Resuscitation With Plasma in Surgical and Trauma Patients With Septic Shock

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Summary: ***There is a knowledge gap regarding the optimal initial fluid to achieve effective resuscitation and improved outcomes in septic shock. Shock-induced endotheliopathy (SHINE) may be an underlying pathologic mechanism for worsened outcomes in septic shock and a potential therapeutic target that can be modulated by resuscitation fluids. This project proposes a pilot randomized controlled trial to address this knowledge gap by evaluating plasma as a potential novel strategy to mitigate SHINE and improve clinical outcomes.***

Background:

Sepsis and septic shock are a major worldwide public health problem. Although implementation of the evidence-based Surviving Sepsis Guidelines has resulted in improvement in sepsis-related deaths, in-hospital mortality continues to range from 12-40%. The guidelines provide strong recommendations for initial resuscitation with crystalloids – 30 mL/kg within the first 3 hours.[1] However, the guidelines state that there is "little available evidence from RCTs to support its practice; this is an area in which research is urgently needed".[1] Randomized trials have primarily compared crystalloids to colloids and have not evaluated the recommended fluid volume. Furthermore, there is observational data from large administrative databases that increased fluid administration in the first 24 hours increases mortality.[2]

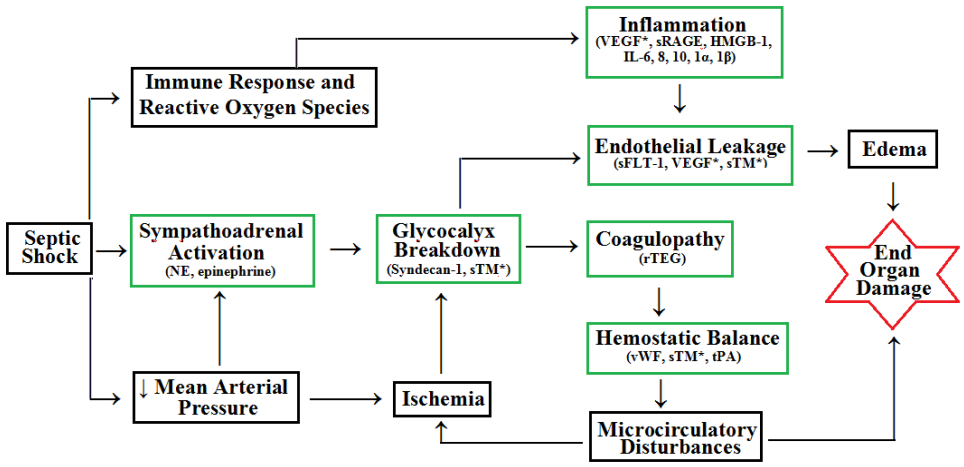

Figure 1: Conceptual model of how septic shock leads to sympathoadrenal activation, inflammation, and ischemia, which affects the endothelial glycocalyx, endothelial permeability, and hemostatic balance, resulting in edema and microcirculatory disturbances that cause organ dysfunction

Abbreviations: sTM = soluble thrombomodulin; sFLT-1 = soluble fms-like tyrosine kinase-1; VEGF = vascular endothelial growth factor; sRAGE = soluble receptor for advanced glycation endproduct; HMGB-1 = high mobility group protein-1; IL = interleukin; vWF = von Willebrand factor; tPA = tissue plasminogen activator; NE = norepinephrine; rTEG = rapid thromboelastogram
*indicates biomarkers that belong to more than 1 category

Recently, shock-induced endotheliopathy (**SHINE**) has been proposed as a shared pathophysiologic mechanism associated with worsened outcomes in patients with critical illness including trauma and sepsis.[3] Activation of the sympathoadrenal system and release of catecholamines due to acute injury (i.e., sepsis or trauma) leads to breakdown of the glycocalyx, or the network of membrane-bound proteoglycans and glycoproteins that covers the endothelium (**Figure 1**).[4-7] This has been associated with capillary leakage and microvascular thrombosis, ultimately resulting in organ dysfunction and increased mortality. Research suggests that

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endotheliopathy is both a marker and a driver of worsened outcome.[3] Thus, interventions to prevent, mitigate, or treat SHINE may improve outcomes in patients with shock. SHINE biomarkers, such as syndecan-1,[8] interleukin-6 (IL-6),[9] and soluble fms-like tyrosine kinase (sFLT-1),[7] have been shown to correlate with clinical outcomes in septic patients.

Resuscitation of shock patients with plasma shows promise as a novel resuscitative strategy. Specifically, plasma may improve outcomes by modulating SHINE as measured by biomarkers of glycocalyx damage (i.e., syndecan-1),[10,11] and endothelial injury (i.e., sFLT-1, VEGF, sTM).[7,8] Resuscitation with plasma as the primary volume expander in trauma patients have been associated with a reduction in serum biomarkers of endotheliopathy,[12] improved survival, and decreased morbidity associated with inflammatory and edema-related complications such as acute lung injury[13] and abdominal compartment syndrome.[14] Animal models of sepsis and a prospective sub-study of a randomized, controlled trial (RCT), have shown that resuscitation with plasma is associated with decreased levels of syndecan-1, which may reflect restoration of endothelial integrity, although the underlying mechanism is unknown.[15-17] Plasma resuscitation in a rat model of sepsis demonstrated attenuation of inflammatory markers, endothelial injury, and catecholamines; significantly reduced pulmonary edema as measured by wet-to-dry weight ratios; and improved 48-hour survival as compared to normal saline.[18] However, although these studies suggest that plasma may be a promising therapy in septic shock, there have been no human RCTs. Furthermore, there have been no studies establishing causation between SHINE and outcome.

Hypothesis and Specific Aims:

Hypothesis: We hypothesize that among patients with septic shock, initial resuscitation with plasma versus balanced crystalloids will decrease biomarkers of endotheliopathy, improve patient outcomes (such as decrease number of ICU-free days, decreased morbidity associated with end-organ damage), and reduce in-hospital all-cause mortality. We propose to perform a pilot RCT to test this hypothesis using the following specific aims:

Specific Aim 1: To evaluate the effects of plasma versus balanced crystalloids on serum markers of glycocalyx breakdown, endothelial leakage, inflammation, hemostasis, sympathy-adrenal activation, and degree of coagulopathy (using rapid thromboelastography parameters) [**Figure 1**].

Specific Aim 2: To evaluate differences in total volume of fluids needed to resuscitate patients in the plasma group versus crystalloids group during the initial 24 hours of resuscitation.

Specific Aim 3: To determine the effect of plasma resuscitation on organ dysfunction, ventilator-free days, intensive care unit (ICU) free days, hospital length of stay, mortality, and adverse events.

Significance:

This will be the first randomized trial comparing plasma, which has been demonstrated to have beneficial effects in animal models and in other types of shock, to usual care or balanced crystalloids. Furthermore, this study will provide insights regarding the mechanism by which fluids can influence outcomes in septic shock.

Preliminary Data:

Plasma Resuscitation in Rat Model of Septic Shock - We randomized rats who underwent cecal ligation and puncture to resuscitation with plasma (n = 14), normal saline (n = 11), and sham (n = 5). Resuscitation with plasma as determined by lactic acid clearance attenuated inflammatory markers (interleukin-6) [**Figure 2**], glycocalyx shedding (syndecan-1) [**Figure 3**], and

catecholamines (norepinephrine). Plasma significantly reduced pulmonary wet-to-dry weight ratios, increased mean arterial pressures (MAPs), reduced volume of total fluids administered, and improved 48-hour survival.

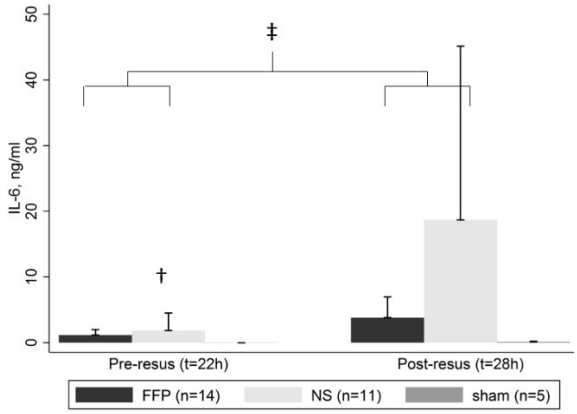

Figure 2 – Significant decrease in serum IL-6 in septic rats resuscitation with plasma as compared to normal saline.[18]

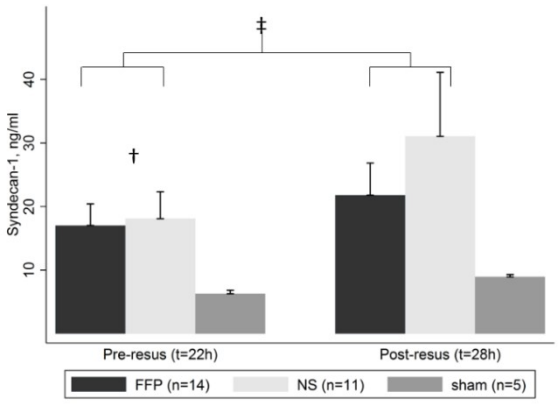

Figure 3 – Significant decrease in serum syndecan-1 in septic rats resuscitation with plasma as compared to normal saline.[18]

<u>Study Design & Methods</u>:

The proposed trial is a pilot, efficacy, single-center RCT comparing initial plasma to balanced crystalloid resuscitation in surgical patients with septic shock. The trial will investigate modulation of SHINE as a strategy by which outcomes in shock patients may be improved. The trial will follow the Consolidated Standards in Reporting of Trials (CONSORT) guidelines[19] and has been registered on ClinicalTrials.gov (NCT03366220).

Setting: The study will take place at Memorial Hermann Hospital – Texas Medical Center (MHH-TMC), a Level I trauma and tertiary care center located in Houston, Texas.

Study population: The target population includes critically ill (including medical patients), traumatically-injured or surgical patients who have sepsis, hypotension with MAP < 65 mmHg, and signs of hypoperfusion such as lactic acid > 2.2 mmol/L, altered mental status or decreased urine output (< 0.5 mL/kg in the past hour).[20]

Inclusion Criteria:

Patients meeting the following criteria will be enrolled:

- ≥ 18 years old and
- Have a Sepsis Screening Score (SSS) ≥ 4 with a suspected source of infection (**Table 1**)
- Written informed consent obtained

Patients meeting any of the following criteria will be randomized:

- Hypotension with MAP < 65 mmHg
- Lactic acid > 2.2 mmol/L,
- Altered mental status
- Decreased urine output of < 0.5 mL/kg in the past hour.

	0	1	2	3	4
Heart rate	70 –109		55 – 69 110 –139	40 – 54 140 –179	≤ 39 ≥180
Temp (°C)	36 – 38.4	34 –35.9 38.5–38.9	32 – 33.9	30 – 31.9 39 – 40.9	≤ 29.9 ≥ 41
Temp (°F)	96.8–101.1	93.1–96–6 101.2– 1–2.0	89.6– 93.0	86 – 89.5 102.1–105.6	≤ 85.9 ≥105.7
Respiratory rate	12 – 24	10 –11 25 –34	6 – 9	35 – 49	≤ 5 ≥ 50
Latest WBC count	3 – 14.9	15 –19.9	1 – 29 20 – 39.9		< 1 ≥ 40
Acute change in mental status SIRS Score (total points)	No	Yes			

Table 1 – The Sepsis Screening Score[22]

This cutoff has a negative predictive value of 96%,[22] which would rule out the majority patients without sepsis. Enrolled patients will be randomized only if they meet criteria for septic shock: 1) hypotension with MAP < 65 mmHg, and 2) evidence of hypoperfusion including lactic acid > 2.2 mmol/L, altered mental status, or decreased urine output of < 0.5 mL/kg in the past hour.

Exclusion Criteria:

-Pregnancy

-Prisoners

-Non-survivable traumatic brain injury

-Evidence of ongoing hemorrhage (eg. active gastrointestinal bleed), history of congenital bleeding disorders, therapeutic anticoagulation

-History of congestive heart failure

-Major burns (>20% total body surface area)

-History of adverse reactions to blood product transfusion

-Contraindications to blood transfusions (eg. Jehovah's Witness)

-Contraindications to central venous line and arterial line placement

-Do-Not-Resuscitate or Comfort Care status

-Participation in another interventional study that specifically focuses on sepsis, involves the use of a non-approved product (medication or equipment), or interventions that affect blood coagulation.

-Pending transfer to another unit within the hospital that is not Shock Trauma Intensive Care Unit (STICU) or Medical Intensive Care Unit (MICU).

Screening and Enrollment: Patient screening and enrollment will take place at Memorial Hermann Hospital. The research team will screen patients by communicating with the on-call STICU and emergency department (ED) physicians daily to identify patients eligible for enrollment. Hospitalized medical patients on the floor who develop severe sepsis will be identified using the rapid response page, which is already in place to alert the rapid response team of medical floor patients with potential severe sepsis.

Enrolled patients will be monitored for up to 72 hours (in time for cultures to result) by the research team for development of septic shock (MAP ≤ 65 mmHg and evidence of poor perfusion, such as urine output < 0.5 mL/kg/hr, venous lactic acid ≥ 2.2 mmol/L, altered mental status from baseline). Upon meeting these criteria for septic shock, patients will be randomized and immediately started on therapy fluid (either plasma or balanced crystalloids).

Crystalloid administration may already be underway prior to patient randomization. Receiving crystalloids prior to randomization *will not* be an exclusion criterion in this study as long as the total volume received has not met or exceeded 30 mL/kg. The research team will work expeditiously to obtain informed written consent, and once consent has been obtained and patient is randomized, prior fluids will be exchanged for therapy fluid (either plasma or balanced crystalloids).

Informed Consent:

Exception from Informed Consent will not be used in this trial. Written informed consent will be obtained from potential subjects or a legally authorized representative prior to randomization.

Randomization: Randomization will occur once the informed consent has been obtained. A 1:1 allocation will be used for the randomization. Subjects will be randomized to either the intervention arm (use of plasma) or the control arm (standard of care). Randomization will be performed using a computer-generated random sequence placed in opaque, consecutively-numbered, sealed envelopes kept in the locked Center for Translational Injury Research (CeTIR) office. A CeTIR research coordinator is available 24 hours a day, 7 days a week. Allocation will be 1:1. Patients will be stratified by enrollment location (STICU, ED, and Medical) in 5 blocks of 4 and 1 block of 6 for a total of 26 patients. [**Figure 4**].

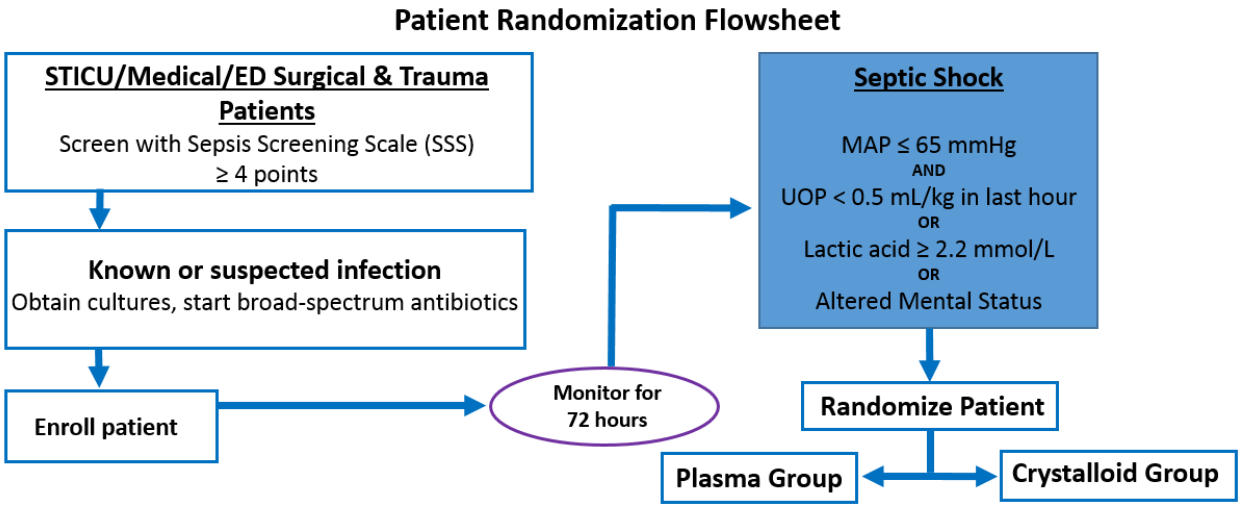

Figure 4 – Flow diagram depicting patient screening, enrollment, and randomization.

Intervention: Initial resuscitation with plasma will be 10 mL/kg (700 mL in a typical 70 kg adult). Traditional doses of plasma, when used to correct coagulopathy range from 10-15 mL/kg.[23] The plasma will be administered at a rate of 2-3 mL/kg/hr (140-210 mL/hr in a typical 70 kg adult). A research physician will be at bedside to follow patient resuscitation. Plasma administration may be terminated before the entire dose is administered if patients show clinical improvement, or if the treating clinician has concerns about circulatory overload. After the initial dose of plasma has

been given, subsequent fluid resuscitation (crystalloid or colloid) will be given at the discretion of the treating clinician.

The blood bank will have thawed plasma available on call as soon as an eligible patient has been identified. Type and screen will be performed concurrently to provide donor-matched plasma for subjects randomized to intervention group. For patients who proceed to the operating room during fluid resuscitation, the anesthesiology team will continue fluid administration per study protocol.

Control: Usual care using balanced crystalloids (Iso-Lyte or Plasma-Lyte) only will follow Surviving Sepsis Campaign guidelines. Controls will receive 30 mL/kg (2100 mL in a typical 70 kg adult) of crystalloids within the first 3 hours.[1] Crystalloid administration may be terminated before the entire dose has been administered if patients show clinical improvement, or if the treating clinician has concerns about circulatory overload. After the initial dose of crystalloids has been given, subsequent fluid resuscitation (crystalloid or colloid) will be given at the discretion of the treating clinician.

Observational Arm: Patients with suspected sepsis who do not meet the criteria for randomization or unable to obtain informed consent in a timely fashion (within 3 hours of research team being notified) will be enrolled in a prospective observational arm of the study. Baseline demographic and hospitalization data including the fluid therapy per the attending physician's discretion will be collected. Blood samples will also be collected at 0, 2, 3, 6, 12, and 24 hours upon determination of patients' eligibility for the observational study arm. A waiver of informed consent with be requested given that no intervention will be performed on the patient and that the study will be at minimal risk to the patient. The research team will attempt to obtain written informed consent from the patient or his/her legal authorized representative for 24 hours after patient enrollment into the observational study arm. If informed consent is denied by the patient or his/her legal authorized representative, no further data or blood samples will be collected and any data or blood samples collected prior to decline of participation will not be used in this study.

Endpoints of Resuscitation: Fluid resuscitation in both the intervention and the control arms will be titrated to serial reassessments of the patient's volume status via blood pressure monitoring (MAP > 65 mmHg), urine output measurements (goal of ≥ 0.5 cc/kg/hr), CVP measurements (>8 mmHg), stroke-volume variation on hemodynamic monitors (such as the Vigileo), inferior vena cava (IVC) collapsibility index via bedside ultrasound,[24] and lactate clearance (goal of ≥ 50% clearance after 6 hours of resuscitation). Serial laboratory examinations including lactate levels will be performed per standard of care in the ICU, until the lactate has normalized. Additional fluid support after the initial plasma or crystalloid bolus will be given at the discretion of the treating clinician, keeping in mind that septic shock patients in several randomized trials required 6-8L crystalloid per day.[25-27]

Co-interventions: Both groups will receive standard care following Surviving Sepsis Guidelines, including procurement of blood cultures, administration of broad-spectrum antibiotics, transfusion of packed red blood cells for hemoglobin < 7 mg/dL, and use of vasopressors to maintain MAP > 65 mmHg.

Data Collection:

Data collected will include: demographics, past medical history, hospital information including

initial resuscitation information and post-operative care, complications (**Appendix A**), and discharge information. A list of the data elements to be collected can be found in Appendix A. Data will be collected from the subject's medical record and the trauma registry. Risk/Safety evaluation will be performed at half enrollment (at 13 enrolled and randomized patients).

All subjects enrolled in this study will be assigned a study specific number. The de-identified data will be entered into a secure, password protected database accessible to only those involved in the study. A study linking log which will link subject identifiers to the study number will be kept by the study PI.

To ensure patient confidentiality is maintained at all times, all data will be maintained in accordance with HIPAA rules and regulations. Hard copy source documentation will be kept in a secure area in a locked office and electronic data will be stored on secure, password-protected computers accessible to only those study specific personnel.

Outcomes - Biomarkers of Endothelial and Glycocalyx Injury: The **primary outcome** is a reduction in serum biomarkers associated with glycocalyx breakdown (syndecan-1, sTM), endothelial leakage (sFLT-1, VEGF, sTM), sympatho-adrenal activation (NE, epinephrine), and inflammation (VEGF, sRAGE, HMGB-1, IL-6, 8, 10, 1α, 1β) in the plasma group. A rodent model has shown evidence of glycocalyx restoration after 2 hours of resuscitation with plasma as compared to crystalloid.[15] Biomarkers will be drawn at 0, 2, end of initial bolus of fluid administration, 6, 12, and 24 hours to evaluate their trend in response to plasma versus crystalloid resuscitation. Timing of biomarker lab draw at the end of the initial fluid bolus will be variable since termination of fluid resuscitation depends on patients' clinical response. Lactic acid will be drawn per standard of care to guide resuscitation. Standard labs for critically ill patients (such as complete blood count, basic metabolic panel, and arterial blood gases) will be obtained per STICU protocol. See **Table 2** for timing of biomarker lab draws. Funding for measuring biomarkers will be obtained from an additional source if the grant is awarded.

Table 2: Timing of Lab Draws Upon Randomization (T=0) in hours

	T = 0	T = 2	T = EoR	T = 6	T = 12	T = 24
Serum Biomarkers	✓	✓	✓	✓	✓	✓

Serum biomarkers = syndecan-1, sTM, sFLT-1, VEGF, sRAGE, HMGB-1, IL-6, 8, 10, 1α, 1β, vWF, tPA, NE, and epinephrine;
EoR = End of Resuscitation (variable, depending on patient response to fluids)

Secondary outcomes include additional volume of fluid required for resuscitation after the initial bolus of study fluid (crystalloid or plasma) within the first 24 hours of resuscitation, time on vasopressors, time until lactate normalization, ventilator days, ICU-free days, and hospital length of stay. Organ dysfunction will be measured including acute lung injury and acute renal failure. Standardized definitions will be used as outlined in the method of operation used in previously conducted trials by our group.[28] Potential harms of plasma administration will be assessed including symptomatic and asymptomatic venous thromboembolisms, transfusion-related allergic reactions, febrile non-hemolytic transfusion reaction, delayed-serological transfusion reactions, and transfusion-associated circulatory overload. Risk/safety evaluation will be performed at half recruitment (13 randomized patients).

Blinding: The healthcare provider will not be able to be blinded to the study intervention. The outcome assessors will be blinded when feasible, and the laboratory technicians and statisticians will be blinded.

Sample Size: We propose to enroll 26 patients (13 in each treatment arm) for the pilot randomized study to obtain unbiased estimates of treatment effect. We propose to enroll up to 100 patients to the observational study arm. Because this is a feasibility pilot study, we do not provide a power analysis for any outcomes since no formal hypothesis testing will be conducted. Instead, we will calculate estimates of treatment effect and 95% confidence intervals for all measures. We will also calculate probabilities of treatment benefit/harm using Bayesian analyses and conservative neutral priors. These estimates will inform the design of a future larger trial.

Statistical Analysis: Because this is a pilot, efficacy trial, we will perform both a per-protocol and an intention-to-treat analysis. Both frequentist and Bayesian analysis will be performed. For the primary outcome and all continuous outcomes (using variable transformations if needed), we will use mixed models that include group and time period as covariates with a random subject effect. We will report group differences and 95% CIs from these models. For binary outcomes, a log binomial (or Poisson in case of non-convergence) will be used to estimate relative risks and 95% CIs. Hazard ratios and 95% CIs will be reported for time-to-event comparisons. For the Bayesian analysis, neutral conservative priors (that exclude large treatment effects almost never seen with medical interventions) will be used to estimate the probability of both benefits and harms, as defined by our primary and secondary outcomes.

References

1. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med.* 2017;45(3):486-552.
2. Marik PE, Linde-Zwirble WT, Bittner EA, Sahatjian J, Hansell D. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. *Intensive Care Med.* 2017;43(5):625-632.
3. Johansson P, Stensballe J, Ostrowski S. Shock induced endotheliopathy (SHINE) in acute critical illness - a unifying pathophysiologic mechanism. *Crit Care.* 2017;21(1):25.
4. Chignalia AZ, Yetimakman F, Christiaans SC, et al. The Glycocalyx and Trauma: A Review. *Shock.* 2016;45(4):338-348.
5. Ince C, Mayeux PR, Nguyen T, et al. The Endothelium in Sepsis. *Shock.* 2016;45(3):259-270.
6. Chelazzi C, Villa G, Mancinelli P, De Gaudio AR, Adembri C. Glycocalyx and sepsis-induced alterations in vascular permeability. *Crit Care.* 2015;19:26.
7. Hou PC, Filbin MR, Wang H, et al. Endothelial Permeability and Hemostasis in Septic Shock: Results From the ProCESS Trial. *Chest.* 2017;152(1):22-31.
8. Ostrowski SR, Berg RM, Windelov NA, et al. Coagulopathy, catecholamines, and biomarkers of endothelial damage in experimental human endotoxemia and in patients with severe sepsis: a prospective study. *J Crit Care.* 2013;28(5):586-596.
9. Oberholzer A, Souza SM, Tschoeke SK, et al. Plasma cytokine measurements augment prognostic scores as indicators of outcome in patients with severe sepsis. *Shock.* 2005;23(6):488-493.

10. Torres Filho IP, Torres LN, Salgado C, Dubick MA. Plasma syndecan-1 and heparan sulfate correlate with microvascular glycocalyx degradation in hemorrhaged rats after different resuscitation fluids. *Am J Physiol Heart Circ Physiol.* 2016;310(11):H1468-1478.
11. Nelson A, Johansson J, Tyden J, Bodelsson M. Circulating syndecans during critical illness. *APMIS.* 2017;125(5):468-475.
12. 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(2):127-136.
13. Robinson BR, Cotton BA, Pritts TA, et al. Application of the Berlin definition in PROMMTT patients: the impact of resuscitation on the incidence of hypoxemia. *J Trauma Acute Care Surg.* 2013;75(1 Suppl 1):S61-67.
14. Balogh Z, McKinley BA, Cocanour CS, et al. Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. *Arch Surg.* 2003;138(6):637-642; discussion 642-633.
15. Kozar RA, Peng Z, Zhang R, et al. Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. *Anesth Analg.* 2011;112(6):1289-1295.
16. Rahbar E, Cardenas JC, Baimukanova G, et al. Endothelial glycocalyx shedding and vascular permeability in severely injured trauma patients. *J Transl Med.* 2015;13:117.
17. Straat M, Muller MC, Meijers JC, et al. Effect of transfusion of fresh frozen plasma on parameters of endothelial condition and inflammatory status in non-bleeding critically ill patients: a prospective substudy of a randomized trial. *Crit Care.* 2015;19:163.
18. Chang R, Holcomb JB, Johansson PI, Pati S, Schreiber MA, Wade CE. Plasma Resuscitation Improved Survival in a Cecal Ligation and Puncture Rat Model of Sepsis. *Shock.* 2017.
19. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol.* 2010;63(8):834-840.
20. Zanotti Cavazzoni SL, Dellinger RP. Hemodynamic optimization of sepsis-induced tissue hypoperfusion. *Crit Care.* 2006;10 Suppl 3:S2.
21. Moore LJ, Jones SL, Kreiner LA, et al. Validation of a screening tool for the early identification of sepsis. *J Trauma.* 2009;66(6):1539-1546; discussion 1546-1537.
22. Wawrose R, Baraniuk M, Standiford L, Wade C, Holcomb J, Moore L. Comparison of Sepsis Screening Tools' Ability to Detect Sepsis Accurately. *Surg Infect (Larchmt).* 2016;17(5):525-529.
23. Tinmouth A. Assessing the Rationale and Effectiveness of Frozen Plasma Transfusions: An Evidence-based Review. *Hematol Oncol Clin North Am.* 2016;30(3):561-572.
24. Gui J, Yang Z, Ou B, et al. Is the Collapsibillity Index of the Inferior Vena Cava an Accurate Predictor for the Early Detection of Intravascular Volume Change? *Shock.* 2017.
25. Investigators A, Group ACT, Peake SL, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med.* 2014;371(16):1496-1506.
26. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med.* 2015;372(14):1301-1311.
27. Pro CI, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med.* 2014;370(18):1683-1693.
28. 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(5):471-482.

29. Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303(8):739-746.

Appendix A: List of Data Elements

Demographics

- Age
- Gender
- Race
- Ethnicity
- Height/Weight/BMI

Past Medical History

- Admitting Diagnosis (type of injury - blunt/penetrating)
- Concomitant medical conditions/diseases
- Current home medications

Hospital Information

- Admission date/time (ED and STICU/SIMU)
- Time of injury
- Type of injury
- Pre-hospital treatment (LSIs)
- Initial resuscitation therapy (blood products, IR, OR, LSIs)
- Vital signs
- Degree of pretibial edema
- Laboratory results
- Diagnostic procedure results
- Daily STICU/SIMU data (i.e. ventilator settings, vital signs)
- Vasopressor use (medication, dose)
- Blood products and fluids
- Sepsis diagnostic information
- Operative and endovascular interventions
- Complications (ARDS, AKI, venous thromboembolic events, sepsis, severe sepsis, septic shock, transfusion reactions, infections, multi-organ failure, pneumonia)

Discharge Information

- Date/time of discharge
- Disposition
- ISS
- AIS
- Cause of death (as applicable)
- Number of ventilator days
- Number of ICU days