawed plasma. The intervention consisted of the administration of 2 units of thawed plasma, which was initiated in the prehospital setting by the air transport team. Plasma was administered once a patient met all the inclusion criteria and none of the exclusion criteria and before other resuscitative fluids were initiated. The protocol required that both units of the prehospital-initiated plasma be infused to completion even if the infusion was still ongoing at the time of arrival at the trauma center. In cases in which completion of the infusion of the 2 units of plasma occurred during flight, standard trauma resuscitation (as defined

by the local protocol) resumed until arrival at the trauma center. Plasma units that were used were replenished, and unused plasma units were exchanged before their expiration dates were reached.

For the air medical bases that were assigned to the standard-care group for the month, patients who met all the inclusion criteria and none of the exclusion criteria received standard-care resuscitation, which included infusion of a crystalloid solution as the primary resuscitative fluid, during the flight. As part of their standard resuscitation practice, air transport teams at 13 of the 27 air medical bases that participated in the trial also carried 2 units of universal donor red cells on all their flights. Indications for administration of red cells followed local protocols and were equivalent across the bases (Table S3 in the Supplementary Appendix). Air transport teams at bases that were assigned to the plasma group during a given month and that carried red cells on all their flights administered the 2 units of thawed plasma first. If a patient remained hypotensive after the plasma infusion or had obvious bleeding, transfusion of red cells then proceeded according to the local protocol. A standard operating procedure for goal-directed, crystalloid-based resuscitation on the basis of hemodynamic status was established to minimize the use of overly aggressive crystalloid-based resuscitation in both trial groups<sup>15,20</sup> (Fig. S1 in the Supplementary Appendix).

#### OUTCOMES

The primary outcome of the trial was mortality at 30 days. Prespecified secondary outcomes included mortality at 24 hours and in-hospital mortality; volumes of blood components and resuscitation fluid administered within 24 hours after enrollment; the incidence of multiorgan failure, acute lung injury–acute respiratory distress syndrome, transfusion-related acute lung injury, and nosocomial infection; and indexes of coagulopathy on the basis of measurements of prothrombin-time ratio and results of thromboelastography. We also analyzed the treatment effect on the primary outcome in prespecified subgroups defined according to receipt of a massive transfusion (defined as  $\geq 10$  units of packed red cells during the first 24 hours after the injury) (yes vs. no), receipt of 4 or more units of packed red cells during the first 24 hours after

the injury (yes vs. no), receipt of packed red cells in the prehospital setting (yes vs. no), occurrence of severe traumatic brain injury (defined as a score for injury to the head of  $>2$  on the Abbreviated Injury Scale, on which scores range from 0 to 6, with higher scores indicating more severe injury) (yes vs. no), trial enrollment location (at the scene of injury vs. at a referral emergency department), history of treatment with a vitamin K antagonist (yes vs. no), history of treatment with an antiplatelet medication (yes vs. no), type of injury (blunt vs. penetrating), and prehospital transport time (short vs. prolonged).

#### STATISTICAL ANALYSIS

To determine an appropriate sample size, we assumed a 1:1 randomization of equal cluster sizes, with 32 clusters of 16 patients each, using an estimated intracluster correlation coefficient of 0.05 to adjust for potential unequal cluster sizes. We estimated that enrollment of 530 prehospital patients would result in 504 eligible patients with complete data and would provide the trial with 88% power to detect a difference of 14 percentage points (8.0% vs. 22.0%) in 30-day mortality between the plasma group and the standard-care group, on the basis of published mortality estimates.<sup>21-26</sup> Approximately 2 years and 8 months after trial enrollment began, with approval from the data and safety monitoring board, the institutional review board at each site, and the Food and Drug Administration, we increased the planned sample size to 564 patients owing to a higher rate of ineligible patients in the prehospital setting than was initially estimated.

For the primary analysis, which was based on the modified intention-to-treat principle, we compared 30-day mortality in the plasma group with that in the standard-care group using a two-sided pooled z test with continuity correction. We calculated the intraclass correlation, which was used to account for the cluster design in our primary analysis. When a patient's vital status at 30 days was unknown, the missing data were imputed with the use of multiple imputation (Table S5 in the Supplementary Appendix). We performed the following sensitivity analyses of the primary outcome: one that excluded all the patients whose vital status at 30 days was unknown, one that assumed that all the patients whose vital status at 30 days was unknown sur-

vived, and one that assumed 50% mortality among patients whose vital status at 30 days was unknown. A multivariate regression model with generalized estimating equations was used in the analysis of the primary outcome to adjust for unbalanced baseline variables between the two trial groups while accounting for clustering at the air medical base level, as specified in the protocol. The critical level of statistical significance for the primary analysis ( $P < 0.038$ ) was adjusted for two interim analyses, and all comparisons were conducted with the use of two-sided tests.<sup>27</sup> A Bonferroni correction was used to account for multiple comparisons across the prespecified secondary outcomes and subgroup analyses (Table S6 in the Supplementary Appendix). Analyses were performed with the use of Stata software, version 15MP (StataCorp).

## RESULTS

### PATIENTS

From May 2014 through October 2017, a total of 7275 patients who were transported by air medical transport by personnel from 27 individual air medical bases to 9 participating trauma centers were assessed for eligibility. A total of 564 patients were eligible for enrollment in the prehospital setting. Of these patients, 230 were transported from air medical bases that were randomly assigned to the plasma group, and 271 were transported from bases randomly assigned to the standard-care group; these 501 patients met all the inclusion criteria and none of the exclusion criteria and comprised the modified intention-to-treat cohort (Fig. 1).

Most of the patients (72.7%) were men, and most (82.4%) had an injury caused by blunt trauma, with a median Injury Severity Score of 22 (interquartile range, 13 to 30; scores range from 0 to 75, with a score of  $>15$  indicating major trauma) and an overall 30-day mortality rate of 29.6%. Prehospital intubation occurred in 256 patients (51.1%), and 174 patients (34.7%) received a prehospital red-cell transfusion. Surgeons performed urgent operative procedures in 58.4% of patients during the initial 24 hours after enrollment.

Owing to the pragmatic design of the trial, patients who met all the inclusion criteria and none of the exclusion criteria could be enrolled

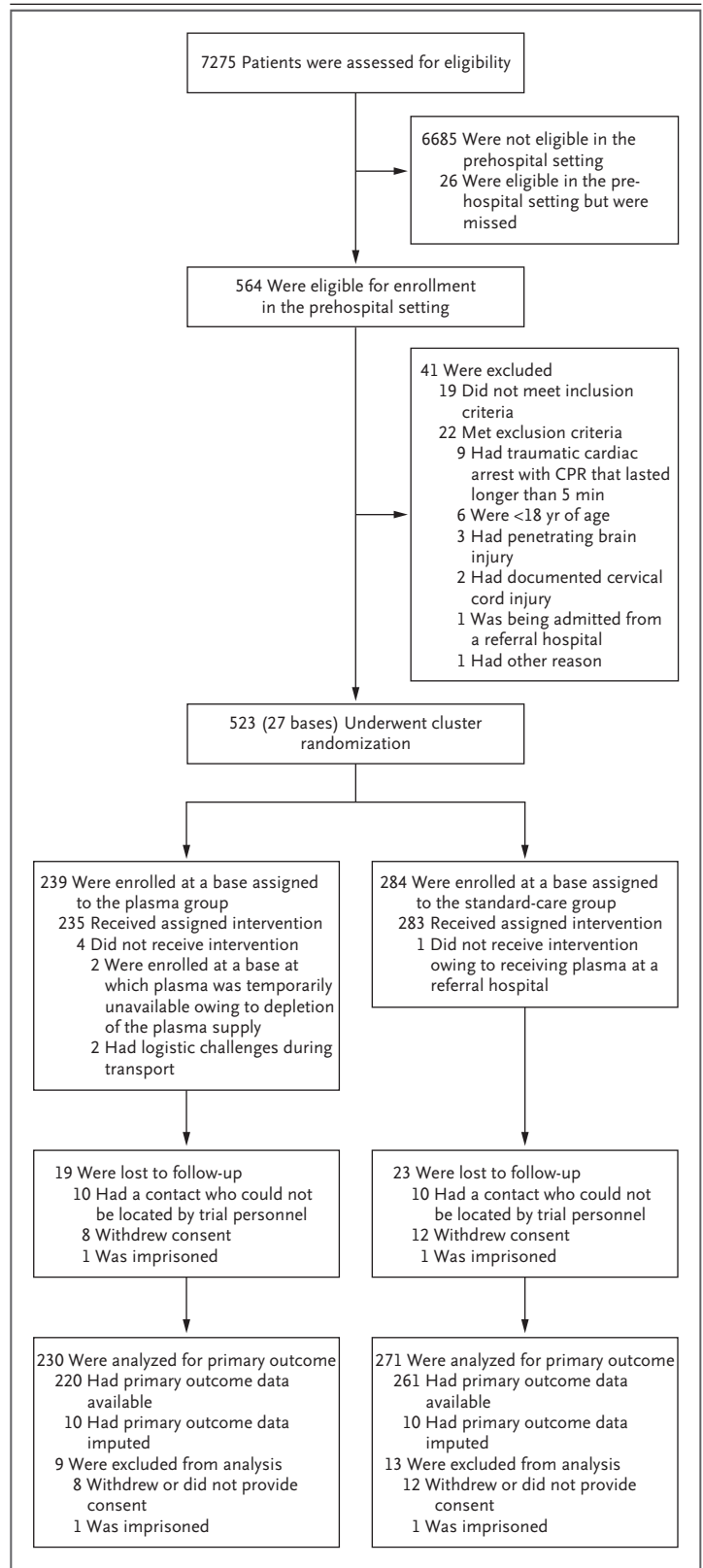
**Figure 1. Screening, Randomization, and Follow-up.**

In accordance with approval requirements of the Food and Drug Administration and of the institutional review board at each site, data from participants who either withdrew consent or were excluded because of ineligibility could not be included in the analyses. Owing to the randomization scheme that was used, there was an imbalance between the two groups in the number of patients enrolled. As prespecified in the study protocol, multiple imputation of missing data was used in the primary analysis for the 20 participants whose vital status at 30 days was unknown. The primary outcome was mortality at 30 days.

either during transfer directly from the scene of an accident or during transfer from an outside referral emergency department that did not have the appropriate capabilities to treat severely injured trauma patients. The 111 patients who were transferred from outside referral emergency departments had demographic and injury characteristics that were similar to those of the 390 patients who were enrolled during transfer directly from the scene of their injury but had longer prehospital transport times from the time of measurement of qualifying vital signs to arrival at the trauma center (52 minutes [interquartile range, 40 to 70] vs. 39 minutes [interquartile range, 31 to 49]). The percentage of patients who underwent prehospital intubation was lower among those who were transferred than among those who were enrolled at the scene (37.3% vs. 51.9%), and the percentage who received prehospital transfusion of packed red cells was higher among those who were transferred (45.9% vs. 30.8%). The percentage of patients who were transferred from outside referral emergency departments was similar in the two trial groups (21.8% in the standard-care group and 22.6% in the plasma group).

**PROTOCOL ADHERENCE**

Prehospital treatment teams administered the assigned treatment (irrespective of volume) in 496 of the 501 participants (99.0%). In the plasma group, 205 patients (89.1%) received 2 units of plasma, 21 patients (9.1%) received 1 unit of plasma, and 4 patients (1.7%) received no plasma owing to logistic challenges during prehospital care. The plasma infusion was completed during air medical transport in 84.4% of the patients, with the plasma infusion in the remaining pa-





tients completed soon after their arrival at the trauma center. One patient (0.4%) in the standard-care group received prehospital plasma at the referral hospital before transport.

Patients in the standard-care group, for whom plasma was unavailable, received greater volumes of prehospital crystalloid solution than the patients in the plasma group, and a higher percentage of patients in the standard-care group received red-cell transfusions before their arrival at the trauma center (Table 1). The demographic characteristics, prehospital vital signs, and injury characteristics were similar in the two trial groups.

#### PRIMARY OUTCOME

Data on the primary outcome were available for 481 patients (96.0%). At 30 days after randomization, there were 89 deaths in the standard-care group and 53 deaths in the plasma group. After multiple imputation was performed for the 20 patients whose vital status at 30 days was unknown (10 patients in each group), 30-day mortality, accounting for intracluster variation, was lower among patients who received thawed plasma than among those who received standard care (23.2% vs. 33.0%; difference, -9.8 percentage points; 95% confidence interval [CI], -18.6 to -1.0;  $P=0.03$ ; intracluster correlation coefficient, 0.02). In sensitivity analyses of 30-day mortality that were based on various methods of handling missing data on vital status, significant differences remained between the two trial groups (Table S9 in the Supplementary Appendix). When multivariate regression was used to adjust for the volume of prehospital crystalloid solution administered and for the percentage of patients who received prehospital red-cell transfusion, while also accounting for clustering at the base level, administration of prehospital plasma was associated with a risk of death within 30 days after randomization that was 39% lower than the risk with standard care (adjusted odds ratio, 0.61; 95% CI, 0.40 to 0.91;  $P=0.02$ ). The Kaplan-Meier survival curves showed an early separation of the two groups that began 3 hours after randomization (Fig. S2 in the Supplementary Appendix) and remained until 30 days (720 hours) after randomization (log-rank chi-square test, 5.70;  $P=0.02$ ) (Fig. 2A).

The results of the analysis of mortality at 30 days in the nine prespecified subgroups revealed lower mortality at 30 days in the plasma group

than in the standard-care group in a majority of the subgroups (Fig. 2B). There was no heterogeneity of the treatment effect across the subgroups (heterogeneity chi-square test, 12.21;  $P=0.79$ ). We tested the interaction between treatment group and each subgroup variable; no significant interactions were observed after adjustment for multiple comparisons.

#### SECONDARY OUTCOMES

Mortality at 24 hours and in-hospital mortality were lower in the plasma group than in the standard-care group (Table 2). Patients in the plasma group received fewer units of blood components overall and fewer units of packed red cells within 24 hours after enrollment and had a lower median prothrombin-time ratio at the time of the first blood sampling after arrival at the trauma center than patients in the standard-care group. When  $P$  values were adjusted for multiple comparisons, only the difference in prothrombin-time ratio between the trial groups remained significant. No significant differences between the groups were noted with respect to other resuscitation-related variables at 24 hours; the incidence of multiorgan failure, acute lung injury-acute respiratory distress syndrome, or nosocomial infections; or the results of thromboelastography at admission.

#### SAFETY

We observed no documented cases of transfusion-related lung injury during the trial. Five patients (2.2%) in the plasma group had transfusion-related reactions or allergic reactions that were considered to be possibly related to the trial treatment; these reactions were assessed as minor by personnel at the blood bank services at each site at which the reaction was reported. The management of each such reaction occurred during transport or at the time of arrival at the trauma center without further complication. One transfusion-related or allergic reaction (0.4%) was reported in the standard-care group. A total of 10 adverse events, which were defined as any events that were considered to be related to the trial regimen, were reported in the trial population; 3 of these were designated as serious adverse events (1 in the plasma group and 2 in the standard-care group) (Table 3). A list of protocol violations according to trial group is provided in Table S11 in the Supplementary Appendix.

**Table 1. Patient Characteristics.\***

Variable	Standard-Care Group (N = 271)	Plasma Group (N = 230)
Median age (IQR) — yr	46 (28–60)	44 (31–59)
Male sex — no. (%)	200 (73.8)	164 (71.3)
Race — no. (%)†		
White	228 (84.1)	207 (90.0)
Black	29 (10.7)	14 (6.1)
Asian	1 (0.4)	0
Other	6 (2.2)	2 (0.9)
Unknown	7 (2.6)	7 (3.0)
Hispanic ethnic group — no. (%)‡	9 (3.3)	6 (2.6)
Any injury caused by blunt trauma — no. (%)‡‡	226 (83.4)	187 (81.3)
Fall from height	23 (10.2)	12 (6.4)
Motor vehicle collision	120 (53.1)	106 (56.7)
Motorcycle collision	46 (20.4)	29 (15.5)
Pedestrian or bicycle collision	14 (6.2)	15 (8.0)
Assault	10 (4.4)	9 (4.8)
Other	13 (5.8)	16 (8.6)
Any injury caused by penetrating trauma — no. (%)‡‡	49 (18.1)	46 (20.0)
Firearm	25 (51.0)	26 (56.5)
Impalement or stabbing	24 (49.0)	20 (43.5)
Transported from referral hospital — no. (%)	59 (21.8)	52 (22.6)
Median prehospital volume of crystalloid solution (IQR) — ml§	900 (0–1500)	500 (0–1250)
Prehospital red-cell transfusion — no. (%)¶	114 (42.1)	60 (26.1)
Initial Glasgow Coma Scale score <8 — no. (%)	129 (47.6)	103 (44.8)
Median prehospital systolic blood pressure (IQR) — mm Hg**	69 (61–81)	71 (64–81)
Median prehospital heart rate (IQR) — beats/min	115 (96–126)	117 (104–128)
Prehospital intubation — no. (%)	141 (52.0)	115 (50.0)
Prehospital cardiopulmonary resuscitation — no. (%)	18 (6.6)	13 (5.7)
Median prehospital transport time (IQR) — min	40 (33–51)	42 (34–53)
Median Injury Severity Score (IQR) ††	21 (12–29)	22 (14–33)
Abbreviated Injury Scale score for head‡‡‡		
Median (IQR)	1 (0–3)	2 (0–3)
Score >2 — no. (%)	97 (35.8)	88 (38.3)
History of treatment with vitamin K antagonist — no. (%)	8 (3.0)	6 (2.6)
History of treatment with antiplatelet medication — no. (%)	18 (6.6)	20 (8.7)

\* No significant differences were observed between the two groups in the above characteristics except where noted. Continuous variables were compared with the use of the Mann-Whitney U test, and categorical variables were compared with the use of Fisher's exact test. IQR denotes interquartile range.

† Race and ethnic group were determined by patient or family-member report.

‡ The percentages for the subcategories of this variable are based on the number of patients assessed for this variable rather than on the total number of patients in each trial group.

§ P=0.01.

¶ P<0.001.

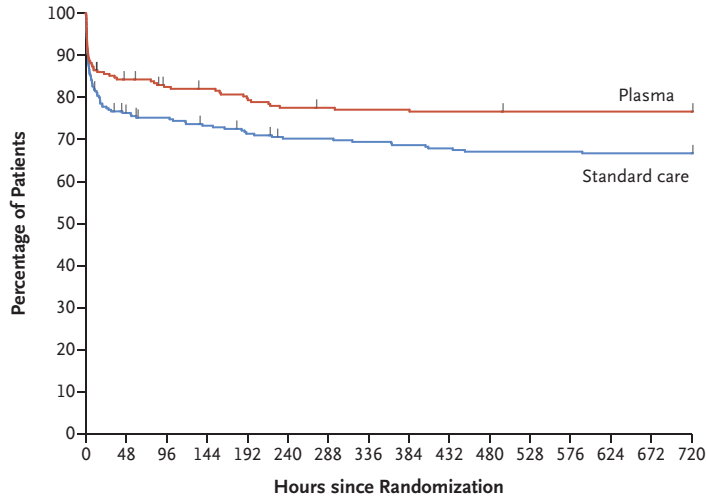
|| Scores range from 3 to 15, with lower scores indicating worse mental status.

\*\* Data were unavailable for one patient in the plasma group.

†† Scores range from 0 to 75, with a score of greater than 15 indicating major trauma. Data were unavailable for two patients in the standard-care group and four patients in the plasma group.

‡‡‡ Scores range from 0 to 6, with higher scores indicating more severe injury; a score of greater than 2 indicates a severe traumatic brain injury. Data were unavailable for two patients in the standard-care group and three patients in the plasma group.

**A Survival**



No. at Risk	0	48	96	144	192	240	288	336	384	432	480	528	576	624	672	720
Plasma	230	183	172	170	169	168	168	168	168	168	168	168	168	168	168	168
Standard care	271	194	181	179	173	172	172	172	172	172	172	172	172	172	172	172

**B 30-Day Mortality in Prespecified Subgroups**

Subgroup	No. of Patients	Standard Care <i>no. of events/total no. (%)</i>	Plasma	Odds Ratio (95% CI)	Adjusted P Value for Interaction
<b>≥10 units packed red cells in 24 hr</b>					>0.99
No	377	63/198 (31.8)	35/179 (19.6)	0.52 (0.32–0.84)	
Yes	104	26/63 (41.3)	18/41 (43.9)	1.11 (0.50–2.47)	
<b>≥4 units packed red cells in 24 hr</b>					>0.99
No	243	32/124 (25.8)	20/119 (16.8)	0.58 (0.31–1.09)	
Yes	238	57/137 (41.6)	33/101 (32.7)	0.68 (0.40–1.17)	
<b>Prehospital packed red cells</b>					>0.99
No	309	50/148 (33.8)	36/161 (22.4)	0.56 (0.34–0.93)	
Yes	172	39/113 (34.5)	17/59 (28.8)	0.77 (0.39–1.52)	
<b>Traumatic brain injury</b>					>0.99
No	295	36/165 (21.8)	22/130 (16.9)	0.73 (0.41–1.32)	
Yes	181	51/94 (54.3)	29/87 (33.3)	0.42 (0.23–0.77)	
<b>Enrollment location</b>					>0.99
Scene	373	76/203 (37.4)	40/170 (23.5)	0.51 (0.33–0.81)	
Referral emergency department	105	11/56 (19.6)	13/49 (26.5)	1.48 (0.59–3.69)	
<b>Mechanism of injury</b>					>0.99
Blunt	402	83/220 (37.7)	47/182 (25.8)	0.57 (0.37–0.88)	
Penetrating	79	6/41 (14.6)	6/38 (15.8)	1.09 (0.32–3.74)	
<b>Prehospital transport time</b>					>0.99
Short	225	41/131 (31.3)	21/94 (22.3)	0.63 (0.34–1.16)	
Prolonged	253	48/130 (36.9)	29/123 (23.6)	0.53 (0.30–0.91)	
<b>Vitamin K antagonist</b>					>0.99
No	353	32/186 (17.2)	18/167 (10.8)	0.58 (0.31–1.08)	
Yes	14	2/8 (25.0)	1/6 (16.7)	0.60 (0.04–8.73)	
<b>Antiplatelet medication</b>					>0.99
No	338	33/181 (18.2)	16/157 (10.2)	0.51 (0.27–0.97)	
Yes	38	3/18 (16.7)	5/20 (25.0)	1.67 (0.34–8.26)	
<b>Overall</b>	481	89/261 (34.1)	53/220 (24.1)	0.61 (0.41–0.92)	

0.03 0.05 0.10 0.25 0.50 1.00 2.00 4.00 10.00

← Plasma Better                      Standard Care Better →



**Figure 2 (facing page). Survival and Subgroup Analyses of Mortality at 30 Days.**

Panel A shows Kaplan–Meier estimates of survival among patients who received standard-care resuscitation or plasma resuscitation in the prehospital setting. The time at which qualifying vital signs were recorded in the prehospital environment represents time zero. A Cox proportional-hazards regression model, which was adjusted for imbalances between the groups in the volume of prehospital crystalloid solution administered and in the percentage of patients who received prehospital red-cell transfusion, stratified according to air medical base, showed a lower risk of death within 30 days after randomization in the plasma group than in the standard-care group (hazard ratio for death, 0.64; 95% CI, 0.45 to 0.91;  $P=0.01$ ). Panel B shows the odds ratio of 30-day mortality in the nine prespecified subgroups. The solid vertical line represents an odds ratio of 1.0, indicating no difference in mortality between the standard-care group and the plasma group. The dotted vertical line represents the overall odds ratio for treatment effect in the modified intention-to-treat cohort of patients for whom information on vital status at 30 days was not missing. Adjusted  $P$  values were calculated for the interaction between treatment group and each subgroup in a logistic-regression model with 30-day mortality as the outcome to determine whether there was a significant effect of treatment on the outcome across each subgroup; significance levels were adjusted for multiple comparisons with the use of a Bonferroni correction.

or nosocomial infections.<sup>15,20,25,26,29</sup> Despite the potential concerns that administration of prehospital plasma may be associated with transfusion-related complications, no cases of transfusion-related lung injury were documented in our trial, and only a low incidence of minor allergic reactions and transfusion-related reactions potentially related to plasma administration was noted.

This clinical trial has a number of strengths. First, the trial was pragmatic in design, with simple inclusion criteria that were based on vital signs and with limited exclusion criteria. Second, given that each patient's injuries could not be fully characterized before their arrival at the trauma center, patients with a wide spectrum of injuries and severities of injury were enrolled. Prespecified subgroup analyses showed a consistent survival benefit in the plasma group across various injury types, which suggests broad generalizability of the results. Third, the intervention consisted of a relatively small volume of prehospital plasma, which resulted in a robust mortality benefit. Previous trials have shown benefit when plasma is incorporated into resuscitation practice after the patient's arrival at the trauma center.<sup>3,30,31</sup> These benefits may be magnified when plasma is provided close to the time of injury. The underlying mechanisms responsible for this survival benefit may include a reduction in bleeding or coagulopathy, a diminution of the inflammatory response or endothelial dysfunction of trauma, or both.<sup>6,10,32,33</sup>

Limitations of the trial include its cluster design, which was essential for the conduct of the trial because of the limited availability and short shelf-life of the thawed plasma intervention. The randomization scheme resulted in imbalanced enrollment, and the inability to mask the intervention resulted in the potential for treatment bias. There were differences between the two groups in the volume of prehospital crystalloid solution administered and in the percentage of patients who received red-cell transfusions before their arrival at the trauma center, although we adjusted for these differences in the primary analysis. These differences were inherent in the design of the trial owing to the need to resuscitate hypotensive patients with trauma in the standard-care group without the use of plasma. Despite the fact that the percentage of patients who were transferred from outside referral

## DISCUSSION

Resuscitation strategies for the acutely injured patient in hemorrhagic shock have evolved, with patients benefitting from receiving less crystalloid-based therapy and early balanced blood component-based therapy once they arrive at a facility for definitive care.<sup>2,3,22</sup> Despite these changes, a majority of deaths from traumatic hemorrhage continue to occur in the first hours after arrival at the trauma center, which underscores the importance of the prehospital environment for early interventions that provide benefit.<sup>2,3,22,28</sup>

Among the 501 eligible patients who were enrolled in the prehospital setting in our trial, the group that received prehospital plasma had significantly lower mortality at 24 hours and at 30 days and a lower median prothrombin-time ratio than the patients who received standard care. Patients in the plasma group did not have a higher incidence of inflammatory-mediated complications, such as multiorgan failure, acute lung injury–acute respiratory distress syndrome,

**Table 2. Secondary Trial Outcomes.\***

Outcome	Standard-Care Group (N = 271)	Plasma Group (N = 230)	Difference (95% CI)†	Observed P Value‡	Adjusted P Value§
24-hr mortality — no. (%)	60 (22.1)	32 (13.9)	-8.2 (-14.9 to -1.6)	0.02	0.55
In-hospital mortality — no. (%)	88 (32.5)	51 (22.2)	-10.3 (-18.0 to -2.6)	0.01	0.33
Median total 24-hr volume of blood components transfused (IQR) — units	4 (2 to 16)	3 (0 to 10)		0.02	0.41
Median 24-hr volume of packed red cells transfused (IQR) — units	4 (1 to 9)	3 (0 to 7)		0.03	0.69
Median 24-hr volume of plasma transfused (IQR) — units	0 (0 to 4)	0 (0 to 3)		0.26	>0.99
Median platelet transfusion volume at 24 hours (IQR) — units	0 (0 to 1)	0 (0 to 1)		0.22	>0.99
Median 24-hr volume of crystalloids infused (IQR) — ml	4500 (3000 to 6800)	4388 (2225 to 6320)		0.14	>0.99
Vasopressors received in first 24 hr — no. (%)	138 (50.9)	104 (45.2)	-5.7 (-14.4 to 3.1)	0.21	>0.99
Multiorgan failure — no. (%)	156 (57.6)	145 (63.0)	5.4 (-3.1 to 14.1)	0.23	>0.99
Acute lung injury—acute respiratory distress syndrome — no. (%)	50 (18.5)	48 (20.9)	2.4 (-4.8 to 9.4)	0.50	>0.99
Nosocomial infection — no. (%)	49 (18.1)	46 (20.0)	1.9 (-4.9 to 8.8)	0.65	>0.99
Allergic reaction or transfusion-related reaction — no. (%)	1 (0.4)	5 (2.2)	1.8 (-0.2 to 3.8)	0.10	>0.99
Median initial prothrombin-time ratio (IQR)¶	1.3 (1.1 to 1.6)	1.2 (1.1 to 1.4)		<0.001	<0.001
Median initial results of rapid thromboelastography (IQR)¶¶					
Activated clotting time — sec**	113 (101 to 136)	113 (97 to 132)		0.39	>0.99
K-time — min††	1.9 (1.3 to 3.0)	1.8 (1.2 to 2.7)		0.17	>0.99
Alpha-angle — deg‡‡	68.3 (59.1 to 73.9)	70.6 (62.1 to 75.2)		0.08	>0.99
Maximal amplitude — mm§§	57.2 (48.6 to 63.2)	58.3 (49.1 to 63.6)		0.30	>0.99
LY30 — %¶¶¶	2.0 (0 to 30.0)	1.3 (0 to 20.0)		0.38	>0.99

\* All transfusion and resuscitation volumes were totaled over the course of 24 hours beginning at the time of measurement of prehospital qualifying vital signs and enrollment; the 24-hour volumes of plasma transfused do not include the volume of plasma intervention.

† Differences are expressed as percentage points.

‡ Continuous variables were compared with the use of the Mann-Whitney U test, and categorical variables were compared with Fisher's exact test.

§ Significance levels were adjusted with the use of a Bonferroni correction to account for multiple comparisons. Adjusted P values were calculated by multiplying the observed P value by the number of comparisons (27 tests, which included all the secondary outcomes and subgroup interactions).

¶ Data were unavailable for 29 patients in the standard-care group and 24 patients in the plasma group.

¶¶ Thromboelastography was used to assess the viscoelastic properties of blood samples obtained during the trial.

\*\* Activated clotting time is the time between the initiation of the test and the initial formation of fibrin and is longer when a patient has a clotting factor deficiency or severe hemodilution.

†† Data were unavailable for 73 patients in the standard-care group and 66 patients in the plasma group.

‡‡ K-time is the time that is needed to reach 20-mm clot strength and is generally longer when a patient has hypofibrinogenemia or a platelet deficiency. Data were unavailable for 72 patients in the standard-care group and 66 patients in the plasma group.

§§ Alpha-angle is the slope of the tracing that represents the rate of clot formation; the value decreases when a patient has hypofibrinogenemia or a platelet deficiency. Data were unavailable for 64 patients in the standard-care group and 60 patients in the plasma group.

¶¶ The maximal amplitude is the greatest amplitude of the tracing and reflects the contribution of platelets to clot strength. Data were unavailable for 63 patients in the standard-care group and 60 patients in the plasma group.

¶¶¶ LY30 is the percent reduction in amplitude 30 minutes after the maximal amplitude is reached; when elevated, it reflects a state of hyperfibrinolysis. Data were unavailable for 113 patients in the standard-care group and 98 patients in the plasma group.

emergency departments and the percentage of patients who were enrolled at the scene of injury were similar in the two treatment groups, the inclusion of transfer patients in the trial had the potential to introduce bias owing to differences in treatment before arrival at the trauma center.<sup>34</sup>

In the PAMPer trial, we planned for potential intracluster variation with an adequate sample size and robust statistical power. Because the trial was a multicenter trial, there were differences among the sites in their standard-care resuscitation practices and in their ability to carry other blood components. Although we cannot determine the independent or additive effects of prehospital administration of plasma and packed red cells, the survival benefits attributable to plasma administration persisted after adjustment for prehospital red-cell administration, and a subgroup analysis showed no heterogeneity of the treatment effect. Although we adjusted for differences between the groups in the volume of prehospital crystalloid solution in our primary analysis, we are unable to determine whether the lower volume of prehospital crystalloid solution in the plasma group had an additive benefit to patient outcomes. It is possible that specific mechanisms of injury, types of injury, patient characteristics, or prehospital modes of transport may alter the benefit derived from an intervention of prehospital plasma.<sup>34,35</sup> Missing data limited the ability to draw conclusions from comparisons of laboratory measurements and results of thromboelastography. We used a modified intention-to-treat approach for the analysis of the primary outcome that was not prespecified in the protocol because of the limitations of prehospital enrollment of critically injured patients and the regulatory challenges associated with trial designs based on exception from informed consent.

In conclusion, in patients at risk for hemorrhagic shock, the administration of thawed plasma during prehospital air medical transport

**Table 3. Adverse Events.\***

Variable	Standard-Care Group (N = 271)	Plasma Group (N = 230)
No. of patients who had an adverse event	2	6
No. of adverse events	4	6
Adult respiratory distress syndrome	1†	0
Allergic reaction	0	2
Anaphylaxis	0	1
Fever	1	0
Hypotension	0	1
Pain	1	0
Sepsis	1†	0
Transfusion-related reaction	0	1†
Urticaria	0	1

\* Adverse events were identified and reported at the discretion of the treating physician. Prospective definitions of adverse events are provided in Section XII of the protocol. An adverse event was defined as any adverse reaction that was considered to be related to the trial regimen. A serious adverse event was defined as any adverse reaction that was fatal or life-threatening, resulted in prolongation of hospitalization, or resulted in persistent or clinically significant disability or incapacity. The severity of adverse events was assessed by the site investigator. Potential allergic reactions and transfusion-related reactions were independently evaluated by personnel at blood bank services and by site investigators.

† This event was reported as a serious adverse event by the site investigator.

was safe and resulted in lower 30-day mortality and a lower median prothrombin-time ratio than standard-care resuscitation.

Supported by a grant (W81XWH-12-2-0023) from the U.S. Army Medical Research and Materiel Command.

Dr. Neal reports receiving grant support and consulting fees from Janssen Pharmaceuticals, advisory board fees from CSL Behring, grant support and equipment provision from Haemonetics, and grant support from Accriva Diagnostics and being named on a patent (9,072,760) on TLR4 inhibitors for the treatment of human inflammatory and infectious disorders. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the prehospital providers, who were essential for the successful execution of the trial.

#### APPENDIX

The authors' full names and academic degrees are as follows: Jason L. Sperry, M.D., M.P.H., Francis X. Guyette, M.D., M.P.H., Joshua B. Brown, M.D., Mark H. Yazer, M.D., Darrell J. Triulzi, M.D., Barbara J. Early-Young, B.S.N., Peter W. Adams, B.S., Brian J. Daley, M.D., Richard S. Miller, M.D., Brian G. Harbrecht, M.D., Jeffrey A. Claridge, M.D., Herb A. Phelan, M.D., M.S.C.S., William R. Witham, M.D., A. Tyler Putnam, M.D., Therese M. Duane, M.D., Louis H. Alarcon, M.D., Clifton W. Callaway, M.D., Ph.D., Brian S. Zuckerbraun, M.D., Matthew D. Neal, M.D., Matthew R. Rosengart, M.D., M.P.H., Raquel M. Forsythe, M.D., Timothy R. Billiar, M.D., Donald M. Yealy, M.D., Andrew B. Peitzman, M.D., and Mazen S. Zenati, M.D., Ph.D.

The authors' affiliations are as follows: the Division of Trauma and General Surgery, Department of Surgery (J.L.S., J.B.B., L.H.A., B.S.Z., M.D.N., M.R.R., R.M.F., T.R.B., A.B.P., M.S.Z.), and the Departments of Emergency Medicine (F.X.G., C.W.C., D.M.Y.) and Critical Care Medicine (B.J.E.-Y., P.W.A.), University of Pittsburgh Medical Center, and the Department of Pathology, University of

Pittsburgh and Institute for Transfusion Medicine (M.H.Y., D.J.T.), Pittsburgh, and University of Pittsburgh Medical Center, Altoona Hospital, Altoona (A.T.P.) — all in Pennsylvania; the Department of Surgery, University of Tennessee Health Science Center, Knoxville (B.J.D.), and the Department of Surgery, Vanderbilt University Medical Center, Nashville (R.S.M.) — both in Tennessee; the Department of Surgery, University of Louisville, Louisville, KY (B.G.H.); MetroHealth Medical Center, Case Western Reserve University, Cleveland (J.A.C.); and the Department of Surgery, University of Texas Southwestern, Parkland Memorial Hospital, Dallas (H.A.P.) and Texas Health Harris Methodist Hospital (W.R.W.) and the John Peter Smith Health Network (T.M.D.), Fort Worth — all in Texas.

## REFERENCES

- Harris T, Davenport R, Mak M, Brohi K. The evolving science of trauma resuscitation. *Emerg Med Clin North Am* 2018;36:85-106.
- Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma* 2007;62:307-10.
- Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA* 2015;313:471-82.
- Langan NR, Eckert M, Martin MJ. Changing patterns of in-hospital deaths following implementation of damage control resuscitation practices in US forward military treatment facilities. *JAMA Surg* 2014;149:904-12.
- Etchill E, Sperry J, Zuckerbraun B, et al. The confusion continues: results from an American Association for the Surgery of Trauma survey on massive transfusion practices among United States trauma centers. *Transfusion* 2016;56:2478-86.
- Cardenas JC, Holcomb JB. Time to plasma transfusion: a patient centered approach and modifiable risk factor. *Transfusion* 2017;57:869-73.
- Henriksen HH, Rahbar E, Baer LA, et al. Pre-hospital transfusion of plasma in hemorrhaging trauma patients independently improves hemostatic competence and acidosis. *Scand J Trauma Resusc Emerg Med* 2016;24:145.
- Shackelford SA, Del Junco DJ, Powell-Dunford N, et al. Association of prehospital blood product transfusion during medical evacuation of combat casualties in Afghanistan with acute and 30-day survival. *JAMA* 2017;318:1581-91.
- Chang R, Eastridge BJ, Holcomb JB. Remote damage control resuscitation in austere environments. *Wilderness Environ Med* 2017;28:Suppl:S124-S134.
- Holcomb JB, Pati S. Optimal trauma resuscitation with plasma as the primary resuscitative fluid: the surgeon's perspective. *Hematology Am Soc Hematol Educ Program* 2013;2013:656-9.
- Kozar RA, Peng Z, Zhang R, et al. Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. *Anesth Analg* 2011;112:1289-95.
- Pati S, Potter DR, Baimukanova G, Farrell DH, Holcomb JB, Schreiber MA. Modulating the endotheliopathy of trauma: factor concentrate versus fresh frozen plasma. *J Trauma Acute Care Surg* 2016;80:576-84.
- Peng Z, Pati S, Potter D, et al. Fresh frozen plasma lessens pulmonary endothelial inflammation and hyperpermeability after hemorrhagic shock and is associated with loss of syndecan 1. *Shock* 2013;40:195-202.
- Potter DR, Baimukanova G, Keating SM, et al. Fresh frozen plasma and spray-dried plasma mitigate pulmonary vascular permeability and inflammation in hemorrhagic shock. *J Trauma Acute Care Surg* 2015;78:Suppl 1:S7-S17.
- Brown JB, Guyette FX, Neal MD, et al. Taking the blood bank to the field: the design and rationale of the Prehospital Air Medical Plasma (PAMPer) Trial. *Prehosp Emerg Care* 2015;19:343-50.
- Holcomb JB, Swartz MD, DeSantis SM, et al. Multicenter observational prehospital resuscitation on helicopter study. *J Trauma Acute Care Surg* 2017;83:Suppl 1:S83-S91.
- Hernandez MC, Thiels CA, Aho JM, et al. Prehospital plasma resuscitation associated with improved neurologic outcomes after traumatic brain injury. *J Trauma Acute Care Surg* 2017;83:398-405.
- Ford I, Norrie J. Pragmatic trials. *N Engl J Med* 2016;375:454-63.
- FDA Center for Biologics Evaluation and Research. Guidance for institutional review boards, clinical investigators, and sponsors: exception from informed consent requirements for emergency research. April 2013 (<https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf>).
- Brown JB, Cohen MJ, Minei JP, et al. Goal-directed resuscitation in the prehospital setting: a propensity-adjusted analysis. *J Trauma Acute Care Surg* 2013;74:1207-12.
- Zink KA, Sambasivan CN, Holcomb JB, Chisholm G, Schreiber MA. A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study. *Am J Surg* 2009;197:565-70.
- Gonzalez EA, Moore FA, Holcomb JB, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma* 2007;62:112-9.
- Heckbert SR, Vedder NB, Hoffman W, et al. Outcome after hemorrhagic shock in trauma patients. *J Trauma* 1998;45:545-9.
- Teixeira PG, Inaba K, Shulman I, et al. Impact of plasma transfusion in massively transfused trauma patients. *J Trauma* 2009;66:693-7.
- Minei JP, Cuschieri J, Sperry J, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. *Crit Care Med* 2012;40:1129-35.
- Watson GA, Sperry JL, Rosengart MR, et al. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. *J Trauma* 2009;67:221-30.
- O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
- Fox EE, Holcomb JB, Wade CE, Bulger EM, Tilley BC. Earlier endpoints are required for hemorrhagic shock trials among severely injured patients. *Shock* 2017;47:567-73.
- Sauaia A, Moore EE, Johnson JL, et al. Temporal trends of postinjury multiple-organ failure: still resource intensive, morbid, and lethal. *J Trauma Acute Care Surg* 2014;76:582-92.
- Cotton BA, Reddy N, Hatch QM, et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. *Ann Surg* 2011;254:598-605.
- Holcomb JB, del Junco DJ, Fox EE, et al. The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg* 2013;148:127-36.
- Naumann DN, Hazeldine J, Davies DJ, et al. Endotheliopathy of trauma is an on-scene phenomenon, and is associated with multiple organ dysfunction syndrome: a prospective observational study. *Shock* 2018;49:420-8.
- Naumann DN, Hazeldine J, Dinsdale RJ, et al. Endotheliopathy is associated with higher levels of cell-free DNA following major trauma: a prospective observational study. *PLoS One* 2017;12(12):e0189870.
- Holena DN, Wiebe DJ, Carr BG, et al. Lead-time bias and interhospital transfer after injury: trauma center admission vital signs underpredict mortality in transferred trauma patients. *J Am Coll Surg* 2017;224:255-63.
- Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994;331:1105-9.

Copyright © 2018 Massachusetts Medical Society.