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Predicting Life-Threatening Coagulopathy in the Massively Transfused Trauma Patient: Hypothermia and Acidoses Revisited

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Background. **Recalcitrant coagulopathy "the bloody vicious cycle," produces the majority of deaths after torso trauma. A model predicting this life-threatening complication may facilitate clinical decision-making.**

Methods. **We prospectively analyzed patients > 15 years old who received a massive transfusion (> 10 units of packed red blood cells (PRBC)/24 h) over a 2-year period. Excluding massive head injuries and pre-existing disease, the 58 study patients had a mean age = 35.4 years, Injury Severity Score (ISS) = 30.6, and PRBC = 24.2 units/24 h.**

Results. **Defined as prothrombin time of two times that of normal laboratory controls and partial thromboplastin time as two times that of normal laboratory controls, 27 patients (47%) developed life-threatening coagulopathy. Using a multiple logistic regression model, the four significant risk factors (with odds ratio) were (1) pH < 7.10 (12.3), (2) temperature < 34°C (8.7), (3) ISS > 25 (7.7), and (4) systolic blood pressure < 70 mm Hg (5.8). The conditional probability of developing coagulopathy was ISS > 25 + systolic blood pressure < 70 mm Hg = 39%, ISS > 25 + temperature < 34°C = 49%, ISS > 25 + pH < 7.10 = 49%; with all four risk factors the incidence was 98%.**

Conclusion. **Postinjury life-threatening coagulopathy in the seriously injured requiring massive transfusion is predicted by persistent hypothermia and progressive metabolic acidosis.**

Key Words: **Coagulopathy, Massive transfusion, Trauma, Hypothermia, Acidosis.**

Recalcitrant coagulopathy accounts for the majority of trauma deaths occurring within the first 24 hours of hospitalization.[1–6] In 1981, at this Association,[7] we proposed the concept of the "bloody vicious cycle" characterized by persistent core hypothermia, progressive metabolic acidosis, and inability to establish surface hemostasis (Fig. 1). Once established, the mortality for this well-known clinical scenario exceeds that of postinjury multiple organ failure (MOF). Thus, the ability to predict this life-threatening complication has significant decision-making implications.[8] Indeed, the primary objective of staged laparotomy or thoracotomy is to avoid an accelerating coagulopathic state. Furthermore, the risks as well as costs of blood components warrant more precise guidelines for their clinical use.[9] Clearly the avoidance of unnecessary blood products is desirable, but the penalty for delayed intervention may be devastating. With this background, the Departments of Surgery and Pathology embarked on a prospective analysis of acutely injured patients who received a massive transfusion, i.e., > 10 units of packed red blood cells (PRBC) within the first 24 hours. Our study objective was to develop a model that would identify patients at risk for early life-threatening coagulopathy.

METHODS

In the 2-year period ending November of 1995, injured patients > 15 years of age who were admitted to Denver Health Medical Center and received > 10 units PRBC/24 h were entered in a transfusion registry maintained by the blood bank. Data included volume and timing of blood administration, blood component therapy, and coagulation profiles. Of the 148 cases recorded in the registry, 90 cases were excluded from this analysis because of severe head injury (Glasgow Coma Scale (GCS) score < 8), pre-existing coagulation dysfunction (including chronic liver or renal failure), or use of a blood substitute (Polyheme Study). The 58 eligible patients had a mean age of 35.4 ± 2.0 years and 45 patients (78%) were men. Mechanism of injury was blunt in 27 patients (47%), all patients required emergent laparotomy or thoracotomy, and the mean Injury Severity Score (ISS) was 30.6 ± 2.2. The mean transfusion volume (units) during the first 24 hours was PRBC = 24.2 ± 1.6, fresh frozen plasma (FFP) = 14.0 ± 1.2, platelets = 16.1 ± 2.0, and cryoprecipitate = 11.4 ± 1.2. The mean elevation in prothrombin time was 18.8 ± 0.5 seconds, and the partial thromboplastin time was 95.7 ± 7.3 seconds. Additional physiologic measurements were obtained via the prospective, concurrently derived trauma registry. During the first 24 hours, the mean lowest systolic blood pressure (SBP) was 76.7 ± 2.5 mm Hg, pH 7.09 ± 0.02, and temperature 34.3 ± 0.2°C. The mean highest lactate was 5.6 ± 0.3 *m*mol/L.

Trauma management during this study period was believed

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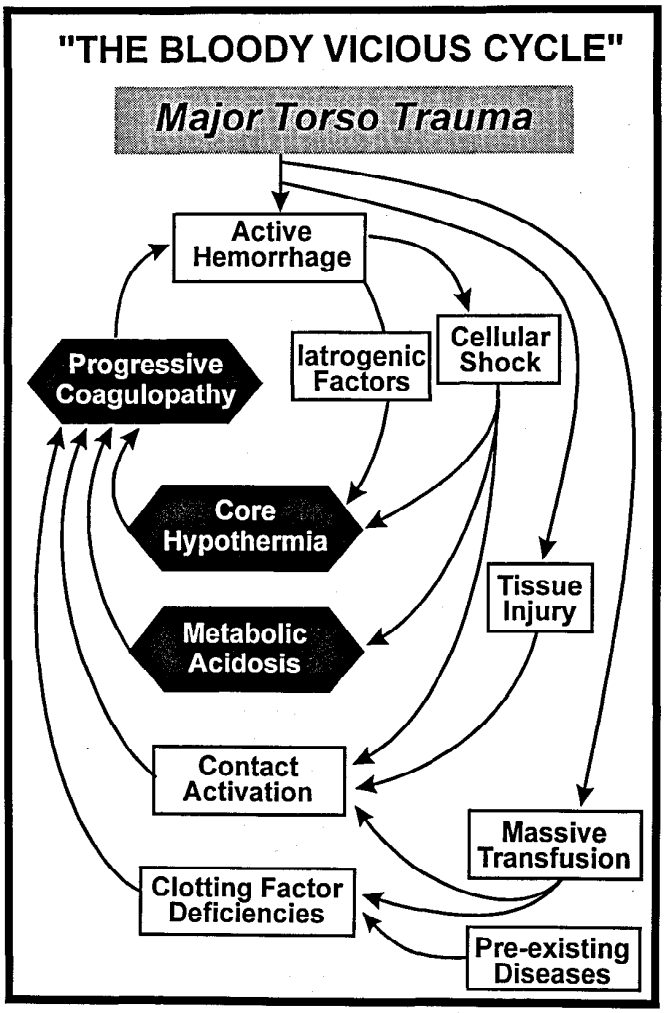

FIG 1. The pathogenesis of the bloody vicious cycle after severe injury is multifactorial, but progressive core hypothermia and persistent metabolic acidosis are pivotal. Reproduced by permission of the publisher from "Staged Laparotomy for the Hypothermia, Acidosis, Coagulopathy Syndrome" by EE Moore, *The American Journal of Surgery*, Vol. 172, pp. 405–410. Copyright 1996 by Excerpta Medica, Inc.

to be consistent. Specifically, care was provided by the same group of trauma surgeons, blood bank pathologists, and anesthesiologists. Our management protocols are detailed in other reports[10,11] and, therefore, will not be reiterated. Of note, patients with or without coagulopathy received similar volumes of FFP (13.9 ± 1.6 vs. 14.1 ± 1.9 units, $p = 0.90$) and platelets (16.5 ± 3.1 vs. 15.8 + 2.7 units, $p = 0.86$). Ultimately 33 (57%) of the 57 patients in this study survived after massive blood transfusion.

Statistical analysis was carried out by using the SAS statistical package (SAS for Windows version 6.10, SAS Institute, Inc., Cary, NC). Univariate analysis was conducted as follows: continuous variables were compared by the Student's *t* test with the appropriate adjustment if the assumption of equal variances was not met, whereas categorical variables were tested using the χ^2 test with Yates' correction for continuity. Risk factors for coagulopathy, which were univariately associated with coagulopathy with a p value < 0.25, will be entered in a multiple logistic regression model (MLR).[12] The use of the 0.25 cutoff is based on studies of linear and logistic regression which show that larger values lead to the inclusion of variables of questionable importance. In contrast, the use of more traditional levels, i.e., 0.05, often failed to identify variables known to be clinically relevant.[12] Potential risk factors for coagulopathy were initially evaluated as continuous variables. A decision was made to establish cutpoints based on clinical judgment without sacrificing predictive power. Hosmer and Lemeshow warned about the "unavoidable dilemma" posed by including continuous variables in logistic models.[12] These authors noted that the logit (coagulopathy) is not linear in the covariate and advise the use of grouping or categorization or alternatively, the use of polynomial terms or transformations, such as log X.[12,13] The chosen cutpoints in this study were age > 55 years, ISS > 25, SBP < 70 mm Hg, pH < 7.10, temperature < 34°C, and lactate > 2.5 mmol/L. In the multiple logistic regression analysis, significance was evaluated at the 0.05 level. The goodness-of-fit of the models was evaluated by the Akaike's Information Criterion, the Hosmer-Lemeshow statistic, as well as sensitivity and specificity of the predictive models.[12] Adjusted odds ratios and 95% confidence intervals were calculated for each of the independent predictors. The conditional probability of developing coagulopathy was calculated as follows: if four risk factors were selected by MLR (XI, X2, X3, X4), then five parameters (a, $B1$, $B2$, $B3$, $B4$) were derived from the analysis, and the conditional probability of developing coagulopathy is $CP = 1/1 + e^{-z}$, where $z = a + B1\ (\times 1) + B2\ (\times 2) + B3\ (\times 3) + B3\ (\times 4)$. A value of "1" is attributed to X1, X2, X3, or X4 if the risk factor is present and "0" if it is absent.

RESULTS

Life-threatening coagulopathy was defined as a prothrombin time more than two times that of normal laboratory control and a partial thromboplastin time more than two times that of normal laboratory control. Based on these criteria, 27 (47%) of the patients developed this potentially lethal complication; 18 of these patients required staged laparotomy due to a refractory coagulopathic state. Comparison of risk factors among patient subgroups with (n = 27) versus without (n = 31) coagulopathy is summarized in Table 1. Univariate analysis suggested the significant factors were ISS ($p = 0.03$), lowest SBP ($p = 0.04$), pH ($p = 0.0004$), and temperature ($p = 0.05$). Of interest, the volume (PRBC/24 h, $p = 0.24$) and rate (PRBC/6 h, $p = 0.55$) of blood transfusion were not predictive. A multivariate analysis using logistic regression was then completed incorporating all factors in the univariate surveillance with a $p < 0.25$. The resulting predictive model for developing life-threatening coagulopathy model is shown in Table 2.

A conditional probability profile was then generated to offer a practical tool for clinical decision making (Table 3). The readily available indices ISS, SPB, pH, and temperature were selected from the predictive model, and threshold levels were again based on clinical judgment with sacrificing predictability. An ISS > 25 represents severe tissue injury, a pH < 7.0 reflects ongoing cellular shock, and a core temperature < 34°C is known to adversely effect the coagulation

TABLE 1. Risk Factors for Postinjury Life-Threatening Coagulopathy

Factor	Coagulopathy	No Coagulopathy	p Value
Age (years)	34.5 ± 2.2	36.2 ± 3.3	0.67
Blunt	48%	45%	0.62
ISS	35.8 ± 3.4	26.1 ± 2.7	0.03
ISS > 25	70%	35%	0.01
SBP mm Hg	71.3 ± 3.6	81.5 ± 3.2	0.04
SBP < 70 mm Hg	52%	19%	0.02
PRBC units/24 h	26.2 ± 2.7	22.4 ± 1.9	0.24
PRBC units/6 h	16.6 ± 2.6	14.8 ± 1.4	0.55
>15 U PRBC/6 h	44%	55%	0.60
Lactate (mmol/L)	6.31 ± 0.65	5.04 ± 0.37	0.10
pH	7.02 ± 0.03	7.15 ± 0.02	0.0004
pH < 7.10	78%	32%	0.0014
Temperature (°C)	33.8 ± 0.3	34.6 ± 0.2	0.05
Temperature < 34°C	59%	23%	0.01

ISS, Injury Severity Score; SBP, systolic blood pressure; PRBC, packed red blood cells.

cascade. In summary, approximately one fourth of patients with major tissue injury requiring massive transfusion will develop a life-threatening coagulopathy; more than half will develop this complication if the clinical scenario is completed by persistent metabolic acidosis (pH < 7.0) or progressive core hypothermia (temperature < 34°C).

Of the 27 patients with coagulopathy, 15 patients (56%) ultimately survived; 12 of these survivors had undergone staged laparotomy. Further analysis of the data according to eventual outcome (survived/died) showed no difference in the relative administration of FFP to PRBC transfused; the FFP/PRBC ratio was 0.61 ± 0.04 versus 0.54 ± 0.06 (Table 4). However, patients who survived had a significantly higher platelet/RBC ratio (0.79 ± 0.09 vs. 0.48 ± 0.09, $p = 0.01$). Specifically, patients who survived received more units of platelets (18.8 ± 12.9 units vs. 12.6 ± 2.6 units), but comparable amounts of PRBCs (22.8 ± 1.8 units vs. 26.0 ± 2.9 units) in the first 24 hours.

TABLE 2. Predictive Model for Life-Threatening Coagulopathy

Predictor	Estimate	p Value	Odds Ratio (95% CI)
Constant	−4.22 ± 1.1	—	—
ISS > 25	2.04 ± 0.8	0.01	7.7 (1.5–38.8)
SBP < 70 mm Hg	1.75 ± 0.8	0.03	5.8 (1.2–28.2)
pH < 7.10	2.51 ± 0.8	0.0003	12.3 (2.4–64.0)
Temp < 34°C	2.16 ± 0.8	0.007	8.7 (1.8–41.8)

TABLE 3. Conditional Probability of Developing Life-Threatening Coagulopathy

No risk factor			=	1%
ISS > 25			=	10%
ISS > 25	+	SBP < 70 mm Hg	=	39%
ISS > 25	+	pH < 7.10	=	58%
ISS > 25	+	Temp < 34°C	=	49%
ISS > 25	+	SBP < 70 mm Hg + Temp < 34°C	=	85%
ISS > 25	+	SBP < 70 mm Hg + pH < 7.10 + Temp < 34°C	=	98%

TABLE 4. Outcome Analysis after Massive Blood Transfusion

	Survived (n = 33)	Died (n = 25)	p Value
PRBC units/24 h	22.8 ± 1.8	26.0 ± 2.9	0.36
PRBC units/6 h	14.6 ± 1.4	17.0 ± 2.7	0.43
FFP units/24 h	14.1 ± 1.5	13.9 ± 2.1	0.92
Platelets units/24 h	18.8 ± 2.9	12.6 ± 2.6	0.13
FFP/PRBC	0.61 ± 0.04	0.54 ± 0.06	0.36
Platelets/PRBC	0.79 ± 0.09	0.48 ± 0.09	0.01

PRBC, packed red blood cells; FFP, fresh frozen plasma.

DISCUSSION

Recalcitrant coagulopathy remains a formidable challenge for the trauma surgeon, despite intensive efforts to elucidate the mechanism[14–22] and control the process.[1–8] Fifteen years ago, we presented an analysis of major abdominal vascular trauma to this Association[7] and reported that the majority of deaths resulted from exsanguination after the vascular wound had been controlled. The pathogenesis of this "bloody vicious cycle" is complex (Fig. 1), but clinically manifests as progressive core hypothermia, persistent metabolic acidosis, and inability to establish surface hemostasis. The classic studies on coagulation defects associated with massive blood transfusion emphasized the importance of presumptive blood component repletion, recognizing the ongoing dilution as well as consumption of clotting factors.[14–22] In the past decade, the most significant advance in arresting this vicious coagulopathic cycle has been the resurrection of staged laparotomy, recognizing the adverse effects of hypothermia and acidosis on the coagulation system.[1–8]

The concept of staged laparotomy emerged from experience with major hepatic trauma.[23,24] Ironically, packing liver wounds to achieve hemostasis was promulgated by Pringle in 1908, but reports of "disastrous hemorrhage, abscesses, and hepatic necrosis" coupled with increasing success at direct operative control of hepatic bleeding led Madding and Kennedy to censor packing during World War II.[25] This military doctrine guided clinical practice, until challenged by the report of Lucas and Ledgerwood in 1976.[23] The merits of perihepatic packing were debated for several years, but compelling evidence was provided by Feliciano et al in 1981.[25] The next chapter in staged laparotomy began with the seminal report of Stone et al.,[26] who extended staging to other abdominal injuries and crystallized the fundamentals: "This technique of initial abortion of laparotomy, establishment of intra-abdominal pack tamponade, and then completion of the surgical procedure once coagulation has returned to acceptable level has proven to be lifesaving." By 1993, several groups[1,8] had critically analyzed their sizable experience and initiated the current phase of conceptual refinement. The most recent adjustment has emerged from intensified study of the abdominal compartment syndrome, underscoring the risk: benefit of tamponade versus splanchnic hypoperfusion and cardiopulmonary embarrassment.[27]

Despite the well-recognized dangers of postinjury coagulopathy and widespread practice of staged operations, defining the patient at risk remains elusive.[1–8] The present study offers a predictive model and suggests that after massive

transfusion (> 10 units PRBC) the critical factors are (a) severity of tissue injury (ISS > 25), (b) magnitude of shock (SBP < 70 and pH < 7.10), and (c) inability to maintain core temperature (< 34°C). When all three risk factors are present, the incidence of life-threatening coagulopathy is virtually 100%. These findings are consistent with the respective analysis from Louisville[8] that found early postinjury concurrence of acidosis, hypothermia, and coagulopathy distinguished nonsurvivors from survivors. Based on their experience[2,8] the authors suggested the key risk factors were transfusion >15 units, ISS > 35, pH < 7.20, and hypotension > 70 minutes. The authors cautioned, however, their study population may be unique due to a preponderance of blunt injured patients who required prolonged transport times. The Vanderbilt group[5] qualified high risk for persistent coagulopathy as temperature < 35°C and base deficit ≤ 15 mmol/L (equivalent to pH < 7.20 with a Pco_2 = 35 mm Hg) in the patient with medical bleeding. The Ben Taub group[1] also focused on metabolic acidosis and suggested a threshold pH < 7.20 if the transfusion rate exceeds 15 units/h and pH < 7.10 if > 10 units/h. Their study population had a mean core temperature = 32.7°C at the end of initial operation.

The causal relationship of core hypothermia and postinjury coagulopathy is anticipated from a plethora of studies. The pathophysiology is multifactorial[28,29] and includes retardation of temperature-dependent enzyme-activated coagulation cascades, platelet dysfunction, endothelium abnormalities, and a poorly understood fibrinolytic activity. The implication of metabolic acidosis in the pathogenesis of impaired coagulation is less clear. Interestingly, our preliminary animal work[30] demonstrated impaired hemostasis at a pH = 7.20, and others[31] have suggested pH directly affects platelet function. Hardaway et al.[32] conducted a series of experiments invoking acidosis in the propagation of disseminated intravascular coagulation and secondary consumption of clotting factors. In addition, both hypothermia and metabolic acidosis have potential adverse effects on myocardial performance as well as tissue perfusion. The relationship of tissue disruption (ISS) and coagulopathy is also expected due to a number of events provoked by the contact activation system. Failure to document a statistical correlation between the volume of blood transfusion and the development of coagulopathy may be due to a number of reasons. The coagulopathy versus no coagulopathy subgroups received similar amounts of blood. However, data from our transfusion and trauma registries did not provide sufficient detail to generate a sensitive measure of transfusion rate; i.e., milliliters per minute per kilogram during the initial 6 hours. Furthermore, entry criteria for this prospective study was a minimum of 10 units PRBC/24 h. It is conceivable that inclusion of patients with smaller transfusion requirements would render a threshold where the volume became a more dominant causative factor.

Another interesting finding of this study was the apparent need for more aggressive platelet repletion. Primary hemostasis relies on platelet adherence and aggregation to injured endothelium; i.e., formation of the platelet plug. A platelet count of 50,000/mm^3 is considered adequate for tissue hemostasis if they are normal. However, platelet dysfunction is a well-documented complication of massive transfusion, and clearly this is aggravated by associated hypothermia.[18] Consequently, the recommended target of > 100,000 (mm^3) for platelet transfusion in other high-risk patients[9] should probably be extended to the severely injured.

Despite the prospective design of this analysis, there are a number of conspicuous limitations. Perhaps most frustrating for the authors was the fact that the trauma registry was unable to discern at what point during the initial 24 hours the most abnormal physiologic derangement occurred. Unfortunately, our NIH-sponsored postinjury MOF database[33] does not include all the variables analyzed in this study. Furthermore, as with most single institution prospective studies, the number of patients was relatively small in our efforts to achieve population homogeneity. Finally, although patient care was driven by management guidelines, there was no specific protocol governing blood component replacement, bicarbonate administration, or active rewarming. Clearly, predictive models must be validated on independent databases, and preferably in other centers. Nonetheless, the present report offers a starting point that we believe warrants a prospective multi-institutional study.

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DISCUSSION

Dr. John J. Ferrara (New Orleans, Louisiana): In this prospective analysis of 57 select severely injured adult patients, the following events occurred. All received more than ten units of blood in the initial 24 hours of trauma management. Over one half of the patients died. And almost one half developed what was called life-threatening coagulopathy, defined as a PT and a PTT over two times control.

Their data analysis demonstrated that the development of this coagulopathy was associated with a high ISS and low mean arteriole pressures, arteriole pH, and core body temperature. The authors suggest that these data can be used as a predictive model for the development of coagulopathy to be employed in clinical decision making, presumably to at least define which patients might best be managed by stage celiotomy.

Certainly, most traumatologists have personal experience with the observation that a cold, acidotic, massively injured, hypotensive patient is in serious, serious trouble. This manuscript provides the data to support the bias and relates this finding to the development of coagulopathy.

While I suspect that the authors may prove correct in their assertion that a predictive model can be fashioned from such data as they presented, I'm not quite as certain that their own data are strong enough to support this conclusion at the present.

In a copy of their manuscript, the authors themselves point out some study shortcomings, including the fact that there was no specific protocol governing blood replacement, bicarbonate administration, or active rewarming.

These data alone should give us cause for concern before we uniformly accept this as a particular model, and rather use their data to find whether or not a more controlled prospective study is warranted.

And just finally, I have the following questions for the authors. Number 1: You collected your data over a 24-hour period. Do you know precisely when these lows in mean arterial pressure, pH, and temperature occurred in relationship to the time at which your laboratory confirmation of life-threatening coagulopathy occurred?

Number 2: Eighteen patients in your study underwent a staged laparotomy. How many patients were in the group of survivors and how many patients were in the group that developed coagulopathy, and could not have this clinical interdiction skewed your data?

Number 3: You defined the coagulopathy as life threatening, but was it? How many patients in this study with this entity actually died?

And finally, if both groups of patients received essentially equivalent amounts of blood and blood products during the first 24 hours, I would assume that they must have bled to the same extent, which makes me wonder, at least from a clinical perspective, whether your definition of life-threatening coagulopathy instead reflects something more like life-threatening hepatic insult.

I wish to express my appreciation for the opportunity to review this manuscript and hope the authors will continue to pursue this interesting area of clinical research.

Dr. Richard J. Mullins (Portland, Oregon): The authors report they can predicted coagulopathy in patients requiring massive transfusion. This would be very valuable in our trauma center, where if we could predict who would develop coagulopathy, we would activate additional resources and an algorithm to guide the restoration of normal coagulation tests. The prediction would be useful early in the resuscitation, or even before surgery begins. However, the problem with using their model which includes ISS is that we do not know the number or severity of all the injuries early in the resuscitation. Can the authors use an alternative to ISS which would

correspond to information that could be reliably collected during the first minutes of evaluation?

Dr. David Spain (Louisville, Kentucky): Just a simple question. How many of these patients actually had clinical diagnosis of coagulopathy made? I mean, we have a laboratory diagnosis, but how many times did the surgeon encounter diffuse raw surface bleeding in the operating room that he could not control?

Dr. Jack M. Bergstein (Milwaukee, Wisconsin): I have a concern about the clinical model. We're attempting here to generate a model which can be metastasized or broadened to other centers, so it's important for us to understand the full clinical protocol. So I'd like to know whether your patients received whole blood resuscitation early on, or was it all packed cells. I think this is important, since whole blood resuscitation can clearly delay the development of coagulopathy.

Secondly, was intraoperative cell salvage used? If so, I think that needs to be teased out of the data and pointed out so that this information can be applied in other medical centers.

Dr. Michael F. Rotondo (Coatesville, Pennsylvania): I want to congratulate the authors on attempting to objectify a series of factors which most of us use subjectively to try to make some decisions about managing patients with massive exsanguination.

I have only one question, and it's a technical one in follow-up to Dr. Spain's, which addresses the laboratory assay of the PT and PTT. Were those measurements performed at a temperature of 37°C? Was the machine calibrated to 37°C?

In light of some of the work that's been done in the last couple of years by Michael Rehrer, which simply shows that if you cool pooled plasma from normal volunteers, the PT and the PTT will increase, should we be measuring these values at the patient's temperature and not at a calibrated temperature?

Dr. Ned Cosgriff (closing): I'd like to thank Dr. Ferrara and the other discussants for their thoughtful observations on our study.

Dr. Ferrara, regarding the 24-hour data, when did the loads occur with respect to laboratory values, that data was unavailable at the time of the analysis. We did have laboratory values returning to us; however, in the heat of battle, as it were, it was difficult to log all the times exactly.

As regarding the 18 patients who received a staged celiotomy, all were coagulopathic, and 12 went on to recover.

The final question was how many died with coagulopathy, and the answer to that was 15 of the 27 were coagulopathic by our definition, who did not survive.

Dr. Mullins, regarding the question of a predictive equation and the inability to assign ISS in the emergency department, I do agree with that. It's very difficult to ascertain the extent of injuries on first sight in the emergency room. However, it's our feeling that taking the perspective of predicting coagulopathy in the OR, the first glance at an ISS score or an estimated ISS score has merit.

Dr. Spain, all patients with coagulopathy, laboratory-defined coagulopathy, were said to have, according to the operative note, operative bleeding, hepatic in some cases. Exsanguination was the primary cause of death for some of the patients.

Dr. Bergstein, we used all packed cells in resuscitation. We do not use autotransfusion in our massive transfusion in trauma.

And finally, Dr. Rotondo, the laboratory does correct to 37°C uniformly at our institution.

We thank the Association again for the privilege of the floor.