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**14. ABSTRACT**

The purpose of this grant was to support a national coordinating center for trauma research funding. The application review infrastructure/process was streamlined and efficient leading to the selection of research projects based on a solid scientific, peer review of submitted research proposals and subsequent conduct of important clinical trauma research that impact patient outcomes. Over the last five years, six trauma research studies have been completed across 23 academic trauma centers enrolling 955 trauma patients or healthy volunteers. Findings from these studies advanced scientific knowledge and trauma care in the areas of resuscitation fluid management, TEG-based venous thromboembolism prevention, management of MRSA infection, anemia, and splenic injury, the role early sex hormones, and functional coagulation of banked whole blood in trauma patients. Additionally, the National Trauma Institute provided multiple forums to facilitate military-civilian transfer of medical advances including providing the infrastructure for the Coalition for National Trauma Research (CNTR) and established governance and initial development of a National Trauma Research Repository (NTRR).

**15. SUBJECT TERMS**

Trauma, ICU, education, research, training, analysis, practice

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**INTRODUCTION**

The National Trauma Institute (NTI) utilized $3,845,000 in congressional funding to continue and broaden work begun by NTI in previous congressional special interest funding proposals. NTI's objective was to distribute and manage funding for peer-reviewed research projects for areas of greatest impact in trauma, in order to change practice to save lives and improve outcomes for those affected by trauma, and to disseminate research findings to the trauma community. An 18-month No Cost Extension was approved in August of 2012, extending the period of performance to March 28, 2014. In addition, a contract modification was executed in February of 2015 to add $300,000 to the contract for additional SOW tasks to create a steering committee to guide the development of the National Trauma Research Repository, review existing trauma data sources and initiate identification of existing common data elements to be included in the repository. This modification extended the period of performance to September 28, 2016.

**BODY**

**Statement of Work**

**A. The National Trauma Institute supported a national coordinating center for trauma research funding.**

1) Requests for proposals (RFP) based on areas of scientific merit in trauma and emergency or critical care were prepared and issued.
2) NTI Science Committee scored proposals according to scientific merit, clinical impact, and ability to perform the research, innovation, and military relevance.
3) NTI Board updated trauma research subject areas based upon the impact on survival or care of patients, existing funding, and funding availability annually.
4) NTI performed award management and compliance activities to include all appropriate USAMRMC HRPO requirements.
5) NTI provided research funding for proposals that sought to address areas of urgent need in the treatment of trauma.

**B. The National Trauma Institute provided multiple meeting forums for progress toward methods for military-civilian transfer of medical advances, and development of clinical protocols from promising funded pilot studies, as determined by the NTI Science Committee. These meetings included military and civilian researchers.**

**C. The National Trauma Institute established governance and initial development of a National Trauma Research Repository (NTRR).**

1) Identified stakeholders and formed appropriate governance and steering committees.
2) Review/evaluate existing trauma data sources.
3) Identify common data elements from currently funded studies.

**A. The National Trauma Institute Supported a National Coordinating Center for Trauma Research Funding.**

**Tasks 1-3: Requests for proposals, scientific peer review, and updated trauma research subject areas**

NTI's national request for proposals attracted 92 pre-proposals from across the United States. The NTI Science Committee conducted a scientific peer-review of all such proposals, giving priority to clinical and translational research studies. Following the pre-proposal review, 22 investigators were invited to submit full proposals.

The Science Committee then reviewed the 22 full proposals, scoring and compiling them before meeting for a face-to-face evaluation and review to make final award recommendations. Proposals were evaluated on the following criteria: relevance to NTI research objectives, scientific excellence, clinical relevance and impact, multicenter collaboration, military relevance, innovation, potential for follow-on studies, and feasibility of completing the objectives in one-year funding period. The full Board of Directors approved the nine proposals recommended by the Science Committee, and these received funding.

NTI Board meetings occurred every two months throughout the performance period, during which updates to trauma research subject areas based upon the impact on survival or care of patients, existing funding, and funding availability were discussed. In order to maximize dissemination of the research outcomes, NTI designed and implemented a Knowledge Translation Plan including Knowledge Translation Agreements (KTAs) between W81XWH-11-1-0841 investigators and NTI. (Appendix A) Knowledge Translation Agreements have been executed with the following researchers funded by this grant: Drs. Cryer, Doucet, Schreiber, and Zarzaur.

**Tasks 4-5: Perform award management and compliance to include all appropriate USAMRMC HRPO requirements and provide research funding.**

There were nine research projects, including the Delayed Splenic Rupture after Non-Operative Management of Blunt Splenic Injury (PI: Dr Ben Zarzaur), as well as a tenth project that received a modest amount of funding from this grant in order to finish work originally funded on an earlier grant (W81XWH-10-1-0924). The Blunt Splenic Injury study was an American Association for the Surgery of Trauma (AAST) Multi-Institutional Prospective Trial and included 11 research sites. NTI subcontracted with each participating site for this award; therefore, there were a total of 19 research subcontracts, each executed upon HRPO approval.

Throughout the period of performance, all regulatory compliance activities, such as amendments, continuing reviews, protocol deviations, adverse events, and study close out upon completion were managed per the guidelines set forth by the HRPO. Three of the studies closed before completion, due to various reasons, documented below.

The 10 projects are detailed in the following section:

**Project 1:**
**Project Title:** Detection and Management of Non-Compressible Hemorrhage by Vena Cava Ultrasonography
**Principal Investigator:** Jay Doucet, MD
**Lead Site:** University of California at San Diego (UCSD)
**Participating Sites:** University of Utah, Emory University, and University of Maryland School of Medicine.
**HRPO:** *Log#A-16977.2a*
**Project Abstract:**
This was a prospective, observational clinical trial of major trauma victims presenting at four academic trauma centers using bedside ultrasound to identify patients with evidence of hypovolemia as determined by inferior vena cava (IVC) collapsibility within 15 minutes of admission. Patients with significant IVC collapsibility were enrolled and received the institutions' standard of care resuscitative intravenous solutions. Enrolled subjects were stratified at a second ultrasound IVC exam 30-40 minutes after admission by response or non-response to an intravenous fluid challenge. The objective was to demonstrate whether such non-responder subjects identified by serial IVC ultrasound examinations have significant shock physiology as determined by markers of shock such as lactate, base deficit, and complications.

Demographics, mechanisms of injury, diagnoses, fluids and transfusions given, interventions required, complications, mortality and discharge disposition were recorded. Prior small studies of ultrasonographic assessment of IVC diameters and collapsibility demonstrated it to be a sensitive detector of blood volume loss and hemorrhagic shock. This technique may predict those patients who will require transfusions, surgery, or angiographic embolization. This technique may also allow better triage of major trauma victims and, thereby, avoid therapeutic delays and complications.

This study provided an opportunity to demonstrate the ability of handheld ultrasound devices to detect and monitor hemorrhagic shock in initial trauma care and in the ICU. The study has significant military relevance, as handheld ultrasound is readily available to forward echelons of combat casualty care and can provide clinical decision support when evaluating casualties with hemorrhagic shock.

**Results:**
While the initial goal of the study had been to enroll 396 subjects, at the time of study closing in July of 2014, 2,336 subjects had been screened and 59 enrolled. The research team determined that IVC collapsibility of greater than 75% is uncommon in civilian trauma patients. It was seen about 213 of 3239 patients or 6.5%. Interestingly this was close to the observed rate of admission systolic hypotension (Systolic Blood Pressure (SBP) <90 mmHg)) of 6.1%, but only 8 of 213 or 3.8% of those with collapsibility had hypotension at admission, indicating most trauma patients with IVC collapsibility are not hypotensive. However, patients with persistent collapsibility on a second measurement 60 minutes after admission had significantly higher intravenous fluid requirements during initial resuscitation (176ml $\pm$ 877 vs. 1194ml $\pm$ 489, $p<0.001$) (Doucet et al., unpublished).

The research team continued this study after the funding period for this award ended and recruited additional subjects (total n = 74). Among this sample, Focused Assessment with Sonography for Trauma-Inferior Vena Cava Collapsibility (FAST-IVC) was found to be useful in predicting 24-hour fluid resuscitation requirements (Appendix B).

This ongoing research study met the Joint Warfighter Medical Research Program's (JWMRP) goal to augment and accelerate high priority DoD and service medical requirements to continue prior year initiatives that are close to achieving the objectives. In October of 2015, the study received additional funding of $498,269 through the JWMRP. Subsequent progress is discussed within the reports related to the JWMRP Award W81XWH-15-1-0709 (POP: 9/15/2015 – 9/16/2017).

Dr. Doucet produced "Protocol Video USA-IVC Study (Version 5) that is posted on YouTube: https://youtu.be/54-Z6fiJpPY This video contains study design, procedures, inclusion/exclusion criteria and a demonstration to train clinical sonographers on correct techniques to measure IVC diameter in research participants.

**Project 2:**
**Project Title:** Thrombelastography (TEG®) Based Dosing of Enoxaparin for Thromboprophylaxis: A Prospective Randomized Trial
**Principal Investigator:** Martin A. Schreiber, MD
**Lead Site:** Oregon Health & Science University (OHSU)
**Participating Sites:** University of Texas Health Science Center at Houston, and University of Washington at Harborview.
**HRPO:** *Log #A-16977.7a*

**Project Abstract:**
A standard dose of enoxaparin is used in high risk patients to prevent thromboembolic complications. The prevention of deep vein thrombosis (DVT) is critical, as it can lead to long term venous stasis disease or pulmonary embolus (PE), which causes significant morbidity and mortality. Recent data suggest that standard dosing of enoxaparin may be inadequate in the critically ill or obese patient. Anti-Factor Xa levels (aFXa) measure the relative inhibitory activity of enoxaparin on the clotting process, but accuracy, cost, and availability remain problematic. Therefore, using aFXa to determine if patients are receiving correct dosing to prevent DVT may be inadequate. Thrombelastography (TEG®) is a real-time assay that can evaluate each step of clot formation and breakdown. TEG® analysis has adequate sensitivity to detect enoxaparin--induced changes in coagulation.

Previously, Schreiber et al demonstrated, in a prospective non-interventional study, that TEG® can distinguish patients who will develop DVT while aFXa cannot. Based on that finding, the research team conducted a prospective interventional study of subjects receiving enoxaparin for DVT prevention. Subjects were randomized to receive standard

or variable dosing of enoxaparin. Subjects in the variable dosing group had enoxaparin dosing adjusted to achieve a preset level of anticoagulation as demonstrated by TEG®. Outcomes compared between groups included incidence of DVT, superficial venous thrombosis, bleeding complications, PE, and death. It was hypothesized that TEG® based dosing is superior to standard dosing for the prevention of thromboembolic events without increasing the incidence of major bleeding complications.

**Results:**
This multicenter, prospective randomized controlled trial compared TEG-adjusted versus standard prophylactic enoxaparin administration and VTE incidence in trauma and surgery patients. A total of 18,195 potential subjects were screened, and, after accounting for subjects who were withdrawn or did not complete the study before they were discharged from the hospital, the final dataset to be analyzed included 185 subjects. Few subjects achieved a change in reaction time (time to initial fibrin formation of less than one minute ( $\Delta R$ >1 ), and VTE rates were similar. However, a difference in bleeding complications approached significance. The researchers concluded that TEG-adjusted enoxaparin administration based on Δ*R* is not supported by the current data in this study population. However, these data demonstrate that many trauma and surgical patients are hypercoagulable at baseline, and that further investigations into the effects of platelet activation and obesity, time-to-enoxaparin administration, and AT-III deficiency are needed.

The results from this study were presented at the Pacific Coast Surgical Association in February 2016 (Appendix C) and published in September, 2016 in *JAMA Surgery* online and in the October 2016 issue of *JAMA Surgery*, Volume 151, Number 10 (Appendix D).

**Project 3:**
**Project Title:** Acute Lung Injury Ventilation Evaluation (ALIVE) Trial
**Principal Investigator:** Suresh Agarwal, MD
**Lead site:** Medical College of Wisconsin (MCW)
**Participating Sites:** Boston University Medical Center (BUMC), Brooke Army Medical Center (BAMC), University of Maryland Medical Center, University of Mass Memorial Medical Center, and the University of Penn.
**HRPO:** *Log #A-16977.6b*

**Project Abstract:**
Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) represent a spectrum of clinical syndromes of rapid respiratory system deterioration that are associated with both pulmonary and systemic illness and a mortality of 30 to 40 percent. Multiple studies have examined methodology to reduce mortality and improve outcome. However, there have been few positive outcomes resulting in management of these difficult disease progressions. Furthermore, research comparing the effectiveness of modern ventilator modalities upon patients with ARDS/ALI does not exist.

Low-tidal volume ventilation (ARDSNet) remains the mainstay of management of patients with ALI. However, evidence exists demonstrating that it is not without fault, including increased atelectasis, increased weaning time, and increased incidence of pneumonia. Airway Pressure Release Ventilation (APRV) is a different, non-experimental, pressure-cycled strategy of mechanical ventilation currently in routine clinical use. It allows patients greater respiratory autonomy and has been associated with better oxygenation, less sedative usage, and less ventilator-associated pneumonia compared with other ventilator modes. However, questions regarding whether APRV increases or decreases ventilator-associated lung injury and inflammation continue to exist. This study was a randomized, crossover study of biomarkers of study subjects with ALI using two ventilator modes: APRV and ARDSNet. Furthermore, we examined the physiologic impact of APRV and ARDSNet protocols upon subjects with ALI. The long-term goal is to improve health outcomes of patients with Acute Lung Injury and Acute Respiratory Distress Syndrome.

**Results:**
Because the Principal Investigator relocated, the study was delayed in obtaining HRPO approval for the new lead site, and by 1/23/2014, enrollment totals were still much lower than anticipated. After conferring with Dr. Agarwal, the NTI

Science Committee made the decision to terminate the study due to lack of progress. Thus, this project's period of performance ended on 2/3/14. HRPO close out acknowledgement was received on 6/19/2014.

**Project 4:**
**Project Title:** The Safety and Efficacy of Platelet Transfusion in Patients Receiving Antiplatelet Therapy that Sustain Intracranial Hemorrhage
**Principal Investigator:** Mark Cipolle, MD
**Site:** Christiana Health Care System, Newark DE
**HRPO:** *Log #A-16977.5*

**Project Abstract:**
Intracranial hemorrhage (ICH) is the major cause of death and disability in both trauma and stroke. Most ICHs expand over the first 24 hours, and this expansion correlates with a worsened neurologic outcome. A significant number of ICH patients have exposure to antiplatelet therapy, and this therapy augments bleeding risk. There is a paucity of data to guide early therapy for ICH in patients exposed to antiplatelet therapy. The research team planned to enroll 40 subjects as a single center pilot trial in preparation for a multicenter, randomized, controlled trial designed to examine the safety and efficacy of platelet transfusion in subjects on antiplatelet therapy suffering from ICH. The primary endpoint was to be the change in hemorrhage growth over the first 24 hours. Secondary endpoints included neurologic disability (Glasgow Coma Score, NIH Stroke Scale, modified Rankin Score and Extended Glasgow Outcome Score), thromboembolic complications out to 90 days, and changes in platelet function as measured by point of care platelet aggregometry. Eligible subjects were to be those greater or equal to 18 years old with CT scan evidence of ICH (traumatic or spontaneous) who were being chronically treated with aspirin (81mg and above/day) and/or a thienopyridine (ticlodopine, clopidogrel or prasugrel). Subjects were to be block randomized within four hours of injury or symptom onset. Subjects randomized to platelets were to receive 2 units of apheresis platelets, while control subjects were to receive 400 mL of normal saline. To detect a 50 percent reduction in hemorrhage growth, the research team needed to enroll approximately 150 total subjects.

**Results:** This study was voluntarily closed by the PI after two quarters based upon the inability to enroll enough eligible subjects.

**Project 5:**
**Project Title**: Effect of Antioxidant Vitamins on Coagulopathy and Nosocomial Pneumonia after Severe Trauma
**Principal Investigator:** Jean-Francois Pittet, MD
**Site:** University of Alabama at Birmingham
**HRPO:** *Log# A-16977.6*

**Project Abstract:**
Recent studies reported that one quarter of major trauma patients are coagulopathic prior to fluid resuscitation by a mechanism that is in part dependent on the activation of the anticoagulant protein C pathway. This early coagulopathy is associated with poor outcome. Antioxidant vitamin stores are depleted after severe trauma and vitamin C/E supplementation has reduced mortality and organ failure in trauma patients, although its effect on the severity of post-traumatic coagulopathy and the subsequent development of lung infection is unknown.

Preliminary data showed a significant correlation between early coagulopathy, activation of the protein C pathway, and the later development of nosocomial lung infection and organ injury after severe trauma. The research team postulated that supplementation with vitamins C/E may reduce post-traumatic oxidative stress and, thereby, attenuate the early activation of the protein C pathway and the later depletion of this important endogenous anticoagulant. Thus, they sought to test the hypothesis that the early administration of antioxidant vitamins C/E will attenuate coagulation derangements and the subsequent development of nosocomial pneumonia after severe trauma in humans. A single

center prospective double-blinded randomized cohort study was to determine the effect of the administration of vitamins C/E (a) on the activation of the protein C pathway and coagulation derangements and (b) on the development of nosocomial pneumonia, organ dysfunction, sepsis, and death in 700 severely traumatized patients.

**Results:**
This study was terminated by the NTI Science Committee after a protracted delay in initiating (more than nine months from HRPO approval to subject enrollment initiation) by the PI and enrollment of only 11 subjects in four months. With an enrollment goal of 700 subjects, the NTI Science Committee determined that this study would not finish in a timely fashion.

**Project 6:**
**Project Title:** Hepcidin and Anemia in Trauma
**Principal Investigator**: Lena M. Napolitano, MD
**Site**: University of Michigan Health System, Ann Arbor MI
**HRPO:** *Log #A-16977.8*

**Project Abstract:**
Anemia is common in trauma patients and is associated with a high rate of blood transfusion. The pathophysiology of this anemia is "anemia of inflammation" and develops via three mechanisms: 1) impaired iron regulation, 2) shortened red blood cell life span, and 3) reduced rate of erythropoiesis. Once iron enters cells (enterocytes and macrophages), the iron export protein ferroportin controls egress. Hepcidin, a peptide made in the liver, is the key regulator of iron homeostasis. Hepcidin binds to ferroportin, leading to its ultimate degradation. Hepcidin reduces iron availability via two mechanisms: 1) decreased absorption of iron across the GI tract and 2) decreased release of iron from the reticuloendothelial system. It therefore induces a functional iron deficiency by shuttling iron into the macrophages and making it unavailable for erythropoiesis. Hepcidin is decreased by iron deficiency, most anemias, and tissue hypoxia. Hepcidin is upregulated by iron excess and inflammation. Hepcidin likely plays an important role in the acute inflammatory response that occurs with trauma. However, no studies have measured hepcidin in critically ill trauma patients. If serum hepcidin levels are elevated in trauma, this would confirm that inability to use existing iron stores is part of, if not key to, the anemia of trauma and critical illness. This has important implications, since the use of blood transfusion for anemia treatment may further induce an inflammatory response with resultant suppression of native erythropoiesis. The research team hypothesized that hepcidin would be increased and erythropoietin decreased early after trauma and that resolution of anemia would not occur until late (28-31 days). By measuring time-dependent changes in hemoglobin, hepcidin, cytokine, and erythropoietin concentrations in trauma patients, they expected to critically examine the inter-relationships to target potential therapeutic strategies for the treatment and amelioration of anemia in trauma and critical care. This study addressed two specific aims: 1) to define the temporal relationship between serum and urine hepcidin concentrations, anemia, and iron and erythropoiesis studies (serum iron, TIBC, transferrin, soluble transferrin receptor, zinc protoporphyrin, serum erythropoietin) in critically ill trauma patients, and 2) to assess the correlation between hepcidin levels, anemia, and degree of inflammation as determined by serum inflammatory markers including IL-6, TNF-α, IL-4, β-NGF, and C-reactive protein.

**Results:**
With 526 potential subjects screened, 98 subjects were enrolled. The study provided the first available data regarding the time-dependent changes of the peptide hormone hepcidin in anemia associated with trauma and critical illness. Serum hepcidin and serum erythropoietin concentrations in critically ill trauma patients were measured. The temporal relationship between serum hepcidin concentrations, anemia, and iron and erythropoiesis studies (serum iron, TIBC, transferrin, soluble transferrin receptor, zinc protoporphyrin, serum erythropoietin) was defined. The correlation between hepcidin levels, anemia, and degree of inflammation as determined by serum inflammatory markers was measured. The duration and resolution of anemia was quantified (Napolitano et al. unpublished data).

**Project 7:**
**Project Title**: Delayed Splenic Rupture after Non-Operative Management of Blunt Splenic Injury; an American Association for the Surgery of Trauma (AAST) Multi-Institutional Prospective Trial
**Principal Investigator**: Ben Zarzaur, MD
**Lead site:** University of Tennessee at Memphis
**Participating Sites**: University of California at San Diego (UCSD), University of Texas Health Science Center San Antonio (UTHSCSA), University of Pittsburgh-Mercy Hospital, University of Pittsburgh-Presbyterian Hospital; University of Texas Health Science Center at Houston (UTHSC-Houston), University of Florida Health Science Center at Jacksonville, Yale School of Medicine, Case Western Reserve, Adams Cowley Shock Trauma Center, Medical College of Wisconsin (MCW).
**HRPO:** *Log #A-16977.3a – 3k*

**Project Abstract:**
While current guidelines favor non-operative management of blunt spleen injury (BSI), there is a lack of prospective multi-institutional data to determine the best non-operative strategy. Immediate splenic artery embolization (SAE), screening for splenic pseudoaneurysm (PSA) followed by SAE of detected PSA, and observation only have been proposed as treatment strategies for BSI. The research team proposed recruiting 1,000 patients with non-operatively managed BSI from 11 institutions, and following them for 180 days in order to pursue the following specific aims: 1) Ascertain the 180-day risk of splenectomy after non-operative management of BSI, 2) Determine factors related to failure of non-operatively managed BSI, 3) Demonstrate propensity score matching as a surrogate for a randomized trial in the field of BSI management. Accomplishing Specific Aim 1 provided an estimate of the 180-day risk of splenectomy after non-operative BSI management using prospectively collected data. This information was critical so that adequately powered clinical trials could be designed. By utilizing detailed information about each subject, the research team was able to address Specific Aim 2.

**Results:**
There were a total of 383 subjects enrolled out of 1,002 screened patients. Follow-up at 30, 90, and 180 days was 95%, 88%, and 87%, respectively. The need for splenectomy after 24 hours of successful non-operative management was rare (3.1%). After the initial 24 hours, no additional interventions were warranted for patients with Grade I injuries. For grade II – V, BSI close observation was indicated for 10-14 days, as this is the time of greatest risk of delayed splenectomy (DS). Extravasation of contrast from the spleen at the time of admission was a strong predictor of delayed splenectomy and may be an area where aggressive use of angiography and embolization is warranted. Use of CT to follow splenic healing after discharge was not indicated in patients without symptoms. These findings are significant because they support a limited role of CT scan use in follow-up of patients with non-operatively managed blunt splenic injury. This could lead to lower health care costs and decreased radiation exposure for these patients.

The results of this study were presented at the American Association for the Surgery of Trauma (AAST) 2014 Annual Conference, Philadelphia PA, September 11, 2014 (Appendix E) and published in the *Journal of Trauma Acute Care Surgery* in 2015 (Appendix F).

**Project 8:**
**Project Title:** Methicillin-Resistant Staphylococcus Aureus in a Trauma Population: Does Decolonization Prevent Infection?
**Principal Investigator:** Robert Maxwell, MD
**Lead Site:** University of Tennessee Health Science Center at Chattanooga
**Participating Sites:** Vanderbilt University.
**HRPO:** *Log #A-16977.4a*

**Project Abstract:**
This was a randomized, prospective trial on all trauma patients admitted to the Intensive Care Unit (ICU). Subjects had Methicillin-resistant Staphylococcus aureus (MRSA) nasal swabs performed at the time of admission to determine MRSA

colonization status. The initial analysis was performed using the BD GeneOhm MRSA assay, a PCR amplification technique specific for MRSA. Subjects were deemed colonized if they had a positive MRSA assay. Subjects who were colonized with MRSA at admission were eligible for randomization. Colonized subjects were randomized to receive decolonization treatment or placebo. Decolonization treatment included Hibiclens baths and Bactroban ointment to both nares for five days, and the placebo treatment entailed routine soap baths and a placebo ointment. Repeat nasal swabs were performed at the completion of the treatment regimen and at weekly intervals to determine the treatment efficacy. Subjects were screened for invasive MRSA infections as dictated by their clinical course. Additionally, nasal swabs and body fluid cultures were assessed by pulsed-field gel electrophoresis to determine the MRSA subtypes. The research team anticipated that this data would help delineate which isolates are inducing colonization, and if these same isolates are responsible for causing invasive MRSA infections. The primary outcome measure was invasive MRSA infection rate.

**Results:**
One hundred and two (102) patients tested positive for MRSA colonization of their nares within 30 hours of admission to the ICU. This represents a colonization rate of 15%, which is higher than the preliminary data showing a colonization rate of 10%. Of this colonized group, 56 subjects or their families (55%) consented to participate in this MRSA decolonization study and met inclusion criteria. Amon the 47 subjects who received at least three days of treatment, 55% remained colonized and 45% tested negative, indicating decolonization.

In June of 2013, an article by Huang SS, Septimus E, Kleinman K, et al. was published in the *New England Journal of Medicine* that showed chlorhexidine versus soap for universal bathing of critically ill patients significantly reduced the number of MRSA infections in their population. The PI felt he no longer had clinical equipoise based on this landmark study, and randomization was terminated. After enrollment of the 45$^{th}$ subject, all subjects received chlorhexidine baths and mupirocin ointment to the nares. Overall, the rate of decolonization was 48% in the chlorhexidine/mupirocin group versus 36% in the soap/lubricating jelly treatment group.

With regard to topical anti-infective resistance, three gene loci were probed. Mupirocin resistance was examined by PCR-amplification of the mupA gene, while resistance to topical disinfectants (e.g., chlorhexidine and quarternary ammonium compounds) was examined by PCR-amplification of qac A/B and smr genes. In total, no mupirocin resistance was detected in this collection of isolates nor were qac A/B genes detected. In contrast, 12/54 isolates possessed smr genes. As previously published by this research group, there is often no clear phenotype in those strains that possess smr genes, though increased MIC's to benzalkonium chloride and/or cetyltrimethylammonium bromide have been observed. Formal MIC determination have not been planned or conducted for this collection of strains.

Attempts at decolonization with chlorhexidine and mupirocin are effective in about half the subjects undergoing this treatment. If a trauma patient is colonized with MRSA at the time of admission to the ICU following a traumatic event and develops a subsequent MRSA infection, it will likely be the same species that was present at the time of admission *despite* decolonization attempts.

The results of this study were presented at Western Trauma Association, 46th Annual Meeting, Lake Tahoe, CA, February 28 – March 4, 2016 (Appendix G).

**Project 9:**
**Project Title:** Transfusion of Stored Fresh Whole Blood (FWB) in a Civilian Trauma Center: A Prospective Evaluation of Feasibility and Outcomes
**Principal Investigator:** Henry Gill Cryer, MD
**Site:** University of California-Los Angeles (UCLA)
**HRPO:** *Log #A-16977.1*

**Project Abstract:**
Whole blood (WB) transfusion is a promising alternative to component therapy. Use of banked WB requires filtration of white blood cells (leukoreduction) and an established shelf life during which WB retains coagulant capacities. The goal of this study was to define the time course of coagulation stability in leukoreduced compared to unfiltered WB under standard refrigeration conditions. Twelve WB units were donated by healthy volunteers after routine screening. Five units underwent standard leukocyte filtration and five did not. Two units were aliquoted into filtered and unfiltered samples, with platelets added to each sample on Day 14. Units were stored at 4$^{o}$C and sampled on days 0, 1, 2, 3, 4, 5, 6, 7, 10, 14, 21, 28 and 35 for immediate thromboelastogram (TEG) analysis, and centrifuged and stored at 80$^{o}$C for later Calibrated Automated Thrombogram (CAT) and coagulation factor assays.

**Results:**
Unfiltered banked whole blood had decreased labile clotting factors without impairment of coagulation potential over 35 days. However, despite improved levels of labile clotting factors, filtered blood had significantly less thrombin generation, clot strength, ratio for clot growth, and delayed first sign of clot growth at various time points. Filtered whole blood may not be suitable for hemostatic resuscitation. Further study is needed to determine the mechanism of these filtration lesions.

The results of this study were presented at the American College of Surgeons Committee on Trauma 2013 Resident Competition (Appendix H) and the American Association for the Surgery of Trauma (AAST) 2014 Annual Conference, Philadelphia PA, September 11, 2014 (Appendix I). A manuscript detailing this study is under review at the *Journal of Trauma and Acute Care Surgery* (submitted December 2016) (Appendix J).

This research study met the Joint Warfighter Medical Research Program's (JWMRP) goal to augment and accelerate high priority DoD and service medical requirements to continue prior year initiatives that are close to achieving the objectives. In October of 2015, the study was awarded an additional $499,995 in JWMRP funding to extend this work as a clinical trial (Award # W81XWH-15-2-0039, POP: 8/25/15-8/24/18). Subsequent progress is discussed within the reports related to that award.

**Project 10:**
**Project Title:** Characterization of the Effects of Early Sex-hormone Environment Following Injury
**Principal Investigator:** Jason L. Sperry, MD, MPH
**Site:** University of Pittsburgh
**HRPO:** *Log#: A-16375.1*

**Project Abstract:**
Although significant advances in the care of the injured patient have occurred over the last decade, those who survive their initial injury continue to be plagued with the development of multiple organ failure and sepsis and their attributable morbid effects. One important and persistent finding has been that males and females respond differently following traumatic injury and hemorrhagic shock, with a relative protection afforded to females. A large body of literature has evolved attempting to elucidate the mechanisms responsible for these differences; however, a significant divide continues to exist between what experimental animal investigations have revealed and what has been shown clinically in humans. The ultimate elucidation of the mechanisms responsible for these outcome differences will allow future risk factors and therapeutic targets to be discovered and characterized, having significant potential to improve outcomes in both males and females following injury. The early sex-hormone environment may help shape or determine the intensity of the early inflammatory response that follows injury and may provide a predisposition toward maintenance of any excessive or inadequate response once initiated. Similarly, the early sex-hormone environment may affect the need for resuscitation or blood component transfusion, and knowledge of this early hormonal milieu may allow those patients at highest risk of poor outcome post-injury to be identified.

The overarching goal of this study was to further characterize and investigate the early sex-hormone environment following injury and the associations of early estrogen and testosterone levels with the strength of the innate immune

response, the coagulation response, resuscitation requirements, and clinical outcomes following injury. As few effective interventions exist to alter the morbidity and mortality that inherently follow traumatic injury, investigation into novel mechanisms that may result in a protective effect can provide a route to reduce these sequelae post-injury.

**Results:**
This study, originally funded under W81XWH-10-1-0924, had enrolled 255 subjects. For that cohort, the mortality rate was lower than expected (4%). This was in part due to family reluctance in giving consent for the drawn samples if the patient suffered mortality within the first 48 hours. This inability to obtain consent due to early mortality represented over half of the 33% of families who were offered but were reluctant to consent for the study. The incidence of multiple organ failure (MOF) in the first seven days, and the development of nosocomial infection (NI), were significantly more common in the cohort: 12.5%, 19.4%, respectively. The additional funding under this award enabled Dr. Sperry to enroll additional participants with sufficient power to use MOF and NI as outcomes of interest.

In a cohort of 272 subjects, the prevalence of the IRAK1 variant was 12.5%. Subjects with and without the variant were similar in age, injury severity, and 24-hour blood transfusion. After controlling for important confounders, the IRAK1 variant was independently associated with over a sixfold (OR 6.4; 95% CI1.8-23) and fivefold (OR 5.8; 95% CI1.4-24) greater risk of MOF and mortality, respectively. These differences were most prominent in males, while females heterozygous for the variant demonstrated worse outcome in a dose-dependent fashion. Thus, the IRAK1 polymorphism is a strong independent predictor of MOF and mortality post-injury and represents a common variant with prognostic potential. These data demonstrate the importance of TLR signaling post-injury and support that a genetic mechanism may drive gender outcome differences post-injury.

The results of this study demonstrated that despite a paucity of sex-specific differences in a moderate-sized blunt injury cohort of patients, the evolving sex hormone environment after injury is associated with both clinical outcome and innate immune response differences. Rising total testosterone levels at six hours post-injury were significantly associated with more than a fivefold and twofold higher independent risk of MOF and NI, respectively. Concurrently, estrogen levels were found to be strongly associated with detrimental clinical outcome at the delayed 24-hour period alone.

The results of this study were presented at the 134th Annual Meeting of the American Surgical Association, Boston MA, April 12, 2014 (Appendix K), at the American Association for the Surgery of Trauma in 2014 (Appendix L) at the 28th EAST Annual Scientific Assembly, Lake Buena Vista, FL, January 13-17, 2015 (Appendix M), and were published in *Annals of Surgery,* Volume 260, Number 4 in 2014 (Appendix N) and in the *Journal of Trauma and Acute Care Surgery*, Volume 78, Number 3 in 2015 (Appendix O).

**Lessons Learned**

The NTI board and program staff collected information from the funded principal investigators regarding their experiences conducting the study in order to better understand factors that facilitate success as well as barriers to the research process. The PI interviews began in March 2014. The investigator responses were analyzed and compiled for publication in the Journal of Trauma: “The National Trauma Institute: Lessons learned in the funding and conduct of 16 trauma research studies,” published in *The Journal of Trauma and Acute Care Surgery* (Sept. 2016, Vol. 81, Issue 3) (Appendix P). The article analyzes and discusses how funded researchers approached obtaining regulatory approval, enrolling patients, navigating the Exception from Informed Consent process, coordinating multiple study sites and more.

**B. NTI provided multiple meeting forums for progress toward methods for military-civilian transfer of medical advances, and development of clinical protocols from promising currently funded pilot studies, as determined by the Science Committee. These meetings included military and civilian researchers.**

Registration for the NTI annual trauma conference, originally planned for May 2012, was extremely low, giving NTI no choice but to cancel it. In place of the conference, on May 10, 2012 the NTI Science Committee and NTI Board members met in San Antonio at the Grand Hyatt Hotel. The primary purpose of the meeting was to give the Principal Investigators funded by this grant the opportunity to present their current research progress and status. In addition, PIs were asked to propose follow-on studies. The Board considered the presented ideas and selected three follow-on studies that could be developed with NTI assistance into full proposals for submission to funding agencies or for NTI grants. Collaboration among investigators was encouraged at this closed meeting.

The FDA held a workshop on hemostatic devices in August, 2014, during which the NTI Board was represented. The focus of the workshop was to understand military medical advances from its wartime experiences and if or how those advances could be translated to the civilian trauma provider community more effectively. In addition, the FDA wanted to develop a streamlined process to assist with transfer of knowledge and experience from the military to the civilian sector. NTI assisted the FDA by identifying panel participants and speakers.

NTI organized a meeting with Col. Todd Rasmussen (MRMC) in Baltimore, MD in August 2006. Leadership from AAST also attended this meeting. The purpose was to disclose information about CNTR and the new ability to respond to his requests for civilian collaboration, expertise and other forms of assistance through the national coalition. This began ongoing discussions about ways to assist his office to address military research gaps in trauma.

NTI also facilitated and provided the infrastructure for establishment of the Coalition for National Trauma Research (CNTR). CNTR brings together the nation's most important trauma surgical societies for the first time to pool their resources and effort in order to improve trauma research that advances care in the civilian and military environments. Just two years since its inception, CNTR has made some impressive progress on its agenda to garner federal funding, build trauma research infrastructure, and develop a national research agenda. NTI is one of the five national organizations that comprise CNTR.

In mid-2014 the leadership of the national trauma organizations began discussing common problems including the lack of sustained federal funding for trauma research, the need for an organized national trauma research agenda, and the need for funding of a trauma clinical trials network. This resulted in the formation of the Coalition for National Trauma Research (CNTR). The founding members of CNTR are the American Association for the Surgery of Trauma (AAST), National Trauma Institute (NTI), American College of Surgeons Committee on Trauma (COT), Eastern Association for the Surgery of Trauma (EAST), and Western Trauma Association (WTA). The CNTR Executive Committee comprises current leaders of each member organization and provides leadership. These organizations have agreed to move forward as one organization focused on resolving common problems. CNTR's goals are:

- Sustained, significant federal funding for research that increases understanding of the mechanisms of injury and improves clinical practice;
- Centralized research agenda that establishes priorities bridging combat casualty and civilian trauma care;
- Robust trauma research infrastructure, including a National Trauma Research Repository and a Trauma Clinical Trials Network.

The Organizational Principles governing CNTR were approved and signed by each of the member organizations in September, 2014. The CNTR Executive Committee meets by teleconference each month. CNTR has had communications with the Major Extremity Trauma Research Consortium (METRC), American Association of Neurological Surgeons (AANS), American Burn Association (ABA), National Association of Medical Examiners (NAME), and the American College of Emergency Physicians (ACEP) regarding ways to work together to meet the needs of the spectrum of trauma research. CNTR has formed the following three committees:

***Trauma Research Agenda Committee:*** Chaired by Dr. Raul Coimbra at UC-San Diego, this committee's charter is to develop a centralized research agenda that establishes priorities bridging combat casualty and civilian trauma care. This committee has met several times, created and prioritized a complete agenda of research topics as a map for future

funded research, that has been accepted by the *Journal of Trauma and Acute Care Surgery* (Appendix Q). The Committee is also considering a melding of its results with the list of priority research areas published by the National Academy of Science, Engineering and Medicine in its June 2016 report titled "A National Trauma Care System: Integrating Military and Civilian Trauma Systems to Achieve Zero Preventable Deaths After Injury." (Table 4-6: Examples of High-Priority Trauma Research Needs, p. 181-183).

***Trauma Research Network Committee:*** Chaired by Dr. Ram Nirula, professor at the University of Utah and Chairman of the Multi-Institutional Trials Committee of AAST, this committee was charged with developing a robust trauma research infrastructure, including a network of trauma research centers with the combined capability of research in the areas of general trauma, orthopedics, burns, neurosurgery, emergency medicine, and pre-hospital care, among others.

In June, 2016, CNTR sent invitations via email to participate in the clinical research network to all members of AAST, EAST, and WTA. Invitations linked to an online survey with 37 questions regarding: verification level; service area; and trauma center admissions to ICU, admissions requiring massive transfusion in the first 24 hours, and burn admissions over the previous 12 months. Data were also collected on trauma registry software used; interventional trials in the trauma center and in the Emergency Department; research experience in the pre-hospital setting; linkage to the local EMS system; experience with EFIC; prospective observational studies requiring serial blood draws; previous multicenter clinical trials network participation; and research staffing/infrastructure.

The responses were scored, and 15 Level 1 Anchor sites and two MTFs were chosen based on: 1) volume of major trauma patients treated; 2) presence of a robust research infrastructure and documented success in enrolling and following patients; 3) linkages to emergency medical services in their system; and 4) a site PI with a track record in clinical trauma research. The remaining sites were invited to participate as Affiliate sites to the network, available to supplement the Anchor sites to meet the demands of specific research studies.

The network now includes the 15 Anchor sites and 90 Affiliates, caring for nearly 200,000 trauma patient admissions per year. This network can address a range of multi-center research needs from small observational studies to large randomized trials and can expand or contract based upon the nature of each funded study, i.e., the appropriate sub-network can be formed based on specific study requirements. The list of organizations participating in the research network is attached as Appendix R. CNTR is in the process of seeking additional funding to operationalize the network and support its first clinical trial.

***The National Trauma Research Repository Committee*:** CNTR leadership serve on the NTRR Steering Committee. For more information, see section C that follows.

**C. The National Trauma Institute established governance and initial development of a National Trauma Research Repository (NTRR).**

The National Trauma Research Repository will provide a repository for storage, investigation and analysis of trauma data. This will give trauma researchers and other investigators access to a great deal more data than they are able to collect on their own, providing a much faster route to large datasets. The analyses and recommendations resulting from the shared information in this database will lead to significant changes in practice to save lives and improve patient outcomes after injury in both military and civilian populations. The activities outlined in the Statement of Work are complete, as follows:

Task 1. Identify stakeholders and form appropriate governance and steering committees.

The National Trauma Research Repository (NTRR) Steering Committee is responsible for oversight and governance of the NTRR includes members of stakeholder organizations and the DoD. This committee provides oversight and governance of the project. Individuals were chosen because of national leadership positions, experience with database development, and/or other subject matter expertise. This committee is chaired by Dr. Don Jenkins (Mayo Clinic), with

Dr. Eileen Bulger (University of Washington) as Vice-Chair. The Steering Committee met several times throughout the period of performance and continues its work with funding from Award # W81XWH-15-2-0089. An Executive Committee of the larger body established four subcommittees of injury researchers and technical experts: Architecture, Regulatory/Human Subjects Protection, Data Definitions and Policies and Procedures.

**National Trauma Research Repository Steering Committee**

| Organization Represented | Name | Home Institution |
|---|---|---|
| **Coalition for National Trauma Research (CNTR), Clinician-Scientists and Other Stakeholders** | Don Jenkins, MD—Chair | Mayo Clinic |
| | Eileen Bulger, MD—Vice-chair | University of Washington |
| | Peggy Knudson, MD | UC-San Francisco |
| | Jerry Jurkovich, MD | Denver |
| | Greg Beilman, MD | University of Minnesota |
| | Joe DuBose, MD | Travis AFB |
| | Alex Valadka, MD | Virginia Commonwealth University |
| | Jason Sperry, MD | University of Pittsburgh |
| | Ellen MacKenzie, PhD | Johns Hopkins University |
| | Avery Nathens, MD | Sunnybrook HSC, Toronto |
| | Jim Ficke, MD | Johns Hopkins University |
| **American College of Surgeons/Committee on Trauma** | Ronny Stewart, MD | UTHSC—San Antonio |
| | Len Weireter, MD | Eastern Virginia Med. School |
| **Department of Defense** | LTC Kyle Remick, MD | CCRP, Military Deputy |
| | Jose Salinas, PhD | USAISR, San Antonio |
| | Mary Ann Spott, PhD | Dep. Dir. Joint Trauma System |
| | Tammy Crowder, PhD | CCCRP, Trauma Portfolio |
| | Frank Lebeda, PhD | MRMC, Dir. System Biology |
| **National Institutes of Health** | Matt McAuliffe, PhD | NIH, CIT, Bethesda MD |

Note: Grayed background denotes members of Executive Group of the Steering Committee

**NTRR Subcommittees**

| Architecture | Human Research Protections/Regul. | Data Definitions | Policies & Procedures |
|---|---|---|---|
| Jose Salinas | Len Weireter | Greg Beilman | TBN |
| Matt McAuliff | Peggy Knudson | Alex Valadka | Joe DuBose |
| Avery Nathens | Eileen Bulger | Jim Ficke | Ellen MacKenzie |
| Ronny Stewart | Mary Ann Spott | Jerry Jurkovich | |
| | Laura Brosch | Mary Ann Spott | |

Note: Grayed background denotes subcommittee chair.

The subcommittees were established and charged as follows:

1. Architecture—Determine functional requirements of the physical product, reviewing how other clinical research databases are built and desired level of compatibility with related products such as the FITBIR informatics system; consider how to build the back end and front end of the database, including a plan for data quality and validation, report writing, and the user help desk.
2. Regulatory/Human Protections—Develop complete understanding of factors including protections/use of military data; established regulations in other research databases; how to meet or exceed requirements for human subject research protections; recommendations for future hosting of NTRR based on regulatory or

human research protection requirements. Develop guiding policies and procedures on Data Sharing, Data Submission Requests.

3. Defining Data—Identify Common Data Elements and a well-defined data dictionary, following review of assembled elements from other trauma research databases (GLUE grant, ROC, etc.)
4. Policies & Procedures—Develop standards operating procedures and management policies for launching and maintain the NTRR.

Task 2. Review/evaluate existing trauma data sources.

NTI has determined a starting list of existing trauma data sources to review and compare which include the Glue Grant Trauma, Federal Interagency Traumatic Brain Injury Research (FITBIR), National Trauma Data Bank (NTDB), San Antonio Texas Intensive Care Unit Registry (STICUR), DoD Trauma Registry, Prospective Observational, Multi-center Major Trauma Transfusion Study (PROMMTT), National Burn Registry, and Trauma Quality Improvement Program (TQIP) as starting points. Additionally, existing related data dictionaries and common data elements are being researched including: Clinical Data Acquisition Standards Harmonization (CDASH), the National Trauma Data Standards (within NTDB), the American Burn Association National Burn Data Standards, the National Emergency Medical Services Information System (NEMSIS), the NIH Common Data Elements Repository, and the Patient Reported Outcomes Measurement Information System (PROMIS). Other resources that will be helpful in defining common data elements have been identified. These include Prosettastone, Health Measures, PhenX Toolkit, and REDCap. The Steering committee will provide guidance on criteria for evaluation of elements and their definitions for analysis.

Task 3. Identify common data elements from currently funded studies.

All previous and ongoing NTI-funded studies (15) were reviewed to determine the data elements that were common among them. These studies fall into these categories: infection, hemorrhage/resuscitation, injury complications, and injury treatment/comparisons. They were comprised of six randomized clinical trials, seven prospective observational or cohort studies, one study utilizing healthy volunteers, and one retrospective review study. More than 100 data elements were reviewed, and 25 elements were determined to be common among 50 percent of the studies.

**Overall Award Milestones**

| Milestone | Planned Date | Actual Date | Projected Completion Date | Status |
|---|---|---|---|---|
| Prepare and Issue RFP | Yr1 Qtr1 | Yr1 Qtr1 | N/A | Completed |
| NTI Board Science Committee Review and Select Proposals for Funding | Yr1 Qtr1 | Yr1 Qtr1 | N/A | Completed |
| Award Grants | Yr1 Qtr1 | Yr1 Qtr1 | N/A | Completed |
| Contract with Awardee Organization | Yr1 Qtr1 | Yr5 Qtr4 | Term of the Contract | Completed |
| Manage Compliance of Awards | Ongoing | Yr5 Qtr4 | Term of the Contract | Completed |
| Provide meeting forums | Ongoing | Ongoing | Yr2 Qtr4 | Completed |
| Identify stakeholders and form appropriate governance and steering committees for NTRR | Yr4 Qtr2 | Yr4 Qtr2 | Yr4 Qtr4 | Completed |
| Identify Common Data Elements from currently funded studies | Yr4 Qtr2 | Yr4 Qtr2 | Yr4 Qtr3 | Completed |
| Review/evaluate existing trauma data sources | Yr4 Qtr2 | Yr4 Qtr2 | Yr5 Qtr2 | Completed |

**KEY RESEARCH ACCOMPLISHMENTS**

Key research accomplishments from individual studies are as follows:

**Project 1:**
**Project Title:** Detection and Management of Non-Compressible Hemorrhage by Vena Cava Ultrasonography

This study demonstrated the following:

- IVC collapsibility of greater than 75% is uncommon in civilian trauma patients (6.5%).
- Only 3.8% of trauma patients with IVC collapsibility had hypotension at admission, indicating most trauma patients with IVC collapsibility are not hypotensive.
- Patients with persistent collapsibility on a second measurement 60 minutes after admission had significantly higher intravenous fluid requirements during initial resuscitation (176ml ± 877 vs. 1194ml ± 489, $p<0.001$).
- Focused Assessment with Sonography for Trauma-Inferior Vena Cava Collapsibility (FAST-IVC) is useful in predicting 24-hour fluid resuscitation requirements.

**Project 2:**
**Project Title:** Thrombelastography (TEG®) Based Dosing of Enoxaparin for Thromboprophylaxis: A Prospective Randomized Trial

In this randomized clinical trial of trauma and surgical patients, the data demonstrated:

- Patients receiving thrombelastogram-adjusted doses received a higher median enoxaparin does than control group patients. Venous thromboembolism (VTE) rates were similar between groups.
- This was the third study to demonstrate that a TEG-adjusted strategy using ΔR does not improve VTE rates. However, trauma and surgical patients have hypercoagulation at baseline and further investigations into the effects of platelet activation and obesity, time to enoxaparin administration, and anti-thrombin III (AT-III) deficiency are needed.

**Projects 3-5 were closed as described previously.**

**Project 6:**
**Project Title:** Hepcidin and Anemia in Trauma

The Hepcidin and Anemia in Trauma study provided the first available data regarding the time-dependent changes of the peptide hormone hepcidin in anemia associated with trauma and critical illness (Napolitano et al, unpublished data). It is important to understand the normal regulation of hepcidin production and changes in regulation of hepcidin in response to trauma, inflammation and critical illness. This work could ultimately also provide information to facilitate an alternative treatment modality for anemia, including the development of drugs that can prevent or block the increased expression of hepcidin in inflammation and ameliorate the anemia of inflammation.

**Project 7:**
**Project Title**: Delayed Splenic Rupture after Non-Operative Management of Blunt Splenic Injury; an American Association for the Surgery of Trauma (AAST) Multi-Institutional Prospective Trial

This study was the first attempt to collect multi-institutional, long-term prospective data for patients with blunt splenic injury (BSI). The results shed light on in the management of BSI:

- After the first 24 hours, the risk of splenectomy is rare and occurs in 3.1% of patients while in the hospital. In the outpatient setting, the risk is lower, 0.27% over 180 days.
- The benefits of angiography and embolization to increase splenic salvage in BSI were brought into question, highlighting the need for further multicenter trials.

**Project 8:**
**Project Title:** Methicillin-Resistant Staphylococcus Aureus in a Trauma Population: Does Decolonization Prevent Infection?

Key findings from this study include:

- Preexisting colonization rate of MRSA in a trauma population was verified (15.5%)
- Decolonization occurred among 50% of the treatment arm and 35% of placebo treated patients
- 32% of patients who initially tested positive for MRSA colonization later developed an invasive MRSA infection
- 5% of patients who tested negative initially for MRSA colonization later developed invasive MRSA infections
- There is a slightly higher incidence in the rates of concomitant MRSA infections following treatment in the placebo group versus the treatment group
- There is a significantly higher incidence of all cause infections in the placebo treated group (55%) versus the treatment arm group (47%)
- No mupirocin resistance was detected in this collection of isolates

**Project 9:**
**Project Title:** Transfusion of Stored Fresh Whole Blood in a Civilian Trauma Center: A Prospective Evaluation of Feasibility and Outcomes

This study defined the time course of coagulation stability in leukoreduced compared to unfiltered whole blood (WB) under standard refrigeration conditions. The key findings of this study were:

- Unfiltered WB retains clotting capacity over 35 days despite decreased labile clotting factors.
- Filtered WB has a filtration lesion resulting in a coagulopathic product and may not be suitable as the sole transfusion product for hemostatic resuscitation.
- Addition of platelets to filtered WB restores clot strength as measured by TEG.
- Additional studies are needed to determine the exact timing and ratio of platelet transfusion requirements, and to investigate the coagulation parameters of cold stored WB leukoreduced with a platelet-sparing filter.

**Project 10:**
**Project Title:** Characterization of the Effects of Early Sex-hormone Environment Following Injury

Key research findings of this study that further characterize the early sex-hormone environment following injury and the associations of early estrogen and testosterone levels with the strength of the innate immune and coagulation responses, resuscitation requirements, and clinical outcomes were:

- The IRAK1 polymorphism is a strong independent predictor of MOF and mortality post-injury.
- The evolving sex hormone environment after injury is associated with both clinical outcome and innate immune response differences.

- Rising total testosterone levels at six hours post-injury are significantly associated with more than a fivefold and twofold higher independent risk of MOF and NI, respectively.
- Estrogen levels are strongly associated with detrimental clinical outcome at the delayed 24-hour period.

**Lessons Learned**

In addition to these research project, NTI looked critically at grant-making and research management processes, publishing an article in the Journal of Trauma and Acute Care Surgery (Vol 81, No 3), "The National Trauma Institute: Lessons learned in the funding and conduct of sixteen trauma research studies." The article analyzes how researchers funded by this award and two previous awards approached obtaining regulatory approval, enrolling patients, navigating the Exception from Informed Consent process, coordinating multiple study sites and more. (Appendix P)

The article offers solutions for reducing challenges and lag times inherent in the study completion timeline. Among the insights, 40 percent of the funded investigators reported delays in obtaining regulatory approval at one or more institutional levels, which had serious impact on study management. "The time required to obtain approvals delayed the funding awards considerably and resulted in the loss of study sites, turnover in research trainees, and the need to use alternate sources of funds for research staff salaries, protocol review, and community consultation costs," NTI found.

Active enrollment periods for the completed studies ranged from 104 to 943 days, substantially longer than originally estimated on the applications. The factors associated with lower screening and/or enrollment included lower incidence of disease, sicker patients, early mortality, shorter stays in the ICU, inconsistent or lower screening/enrollment at multiple sites, patient or family refusal, lack of off-hour staffing, insufficient funding for staffing, and shortened enrollment period due to delays in institutional approval. The organization will take these findings into consideration when establishing future granting procedures.

**REPORTABLE OUTCOMES**

Publications, Presentations and Products resulting from this award as of December 28, 2016 are as follows (in order of the appendices):

Connelly CR, Van PY, Hart K, Fair K, Louis S, Rick B, Erickson A, Simeon E, Bulger EM, Arbabi S, Holcomb JB, Moore LJ, Schreiber MA. Thrombelastography Based Dosing of Enoxaparin for Thromboprophylaxis: A Prospective Randomized Trial. Presented at Pacific Coast Surgical Association Annual Meeting, February 2016. (Appendix C)

Connelly CR, Van PY, Hart K, Fair K, Louis S, Rick B, Erickson A, Simeon E, Bulger EM, Arbabi S, Holcomb JB, Moore LJ, Schreiber MA. "Thrombelastography-Based Dosing of Enoxaparin for Thromboprophylaxis in Trauma and Surgical Patients: A Randomized Clinical Trial." *JAMA Surg*. 2016:151(10). (Appendix D)

Zarzaur BL, Kozar R, Myers JG, Claridge JA, Scalea TM, Neideen TA, Maung AA, Alarcon L, Corcos A, Kerwin A, Coimbra, R. The Splenic Injury Outcomes Trial: An American Association for the Surgery of Trauma Multi-Institutional Study. Presented at the American Association for the Surgery of Trauma (AAST) 2014 Annual Conference, Philadelphia PA, September 11, 2014. (Appendix E)

Zarzaur, BL., Kozar, R, Myers, JG, Claridge, JA, Scalea, TM, Neideen, TA, Maung, AA, Alarcon, L, Corcos, A, Kerwin, A, Coimbra, R. The splenic injury outcomes trial: An American Association for the Surgery of Trauma multi-institutional study. *J Trauma Acute Care Surg*. 2015:79(3):335-342. (Appendix F)

Maxwell RA. Methicillin-Resistant Staph Aureus in a Trauma Population: Does Decolonization Work? Erlanger Health System, Western Trauma Association, 46th Annual Meeting, Lake Tahoe, CA, February 28 – March 4, 2016. (Appendix G)

Burruss S, Gruber T, Ziman A, Marder V, Cryer H. Filtration lesions impair functional coagulation in banked whole blood. Presented at the American College of Surgeons Committee on Trauma 2013 Resident Competition. (Appendix H)

Cryer, H, Burruss S, Gruber T, Marder V. Filtration Lesions Impair Functional Coagulation in Banked Whole Blood. American Association for the Surgery of Trauma (AAST) 2014 Annual Conference, Philadelphia PA, September 11, 2014. (Appendix I)

Eastoak Siletz A, Burruss S, Gruber T, Ziman A, Marder V, Cryer H. Leukocyte filtration lesion impairs functional coagulation in banked whole blood. Submitted to *J Trauma Acute Care Surg*., December 2016. (Appendix J)

Sperry J, Zuckerbraun B, Zolin S, Vodovotz Y, Namas R, Peitzman A, Ferrell R, Billiar T. X-Chromosome Linked IRAK1 Polymorphism Is Strong Predictor of Multiple Organ Failure and Mortality Post-Injury. Presented at the 134th Annual Meeting of the American Surgical Association, Boston MA, April 12, 2014. (Appendix K)

Zolin SJ, Vodovotz Y, Forsythe RM, Rosengart M, Namas R, Peitzman AB. Billiart TR, Sperry JL. The early evolving sex hormone environment is associated with significant clinical outcome and inflammatory response differences post-injury. Oral presentation at the American Association for the Surgery of Trauma (AAST) 2014 annual meeting, Philadelphia, PA, September 2014. (Appendix L)

Sperry J, Zhou T, Zolin S, Peitzman A, Billiar T. Sex Based Thromboelastography Disparities Post-Injury: Independently Different Early On But Why? Presented at the 28th EAST Annual Scientific Assembly, Lake Buena Vista, FL, January 13-17, 2015. (Appendix M)

Sperry JL, Zolin S, Zuckerbraum BS, Vodovotz Y, Namas R, Neal MD, Ferrell RE, Rosengart MR, Peitzman AB, Billiar TR. X-Chromosome linked IRAK1 polymorphism is strong predictor of multiple organ failure and mortality post-injury. *Ann Surg.* 2014. Vol. 260(4) 698-705. (Appendix N)

Zolin SJ, Vodovotz Y, Forsythe RM, Rosengart MR, Namas R, Brown JB, Peitzman AB, Billiar TR, Sperry JL. The early evolving sex hormone environment is associated with significant outcome and inflammatory response differences after injury. *J Trauma Acute Care Surg*, 2015, Vol. 78(3): 451-458. (Appendix O)

National Trauma Institute Research Group, Price MA, Beilman GJ, Fabian TC, Hoyt DB, Jurkovich GJ, Knudson MM, MacKenzie EJ, Marshall VS, Overton KE, Peitzman AB, Phillips MJ, Pruitt BA, Smith SL, Stewart RM, Jenkins DJ. The National Trauma Institute: Lessons learned in the funding and conduct of 16 trauma research studies. *J Trauma Acute Care Surg.* 2016;81: 548–554. (Appendix P)

Coimbra R, Kozar RA, Smith JW, Zarzaur BL, Hauser CJ, Moore FA, Bailey JA, Valadka A, Jurkovich GJ, Jenkins DH, Davis KA, Price MA, Maier RV. The Coalition for National Trauma Research (CNTR) supports the call for a national trauma research action plan. Accepted for publication/in press. *J Trauma Acute Care Surg.* (Appendix Q)

Jenkins, DH. Impact of Department of Defense Research Funded Research to the National Trauma Institute. Presented at the Military Health System Research Symposium, Orlando FL, August 17, 2016. (Appendix R)

National Trauma Institute Research Group, Price MA, Beilman GJ, Fabian TC, Hoyt DB, Jurkovich GJ, Knudson MM, MacKenzie EJ, Marshall VS, Overton KE, Peitzman AB, Phillips MJ, Pruitt BA, Smith SL, Stewart RM, Jenkins DH. The National Trauma Institute: Lessons learned. Presented at the University of Texas Health Science Center at San Antonio, Department of Surgery, Research Resident Conference, San Antonio TX, March 24, 2016. (Appendix S)

Price MA, Villarreal CL. Evidence-Based Injury Prevention Strategies. In: Cohn SM, Dolich MO, Inaba K, editors. Acute Care Surgery: Evidence-Based Practice. Second ed. Boca Raton, FL: CRC Press Taylor & Francis Group; 2015. 11-9. (Appendix T)

The National Trauma Institute website at: http://nationaltraumainstitute.org/

The Coalition for National Trauma Research (CNTR) website at: http://coalitionntr.org/

Doucet J et al. "Protocol Video USA-IVC Study (Version 5)" posted on YouTube: https://youtu.be/54-Z6fiJpPY This video contains study design, procedures, inclusion/exclusion criteria and a demonstration to train clinical sonographers on correct techniques to measure IVC diameter in research participants.

**CONCLUSION**

During the period of performance, the National Trauma Institute and its subcontracting research institutions successfully completed the Statement of Work for this award. The National Trauma Institute supported a national coordinating center for trauma research funding, provided multiple forums for progress toward methods for military-civilian transfer of medical advances and established governance and initial development of a National Trauma Research Repository (NTRR).

**A National Coordinating Center for Trauma Research Funding**

NTI successfully completed a Request for Proposals and a peer-reviewed process, with selection of nine relevant trauma projects and a tenth for continued funding. It conducted on-going oversight of each project over the five-year period of performance of this award. Findings from these studies advanced scientific knowledge and trauma care in the areas of resuscitation fluid management, TEG-based venous thromboembolism prevention, management of MRSA infection, anemia, and splenic injury, the role early sex hormones, and functional coagulation of banked whole blood in trauma patients.

Six trauma research studies have been completed across 23 academic trauma centers enrolling a total of 955 trauma patients or healthy volunteers as study participants. In total, the studies funded through and managed by this national coordinating center for trauma research generated four publications plus one manuscript under review in national peer-reviewed journals and eight presentations at national, regional, and state or local trauma meetings. Of the six completed studies, half have produced a peer-reviewed publication. This level of productivity, 50 percent, compares favorably to a recent study that found only 29 percent of completed clinical trials conducted at academic medical centers published results within two years of study completion (Chen R, Desai NR, Ross JS, et al, 2016).

**Providing Multiple Forums for Progress Toward Methods for Military-Civilian Transfer of Medical Advances**

NTI facilitated multiple forums for the military-civilian transfer of medical advances. The establishment of the Coalition for National Trauma Research (CNTR) was unique and momentous. CNTR brings together the nation's most important trauma surgical societies for the first time to pool their resources and effort in order to improve trauma research that advances care in the civilian and military environments. Just two years since its inception, CNTR has made some impressive progress on its agenda to garner federal funding, build trauma research infrastructure, and develop a national research agenda. NTI is one of the five national organizations that comprise CNTR. In 2016, CNTR won its first research grant, the Multi-Institutional Multidisciplinary Injury Mortality Investigation in the Civilian Pre-Hospital Environment (MIMIC). CNTR is partnering with the National Association of Medical Examiners (NAME) to establish study panels to review 3,000 pre-hospital deaths, and with the Johns Hopkins Bloomberg School of Public Health to conduct data analysis.

Meeting its goal to produce a national research agenda, CNTR learned in December 2016 that its article on this subject has been accepted for publication in the *Journal of Trauma and Acute Care Surgery*. The research agenda focuses on

three priority areas where military casualty care and civilian trauma care research overlap: acute resuscitation topics, central nervous system trauma and transfer to definitive care. This publication follows release of a report from the National Academies of Science, Engineering and Medicine (NASEM) that recommends focusing trauma research on similar gaps in knowledge and calls for zero preventable deaths following injury. CNTR has participated in NASEM report stakeholder meetings, been consulted in the drafting of legislation that targets NASEM recommendations, published a position paper supporting the NASEM recommendation in *Journal of Trauma and Acute Care Surgery* and anticipates working with the Department of Defense to focus resources on these issues.

**Establishing Governance and Initial Development of a National Trauma Research Repository (NTRR)**

NTI successfully identified civilian and military stakeholders and formed appropriate governance and steering committees for the NTRR. The leadership committees and NTI staff conducted a thorough review of existing trauma research repositories and identified common data elements from currently funded studies.

NTI is completing the elements of the National Trauma Research Repository initiated under this award and has been awarded an additional $4.6 million to fund two studies, design an airway management simulator, and for initial development of the NTRR. NTI has named an executive steering committee for the project as well as four subcommittees of injury researchers and technical experts. The NTRR Architecture Committee is in the process of determining the functional requirements of the product, having completed a review of existing databases and resolving compatibility issues. Already, the Data Definitions committee has identified common data elements among major trauma repositories as a starting point to develop a comprehensive data dictionary. The Human Subjects Protections Committee has laid the groundwork to develop the protocols essential to launching and maintaining the NTRR.

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**ABBREVIATIONS**

| | |
|---|---|
| AAST | American Association for the Surgery of Trauma |
| ALI | Acute lung injury |
| ALIVE | Acute Lung Injury Ventilation Evaluation |
| APRV | airway pressure release ventilation |
| ARDSNet | Acute Respiratory Distress Syndrome Network |
| BMC | Boston Medical Center |
| BSI | Blunt Splenic Injury |
| CDE | Common Data Elements |
| CNTR | Coalition for National Trauma Research |
| FWB | Fresh Whole Blood |
| HRPO | Human Research Protection Office |
| HSPS | Human Subjects Protection Scientists |
| ICU | Intensive Care Unit |
| IRB | Institutional Review Board |
| MCW | Medical College of Wisconsin |
| MRSA | Methicillin-resistant Staphylococcus aureus |
| NCE | No Cost Extension |
| NTI | National Trauma Institute |
| OHSU | Oregon Health & Science University |
| PI | Principal Investigator |
| RFP | Request for Proposal |
| SAMMC | San Antonio Military Medical Center |
| SOM | School of Medicine |
| TEG | Thrombelastography |
| UTHSC | University of Tennessee Health Science Center |
| UTHSC-Houston | University of Texas Health Science Center at Houston |
| UTHSCSA | University of Texas Health Science Center at San Antonio |
| UCLA | University of California, Los Angeles |
| UCSD | University of California, San Diego |
| UCSF | University of California, San Francisco |
| UPitt | University of Pittsburgh |
| USAISR | United States Army Institute of Surgical Research |

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**APPENDICES**

# National Trauma Institute Knowledge Translation Plan

**BACKGROUND:**

The private and public sectors together spend billions of dollars each year on biomedical, clinical and health services research; healthcare student and professional training; patient safety; and risk management. Despite this investment, healthcare systems still often fail to deliver effective (or the most effective) treatments, services and drugs to all who need them, and health professionals too often fail to provide the optimal level of care, as evidenced in studies. One of the most consistent findings from clinical and health services research is the failure to translate research into practice and policy. Evidence-practice gaps result in poorer quality of life and loss of productivity.

The National Trauma Institute's Knowledge Translation Plan (KTP) aims to improve delivery of evidenced-based care by providing a robust knowledge translation pathway and facilitating efficient and effective progress along the pathway—from study completion to bedside recommendation. The KTP facilitates stakeholder awareness of and access to research results in order to inform follow-on research, analysis and synthesis, and ultimately, improved healthcare decision-making and outcomes among civilians and military service members.

**GOALS:**

- Improve information flow to the trauma research community and enhance follow-on research
- Affect agency and government funding, policies and services
- Enhance clinical practices in civilian and military treatment facilities
- Improve health outcomes for the traumatically injured, and enhance public health overall
- Identify and address translational research lags

**THE PLAN:**

NTI's Knowledge Translation Plan is a robust, multi-media effort for access, dissemination, measurement, synthesis and translation that will result in new evidence-based practices that impact public health in a meaningful way:

**Access**

Access to research data will be achieved through research data and publication submissions to:

- Open source research libraries like ResearchGate
- Research data clearinghouses such as clinicaltrials.gov
- Defense Technical Information Center (DTIC: www.dtic.mil)
- The National Trauma Research Repository (NTRR) and the National Trauma Data Base (NTDB)
- FITBIR and other topic-specific repositories, as appropriate

**Dissemination**

Funded researchers will be prepared to publish and present their findings in the following venues:

- Traditional high-impact venues including peer-reviewed journals and scientific conferences and other assemblies
- Open-access journals such as *Trauma Surgery and Acute Care Open* and other publishing platforms like F1000Research that provide high quality and speedier opportunities to disseminate research results
- Informal venues such as grand rounds, lectures, department meetings and board presentations

Following publication in peer-reviewed journals, primary investigators are asked to submit a Publication Report form, which signals NTI to activate its Dissemination Checklist. The checklist includes:

- Collaboration with the PI's institution on media coverage
- Provision of a research summary to relevant medical organizations
- Announcements and amplification via NTI's contact list and social media
- Posting to a publications archive on NTI's website
- Release to popular, science, and health media using one or more technology-enabled platforms such as PRNewswire, AAAS EurekAlert!, and Meltwater

**Measurement**

NTI will combine traditional measures of scholarly impact with alternative metrics to understand and quantify how research is being used in public policy and how scholars, practitioners and health agencies are viewing, saving, sharing and discussing research online. NTI will follow and analyze non-citation based, article-level indicators of impact to track research dissemination beyond academia; show attention, reception and response to a published work prior to its being cited; and apply to non-traditional research outputs like community forums, data-sets, and blog posts.

Every publication resulting from an NTI-funded study will be tagged with electronic retrieval information (i.e., Digital Object Identifier) to enable enhanced tracking and analysis of reach and impact.

**Synthesis, Summary & Translation**

NTI will facilitate the process of synthesis and translation through the National Trauma Research Repository (NTRR), now being built. The data-sharing enabled by the NTRR will reinforce open scientific inquiry, encourage diversity of analysis, illuminate research gaps, enable exploration of novel topics not envisioned by the initial investigators, and facilitate the education and engagement of new researchers. It will also facilitate knowledge translation between military and civilian researchers and care providers.

Additionally, NTI will formally interface with the following synthesizers of medical research, and others, to facilitate translation of trauma-specific research into improved public health outcomes:

- Eastern Association for the Surgery of Trauma (EAST) GRADES system for establishing Clinical Practice Guidelines
- American Association for the Surgery of Trauma (AAST) webinars and scientific assemblies
- American College of Surgeons Trauma Quality Improvement Program (TQIP)

- AHRQ Evidence-Based Practice Centers (EPCs) - http://www.ahrq.gov/research/findings/evidence-based-reports/centers/index.html), potentially nominating trauma treatment as a new, separate EPC
- Cochrane—an independent, global network of researchers, professionals, and care-givers that seeks to improve health through informed, high-quality, relevant and up-to-date synthesized research evidence (http://www.cochrane.org/)

NATIONAL TRAUMA INSTITUTE

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# Knowledge Translation Agreement

This Knowledge Translation Agreement outlines the roles and responsibilities of funded investigators and the National Trauma Institute (NTI) in implementing NTI's Knowledge Translation Plan (KTP). The plan facilitates stakeholder awareness of and access to research results in order to inform follow-on research, analysis and synthesis, and ultimately, improved healthcare decision-making and outcomes. Your participation is vital to the future success of the research activities facilitated by NTI.

NTI-affiliated investigators will:

- Publish findings in peer-reviewed journals, e-publications and open access journals;
- Present results at scientific assemblies and conferences;
- Contribute papers to open source research libraries;
- Disseminate findings less formally in settings such as grand rounds, lectures, department meetings and faculty presentations;
- Engage in online forums such as communities-of-interest related to the research topic (whether sponsored by the National Trauma Institute, surgical societies or other related institutions); and
- Report these and other knowledge translation activities to NTI.

NTI will:

- Facilitate dissemination through alternative and non-scientific channels once studies have been published;
- Monitor dissemination and reach; and
- Measure and report on the impact of these activities.

By signing below, I acknowledge receipt of and compliance with this Knowledge Translation Agreement.

_____ Date: _____

(Signed)
Principal Investigator

_____

(Printed Name)

_____

Institution

KTA v.6/1/2016

# THE IVC-FAST AAST MIT / NTI STUDY

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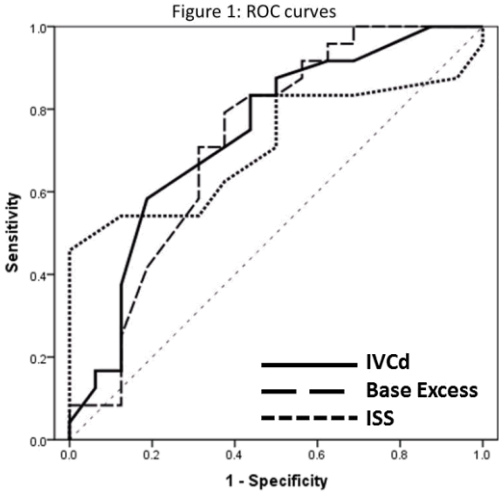
**Introduction:** Identification of occult hypovolemia in trauma patients at admission can be difficult without additional laboratory evaluation or advanced imaging. We hypothesized that in acute trauma patients, the response of ultrasound-measured inferior vena cava diameter (IVCd) in serial FAST examinations (FAST-IVC) during standard-of-care intravenous fluid resuscitation would predict 24 hour resuscitation intravenous fluid requirements.

**Methods:** A NTI / AAST-MITC group prospective, multi-institutional cohort trial was conducted at 4 Level I Trauma Centers. Major trauma patients were screened for an IVCd of 7mm or less on the initial FAST examination for enrollment. A second IVCd was obtained 40-60 minutes later, after the patient received standard-of-care fluid resuscitation. Patients whose second measurement IVCd remained less than 7mm were deemed Non-Responders (NON-RESP), those at or greater than 7 mm were Responders (RESP). Prehospital fluid, initial resuscitation fluid and 24 hour fluid requirements were recorded. Demographics, ISS, arterial blood gasses, ICU admission, length-of-stay, interventions and complications were recorded. Means were compared by ANOVA and categorical variables were compared via Chi-square. Receiver-operator characteristic (ROC) curves were used to compare the FAST-IVC test to Base Excess (BE), ISS and other fluid volume predictors.

Results: There were 2336 patients screened by FAST-IVC, 378 were identified with admission IVCd < 7mm, 76 were enrolled, 74 had useable imagery. There were 46 RESP and 28 NON-RESP. Table 1 shows the univariate analysis. NON-RESP needed significantly more fluid at 24 hours, (2887ml ± 1635 vs. 1881ml ± 790, p= 0.002). ROC (Figure 1) analysis indicates IVCd (AUC= 0.74, C.I.: 0.54-0.90) was comparable to ISS (AUC=0.71, C.I.:0.55-0.87) and BE (AUC=0.72, C.I.: 0.55-0.90) in predicting 24 hour fluid requirements.

| **Table 1: Results** | **RESP (n=46)** | **NON-RESP (n=28)** | ***p* value** |
|---|---|---|---|
| Age (yrs) | 49.9 ± 22 | 50.0 ± 25 | N.S. |
| Gender | 21F/25M | 9F/19M | N.S. |
| ISS | 8.4 ± 7.1 | 11.8 ± 10.5 | N.S. |
| Base Excess | -0.96 ± 4.4 | -2.16 ± 4.9 | N.S. |
| Admission Sys BP (mmHg) | 130 ± 25 | 127 ± 20 | N.S. |
| Prehospital IV Fluids (ml) | 129 ± 246 | 142 ± 279 | N.S. |
| Initial Resus Fluids (ml) | 637 ± 614 | 594 ± 545 | N.S. |
| Post-resus IVCd | 3.63 ± 1.96 | 13.21 ± 5.6 | *p< 0.0001* |
| 24-hour Fluids (ml) | 1881 ± 790 | 2887 ± 1635 | *p= 0.002* |
| Mortality | 1/46 | 1/28 | N.S. |

Figure 1: ROC curves




Conclusion: FAST-IVC was useful in predicting 24 hour fluid resuscitation requirements. A larger study with a pre-hospital FAST-IVC examination is planned.

Authors:
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Title: Thrombelastography Based Dosing of Enoxaparin for Thromboprophylaxis: A Prospective Randomized Trial

Importance: Prophylactic enoxaparin is used to prevent thromboembolic complications (VTE) in surgical and trauma patients. However, VTE remains an important source of morbidity and mortality, potentially exacerbated by antithrombin III (AT-III) deficiency. Anti-Factor Xa (aFXa) levels have been used to determine adequacy of enoxaparin dosing, although accuracy, cost, and availability remain problematic. Recent data suggest thrombelastography (TEG) can predict VTE risk and guide prophylaxis.

Objective: Evaluate effectiveness of TEG-adjusted compared to standard prophylactic enoxaparin dosing.

Design: Multicenter, prospective, randomized controlled trial, from 2012–2015, comparing standard (30mg twice-daily) to TEG-adjusted enoxaparin dosing (using difference in R time between heparinase and standard TEG).

Setting: Three Level 1 US trauma centers.

Participants: 185 general surgery and trauma patients screened for VTE.

Main Outcome Measures: VTE incidence, aFXa levels, AT-III deficiency.

Results: Age, BMI, APACHE score, ISS and reason for admission (69% trauma, 31% general surgery) were similar in both groups. TEG-adjusted patients received a higher median enoxaparin dose than controls (35mg v 30mg BID, $p<0.001$). TEG-adjusted aFXa levels were higher by Day 6 (0.21U/mL v 0.40U/mL, $p=<0.001$). Median time to enoxaparin initiation was 1 day and median proportion of missed doses was similar (0% v 7%, $p=0.23$). VTE rates (6% v 7%, $p=1$) and bleeding complications (14% v 6%, $p=0.08$) were similar. AT-III deficiency was prevalent (18-20%) in both groups.

Conclusions: The incidence of VTE was low in both groups despite the prevalence of AT-III deficiency. These results may be due to a low proportion of missed doses and early time-to-enoxaparin initiation.

JAMA Surgery | Original Investigation | PACIFIC COAST SURGICAL ASSOCIATION

# Thrombelastography-Based Dosing of Enoxaparin for Thromboprophylaxis in Trauma and Surgical Patients
## A Randomized Clinical Trial

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**IMPORTANCE** Prophylactic enoxaparin is used to prevent venous thromboembolism (VTE) in surgical and trauma patients. However, VTE remains an important source of morbidity and mortality, potentially exacerbated by antithrombin III or anti–Factor Xa deficiencies and missed enoxaparin doses. Recent data suggest that a difference in reaction time (time to initial fibrin formation) greater than 1 minute between heparinase and standard thrombelastogram (TEG) is associated with a decreased risk of VTE.

**OBJECTIVE** To evaluate the effectiveness of TEG-adjusted prophylactic enoxaparin dosing among trauma and surgical patients.

**DESIGN, SETTING, AND PARTICIPANTS** This randomized clinical trial, conducted from October 2012 to May 2015, compared standard dosing (30 mg twice daily) with TEG-adjusted enoxaparin dosing (35 mg twice daily) for 185 surgical and trauma patients screened for VTE at 3 level I trauma centers in the United States.

**MAIN OUTCOMES AND MEASURES** The incidence of VTE, bleeding complications, anti–Factor Xa deficiency, and antithrombin III deficiency.

**RESULTS** Of the 185 trial participants, 89 were randomized to the control group (median age, 44.0 years; 55.1% male) and 96 to the intervention group (median age, 48.5 years; 74.0% male). Patients in the intervention group received a higher median enoxaparin dose than control patients (35 mg vs 30 mg twice daily; $P < .001$). Anti–Factor Xa levels in intervention patients were not higher than levels in control patients until day 6 (0.4 U/mL vs 0.21 U/mL; $P < .001$). Only 22 patients (11.9%) achieved a difference in reaction time greater than 1 minute, which was similar between the control and intervention groups (10.4% vs 13.5%; $P = .68$). The time to enoxaparin initiation was similar between the control and intervention groups (median [range] days, 1.0 [0.0-2.0] vs 1.0 [1.0-2.0]; $P = .39$), and the number of patients who missed at least 1 dose was also similar (43 [48.3%] vs 54 [56.3%]; $P = .30$). Rates of VTE (6 [6.7%] vs 6 [6.3%]; $P > .99$) were similar, but the difference in bleeding complications (5 [5.6%] vs 13 [13.5%]; $P = .08$) was not statistically significant. Antithrombin III and anti–Factor Xa deficiencies and hypercoagulable TEG parameters, including elevated coagulation index (>3), maximum amplitude (>74 mm), and G value (>12.4 dynes/cm$^2$), were prevalent in both groups. Identified risk factors for VTE included older age (61.0 years vs 46.0 years; $P = .04$), higher body mass index (calculated as weight in kilograms divided by height in meters squared; 30.6 vs 27.1; $P = .03$), increased Acute Physiology and Chronic Health Evaluation II score (8.5 vs 7.0; $P = .03$), and increased percentage of missed doses per patient (14.8% vs 2.5%; $P = .05$).

**CONCLUSIONS AND RELEVANCE** The incidence of VTE was low and similar between groups; however, few patients achieved a difference in reaction time greater than 1 minute. Antithrombin III deficiencies and hypercoagulable TEG parameters were prevalent among patients with VTE. Low VTE incidence may be due to an early time to enoxaparin initiation and an overall healthier and less severely injured study population than previously reported.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00990236.

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Invited Commentary
Supplemental content

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Venous thromboembolism (VTE) is a major source of potentially preventable morbidity and mortality in critically ill trauma and surgical patients. Deep venous thrombosis (DVT) is estimated to occur in up to 60% of severely injured trauma patients and 13% to 31% of patients in intensive care who do not receive appropriate thromboprophylaxis.[1,2] Pulmonary embolism (PE) occurs in approximately 2% to 22% of trauma patients and is a major cause of preventable death.[3-5] Costs associated with VTE are high.[6] The significance of VTE has led to strong recommendations from the Eastern Association for the Surgery of Trauma and the American College of Chest Physicians for VTE thromboprophylaxis in surgical and trauma patients.[7,8]

Low-molecular-weight heparin (LMWH) is considered the standard of care for VTE prevention. It is estimated to prevent a significant number of VTE events in trauma patients and has been shown to reduce the risk of symptomatic VTE by 80% among patients who undergo abdominal or pelvic operations.[9,10] Enoxaparin sodium is a well-studied and effective form of LMWH used throughout the United States.[11] Despite widespread LMWH use, VTE rates remain high. The incidence of DVT among trauma patients receiving appropriate thromboprophylaxis is greater than 10% in multiple studies,[12,13] and PE is the third most common cause of death in trauma patients who survive the first 24 hours.[14] Pulmonary embolism is also the third most common postoperative medical complication in surgical patients in the United States.[2] These observations indicate that the current approach to thromboprophylaxis is inadequate.

Strategies to monitor enoxaparin thromboprophylaxis have been studied. Low anti-Factor Xa (anti-Xa) 12-hour levels have been demonstrated in 50% of surgical patients in intensive care and are associated with a higher DVT rate.[15] Despite this finding, fixed LMWH doses are generally used, and anti-Xa–guided thromboprophylaxis is not widely accepted because of considerable disagreement in the literature concerning its usefulness and its nonstandardized reference range.[7,16-23] Previously, we quantified the effects of enoxaparin by comparing the change in reaction time (time to initial fibrin formation in minutes; Δ*R*) between standard and heparinase thrombelastograms (TEG) and found that a Δ*R* greater than 1 minute was associated with decreased DVT rates.[24] We also demonstrated an association between missed enoxaparin doses and higher DVT rates as well as a high incidence of anti-thrombin III (AT-III) deficiency in trauma and surgical patients.[12,13] Together, these data suggest that subprophylactic enoxaparin levels, either through inadequate or missed doses, may contribute to persistent VTE incidence.

We hypothesized that a TEG-guided enoxaparin dosing strategy to increase Δ*R* to greater than 1 minute would result in lower VTE incidence compared with standard dosing in trauma and surgical patients. We previously performed a similar single-center study, which demonstrated a similar VTE rate between standard and TEG-guided dosing.[13] However, that study was underpowered to show a significant difference, so the current study was designed as a multicenter trial.

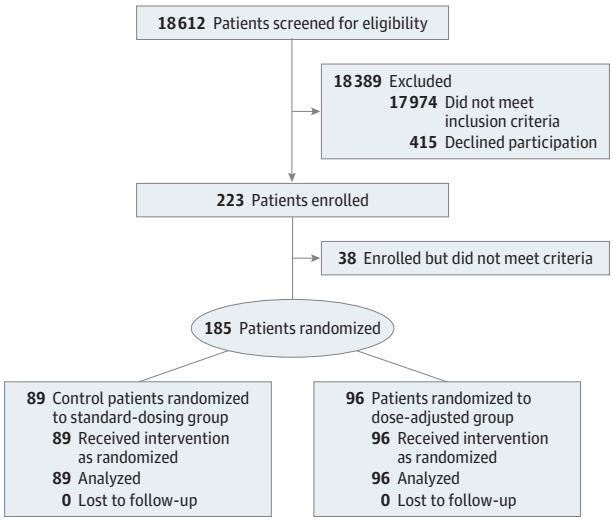
### Key Points

**Question** Is thrombelastogram-adjusted enoxaparin better than standard-dose enoxaparin in the prevention of venous thromboembolism?

**Findings** In this randomized clinical trial that included 185 trauma and surgical patients, patients receiving thrombelastogram-adjusted doses received a higher median enoxaparin dose than control group patients. Venous thromboembolism rates were similar.

**Meaning** Venous thromboembolism incidence was low and was similar between the groups receiving thrombelastogram-adjusted and standard enoxaparin dosing in this study population.

Figure 1. Study CONSORT Diagram

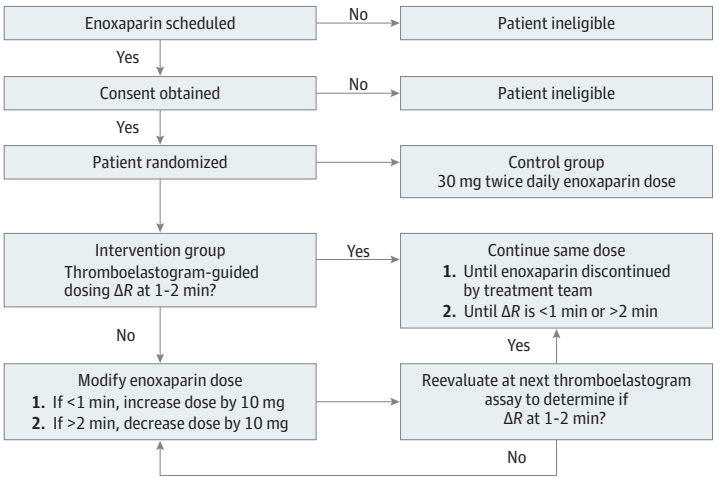



## Methods

We performed a prospective randomized clinical trial at the Oregon Health and Science University, the University of Texas Medical School at Houston, and the University of Washington from October 2012 through May 2015. Institutional review board approval was obtained at each site. Written consent was obtained from all patients or authorized representatives for research prior to enrollment. The trial protocol can be found in the Supplement.

Patients were included in this study if they were admitted to the trauma service; received a general, orthopedic, or urologic surgical procedure; were 15 years or older; had initiated standard enoxaparin thromboprophylaxis dosing (either 30 mg twice daily or 40 mg once daily); received between 3 and 5 doses; and had an expected inpatient stay of 3 or more days. Exclusion criteria included therapeutic or nonstandard enoxaparin dosing, other anticoagulation medications, the presence of intracranial hemorrhage or brain injury, and (in women) pregnancy or lactation (**Figure 1**). Participants were blinded to enoxaparin dose, which was based on prerandomization of each enrollment number.

Figure 2. Enoxaparin Dose Adjustment Protocol




ΔR indicates time to initial fibrin formation in minutes.

Prospectively collected data included patient and injury characteristics (ie, age, sex, length of stay, body mass index [calculated as weight in kilograms divided by height in meters squared; BMI], reason for admission [trauma vs surgical procedure], Injury Severity Score, Acute Physiology and Chronic Health Evaluation score, Glasgow Coma Scale score, smoking status, and existence of comorbidities), enoxaparin dose and administration, and transfusions and procedures performed. Standard citrated and heparinase TEGs were performed using the TEG 5000 Thrombelastograph Hemostasis Analyzer System (Haemonetics Corporation). All standard TEG values were recorded, including coagulation index (CI), a calculated global index of coagulation. We calculated Δ*R* as the difference in time in minutes between a standard TEG and heparinase TEG for each patient sample. We calculated the TEG G value using the following equation: G = (5000 × maximum amplitude [MA])/(100 - MA).[25,26] Peak anti-Xa and AT-III levels were measured 4 to 6 hours after enoxaparin administration and analyzed with the STA Compact Hemostasis System (Diagnostica Stago). Anti-thrombin III deficiency was defined as AT-III activity less than 80% (2 SDs below the mean), and anti-Xa deficiency (peak) was defined as a measurement of 0.2 IU/mL or lower.[13,21-23] Standard laboratory data, including complete blood cell counts, basic metabolic panels, arterial blood gases, and coagulation studies, were also collected.

Patients randomized to the control group received a standard enoxaparin dose (30 mg twice daily). To measure the steady-state enoxaparin effect, blood was drawn 4 to 6 hours after the third consecutive enoxaparin dose. Thrombelastograms were performed for 3 consecutive days and then twice weekly until discharge. Patients randomized to the dose-adjusted group began receiving 30 mg twice daily of enoxaparin for 3 consecutive doses, after which the dose was adjusted based on the Δ*R* value. If Δ*R* was less than 1 minute, then the dose was increased by 10 mg; if Δ*R* was more than 2 minutes, it was decreased by 10 mg; and if Δ*R* was between 1 and 2 minutes, it was unchanged. The maximum dose permitted was a therapeutic dose (1 mg/kg) and the minimum was a standard dose (30 mg twice daily). If a dose adjustment was made, 3 consecutive doses were given to again reach steady state. Additional dose adjustments could then be made. If Δ*R* was between 1 and 2 minutes for 3 consecutive days, then monitoring was decreased to twice weekly. If a dose was held or missed in either group, the monitoring protocol was restarted after the third consecutive dose (**Figure 2**).

Primary end points were VTE and bleeding complication incidence. Venous thromboembolism was defined as DVT and/or PE. Deep venous thromboses were not characterized as symptomatic or asymptomatic. To measure VTE incidence, the study protocol dictated that all patients were to receive standard, screening, bilateral, whole-leg venous duplex ultrasonography prior to discharge. In addition to the required discharge duplex ultrasonography, each institution had variable existing VTE screening protocols. At the Oregon Health and Science University, all trauma patients received weekly screenings, while surgical patients received a screening only for DVT symptoms. At the University of Washington and the University of Texas Medical School at Houston, all patients received a screening only if symptomatic. At all institutions, thoracic computed tomography was used to evaluate patients for suspected PE. Bleeding complications were defined as a bleeding event associated with need for intervention, consistent with International Society for Hemostasis and Thrombosis guidelines.[27] All bleeding events were reviewed by physician study monitors.

During study development, a power analysis was performed to calculate goal enrollment. Using prior data, a 20% overall VTE rate among patients receiving enoxaparin was assumed, with a 10.9% rate for patients with Δ*R* greater than j1 minute and 23.0% for those with Δ*R* less than 1 minute.[24] Three hundred patients were needed to demonstrate a significant difference in VTE rate, with $\beta = 0.80$ and $\alpha = .05$. Therefore, goal study enrollment was 320 participants, to allow for patient dropout.

Table 1. Patient Baseline Characteristics Between Study Groups

| Patient Characteristic | Control (n = 89) | Dose-Adjusted (n = 96) | *P* Value[a] |
|---|---|---|---|
| Age, median (IQR), y | 44.0 (28.0-60.0) | 48.5 (33.8-58.2) | .31 |
| Male, No. (%) | 49 (55.1) | 71 (74.0) | <.01 |
| Length of stay, median (IQR), d | 6.0 (4.5-13.0) | 8.0 (5.0-14.8) | .10 |
| BMI, median (IQR) | 27.5 (23.5-31.7) | 26.7 (23.7-32.4) | .92 |
| Admission reason, No. (%) | | | |
| Trauma | 61 (68.5) | 66 (68.8) | >.99 |
| Surgical operation | 28 (31.5) | 30 (31.3) | |
| ISS, trauma patients only, No./Total No. (%) | | | |
| Mild (0-8) | 13/61 (21.3) | 15/66 (22.7) | |
| Moderate (9-15) | 23/61 (37.7) | 19/66 (28.8) | .51 |
| Severe (16-24) | 16/61 (26.2) | 16/66 (24.2) | |
| Very severe (25-75) | 9/61 (14.8) | 16/66 (24.2) | |
| APACHE score, median (IQR) | 7.0 (4.0-10.0) | 7.0 (4.0-10.0) | .66 |
| GCS score, No. (%) | | | |
| Mild (13-15) | 75 (84.3) | 77 (80.2) | .32 |
| Moderate (9-12) | 6 (6.7) | 4 (4.2) | |
| Severe (3-8) | 8 (9.0) | 15 (15.6) | |
| Active smoking, No. (%) | 36 (40.4) | 38 (39.6) | >.99 |
| Any comorbidity, No. (%) | 48 (53.9) | 46 (47.9) | .46 |
| Enoxaparin administration | | | |
| Time to initiation, median (IQR), d | 1.0 (0.0-2.0) | 1.0 (1.0-2.0) | .39 |
| Treatment duration, median (IQR), d | 5.0 (3.0-9.0) | 6.0 (4.0-9.5) | .11 |
| Average dose prescribed per patient, median (IQR), mg | 30.0 (30.0-31.9) | 37.5 (35.0-42.2) | <.001 |
| Average dose administered, median (IQR), mg | 30.0 (27.9-30.0) | 35.0 (31.7-39.2) | <.001 |
| Missed ≥1, No. (%) | 43 (48.3) | 54 (56.3) | .30 |
| Doses missed per patient, median (IQR), % | 0.0 (0.0-12.5) | 7.0 (0.0-15.8) | .23 |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; GCS, Glasgow Coma Scale; IQR, interquartile range; ISS, Injury Severity Score.

[a] *P* value calculated from Pearson $\chi^2$ test, Fischer exact test, and Wilcoxon test as appropriate.

Data were analyzed with R version 3.1.3 (R Foundation). Comparisons were made between the control and intervention groups and between patients with and without VTE. *t*, Wilcoxon rank sum, Pearson $\chi^2$, and Fischer exact tests were used as appropriate. Significance was defined as $P < .05$.

## Results

### Patient Characteristics and Enoxaparin Dosing

In total, 18 612 patients were screened, and 185 were randomized (89 patients in the control group and 96 in the dose-adjusted group). All patients were analyzed, with no patients lost to follow-up (Figure 1). Baseline characteristics are shown in **Table 1**; characteristics were similar, although there were more males in the dose-adjusted group. The enoxaparin treatment duration was similar between the control and intervention groups, and the time to enoxaparin administration was short in both groups. Patients in the intervention group received significantly higher average prescribed and actually administered doses. A total of 97 patients (52.4%) missed at least 1 dose, but the median percentage of doses missed per patient was low (Table 1).

### Coagulation Characteristics of Study Groups

Thrombelastogram results and coagulation characteristics are shown in **Table 2**. There were no significant differences in standard TEG values (*R*, *K* time [minutes to 20 mm clot strength], α angle [rate of clot strengthening], MA, or degree of clot lysis at 30 minutes) on average or over time. Only 22 patients (11.9%) achieved Δ*R* greater than 1 minute, with similar incidence between groups. No significant difference was found in median Δ*R* overall or over time. There was no statistically significant difference between the control and intervention groups by the sixth Δ*R* measurement (0.08 vs 0.29; $P = .09$). Hypercoagulable TEG parameters at any point during hospital admission (ie, CI >3; MA >74 mm; and G value >12.4 dynes/cm$^2$)[28,29] were compared. Control patients were more often hypercoagulable using CI and MA measurements, but the incidence of hypercoagulable G values was similar. Antithrombin III deficiency was similar between the control and intervention groups (18.0% vs 19.8%; $P = .85$) and less prevalent than previously reported (Table 2).[13] A similar percentage of patients were anti-Xa deficient, and anti-Xa levels for patients with adjusted dosing did not exceed levels in control patients until the sixth measurement (0.4 U/mL vs 0.21 U/mL; $P < .001$).

Table 2. TEG Results and Coagulation Characteristics Between Study Groups

| Patient Characteristic | No. (%) | | P Value[a] |
|---|---|---|---|
| | Control (n = 89) | Dose-Adjusted (n = 96) | |
| TEG results[b] | | | |
| ΔR >1 m | 12 (13.5) | 10 (10.4) | .68 |
| Coagulation index >3[c] | 47 (52.8) | 34 (35.4) | .03 |
| Maximum amplitude >74 mm[c] | 55 (61.8) | 44 (45.8) | .04 |
| G value >12.4 dynes/cm$^2$[c] | 62 (69.7) | 61 (63.5) | .38 |
| Coagulation characteristics[b] | | | |
| Anti-thrombin III deficiency (<80% activity) | 16 (18.0) | 19 (19.8) | .85 |
| Anti-Factor Xa deficiency (≤0.2 IU/mL) | 29 (32.6) | 32 (33.3) | >.99 |
| Monitoring and outcomes | | | |
| Venous duplex completed | 73 (82.0) | 76 (79.2) | .71 |
| DVT | 6 (6.7) | 5 (5.2) | .76 |
| Time to DVT diagnosis, median (IQR), d[d] | 5.5 (3.8-14.8) | 6.0 (3.5-13.0) | >.99 |
| PE | 0 | 1 (1.0) | >.99 |
| Time to PE diagnosis, d[e] | NA | 6.0 | NA |
| Venous thromboembolism | 6 (6.7) | 6 (6.3) | >.99 |
| Bleeding complication | 5 (5.6) | 13 (13.5) | .08 |
| Death | 0 | 2 (2.1) | .50 |

Abbreviations: DVT, deep venous thrombosis; IQR, interquartile range; NA, not applicable; PE, pulmonary embolism; ΔR, difference in time to initial fibrin formation in minutes; TEG, thrombelastogram.

[a] P value calculated from Pearson $\chi^2$ test, Fischer exact test, and Wilcoxon test as appropriate.

[b] Based on occurrence at any point during hospitalization.

[c] Standard citrated kaolin TEG.

[d] Calculated from admission date to diagnostic study date for the 11 patients with DVT.

[e] Calculated from admission date to diagnostic study date for the 1 patient with a PE.

### VTE and Bleeding Complications

Venous duplex ultrasonography completion was similar between the control and intervention groups (Table 2). Overall VTE incidence was low, occurring in only 12 patients (6.5%). The median time to diagnosis was similar. The incidence of DVT, PE, VTE, or death was similar. Compared with control patients, the rate of bleeding complications in intervention patients was not statistically significant (5.6% vs 13.5%; $P = .08$) (Table 2). Patients with bleeding complications had a higher maximum enoxaparin dose.

### Characteristics of Patients With VTE

Characteristics of patients with VTE are shown in **Table 3**. Patients with VTE were older; had higher BMI and Acute Physiology and Chronic Health Evaluation II scores; were nontrauma surgical patients; had longer enoxaparin treatment duration and lengths of stay; and had higher average prescribed and administered enoxaparin doses. While the incidence of at least 1 missed dose was not significantly higher in patients with VTE, these patients missed a higher percentage of prescribed doses than patients without VTE (median [range], 14.8% [3.8%-19.5%] vs 2.5% [0%-8.5%]; $P = .05$). Incidence of ΔR greater than 1 minute and all other coagulation characteristics (CI, MA, G value, and anti-Xa and AT-III deficiencies) were not significantly different between patients with and without VTE (Table 3).

### Interim Analysis and Study Discontinuation

An interim analysis was performed after the enrollment of 185 patients. The incidence of VTE was similar (6.7% vs 6.3%; $P > .99$). Assuming equivalent effect sizes for future enrollments, 3212 total patients would be needed to demonstrate statistical significance. Therefore, the study was discontinued for futility. Furthermore, if the study had reached goal enrollment (320 patients) and a similar difference in bleeding events had occurred, the rate of bleeding events would have been significantly higher in the intervention group.

## Discussion

This multicenter, prospective, randomized clinical trial compared the effectiveness of TEG-adjusted vs standard enoxaparin dosing to prevent VTE among trauma and surgical patients. Patients in the intervention group received significantly higher average prescribed and administered enoxaparin doses than control patients, but there was no significant difference in VTE incidence. To our knowledge, 2 other published studies[13,30] have pursued TEG-adjusted strategies that increase LMWH dosing for a ΔR less than 1 minute. In our initial single-center trial,[13] 87 patients were randomized to TEG-adjusted vs standard enoxaparin dosing. Rates of VTE were similar between the control and intervention groups (16.2% vs 13.6%; $P = .73$). However, a high prevalence of AT-III deficiency (60% of patients) was observed.[13] In addition, Harr et al[30] recently demonstrated similar VTE rates in patients randomized to receive standard (5000 IU daily) and TEG-adjusted dalteparin dosing but suggested a role for antiplatelet therapy for VTE prophylaxis following trauma. To our knowledge, our study is the third to demonstrate that a TEG-adjusted strategy using ΔR does not improve VTE rates.

There are multiple explanations for these findings. A simple hypothesis is that missing 1 or more doses of enoxaparin, which occurred in a high percentage of patients, may counter any possible positive effects of dose adjustment. In a prior prospective observational study of trauma and general surgery patients,[12] 58.9% of patients missed at least 1 enoxaparin dose, and DVTs occurred in nearly a quarter of those patients. On re-

Table 3. Characteristics of Patients With VTE

| Patient Characteristic | No. (%) No VTE (n = 173) | No. (%) VTE (n = 12) | *P* Value[a] |
|---|---|---|---|
| Age, median (IQR), y | 46.0 (32.0-58.0) | 61.0 (50.0-67.5) | .04 |
| Male | 113 (65.3) | 7 (58.3) | .86 |
| Length of stay, median (IQR), d | 7.0 (5.0-13.0) | 10.5 (6.3-20.3) | .03 |
| BMI, median (IQR) | 27.1 (23.3-32.0) | 30.6 (29.6-36.6) | .03 |
| Admission reason | | | |
| Trauma | 122 (70.5) | 5 (41.7) | .08 |
| Surgical operation | 51 (29.5) | 7 (58.3) | |
| ISS, trauma patients only, No./Total No. (%) | | | |
| Mild (0-8) | 28/122 (23.0) | 0 | |
| Moderate (9-15) | 39/122 (32.0) | 3/5 (60.0) | .29 |
| Severe (16-24) | 30/122 (24.6) | 2/5 (40.0) | |
| Very Severe (25-75) | 25/122 (20.5) | 0 | |
| APACHE score, median (IQR) | 7.0 (4.0-10.0) | 8.5 (6.0-10.2) | .03 |
| GCS score | | | |
| Mild (13-15) | 141 (81.5) | 11 (91.7) | .60 |
| Moderate (9-12) | 10 (5.8) | 0 | |
| Severe (3-8) | 22 (12.7) | 1 (8.3) | |
| Active smoking | 69 (39.9) | 5 (41.7) | >.99 |
| Any comorbidity | 88 (50.9) | 6 (50.0) | >.99 |
| Enoxaparin administration | | | |
| Time to initiation, median (IQR), d | 1.0 (0.0-2.0) | 1.0 (0.0-2.2) | >.99 |
| Treatment duration, median (IQR), d | 5.0 (3.8-10.0) | 6.5 (5.0-23.8) | .18 |
| Average dose prescribed per patient, median (IQR), mg | 33.5 (30.0-35.6) | 37.6 (33.1-41.4) | .06 |
| Average dose administered, median (IQR), mg | 30.0 (29.0-35.0) | 33.8 (30.0-37.0) | .22 |
| Missed ≥1 dose | 88 (50.9) | 9 (75.0) | .19 |
| Doses missed per patient, median (IQR), % | 2.5 (0.0-8.5) | 14.8 (3.8-19.5) | .05 |
| TEG results and coagulation characteristics[b] | | | |
| Δ*R* >1 m | 20 (11.6) | 2 (16.7) | .64 |
| Coagulation index >3[c] | 74 (42.8) | 7 (58.3) | .45 |
| Maximum amplitude >74mm[c] | 92 (53.2) | 7 (58.3) | .96 |
| G value >12.4 dynes/cm$^2$[c] | 114 (65.9) | 9 (75.0) | .52 |
| Anti-thrombin III deficiency (<80% activity) | 31 (17.9) | 4 (33.3) | .35 |
| Anti-Factor Xa deficiency (≤0.2 IU/mL) | 58 (33.5) | 3 (25.0) | .75 |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; GCS, Glasgow Coma Scale; IQR, interquartile range; ISS, Injury Severity Score; Δ*R*, difference in time to initial fibrin formation in minutes; TEG, thrombelastogram; VTE, venous thromboembolism.

[a] *P* value calculated from Pearson $\chi^2$ test, Fischer exact test, and Wilcoxon test as appropriate.

[b] Based on occurrence at any point during hospitalization.

[c] Standard citrated kaolin TEG.

gression analysis, a significant association was found between a missed enoxaparin dose and DVT.[12] We demonstrated that 75.0% of patients with VTE missed at least 1 dose and had a higher percentage of doses missed per patient compared with non-VTE patients. These results suggest that improved compliance to minimize missed doses with any thromboprophylaxis protocol may be a very important step needed to lower VTE incidence.

As originally described, the association between Δ*R* less than 1 minute and VTE was observed in patients who were old (mean [SD] age, 54 [3.8] years), severely injured (mean [SD] injury severity score, 44.6 [3.2]), critically ill (mean [SD] Acute Physiology and Chronic Health Evaluation II score, 18.1 [1.5]) and obese (mean [SD] BMI, 33.8 [2.4]).[24] While the association between Δ*R* and VTE was strong in that population, its importance may be diminished in the less critically ill trauma and surgical patients represented in our current study. To our knowledge, to date, 3 prospective randomized trials[13,24] have failed to demonstrate a change in VTE incidence despite LMWH dose adjustments for Δ*R* less than 1 minute. In both this study and our prior trial,[13] the median Δ*R* was less than 1 minute and was equivalent for patients with and without VTE. Also, VTE rates in this study were lower than previously described (28%).[24] These observations do not support TEG-guided thromboprophylaxis among patients similar to our study population. However, it is very possible that a prospective study limited to only those patients with severe injuries and a prolonged expected length of stay with longer term follow-up could yield a different result.

Furthermore, it may be difficult to achieve a Δ*R* greater than 1 minute in the typical patient, given the practical limitations of the protocol and treatment duration. Prior to dose

adjustment, 3 doses are required to achieve steady state after any missed or adjusted dose. In our study, the average treatment duration was only 5 to 6 days, which may not have allowed enough time for adjustments to occur to increase Δ*R* to greater than 1 minute. Only 22 patients (11.9%) in the current study achieved a Δ*R* greater than 1 minute, and the average Δ*R* never met or exceeded 1 minute in any study. More aggressive adjustment strategies or higher initial doses could increase the achievement of Δ*R* greater than 1 minute, although this may increase the risk of bleeding complications, and 30 mg twice daily is the current standard of care.

The difference in bleeding complications approached significance in this study. Sixteen of 18 bleeding complications were intraoperative or postoperative bleeding events associated with hypotension or anemia that required blood transfusion. Significant gastrointestinal bleeding from a gastric ulcer and major bleeding after inadvertent patient removal of a central venous catheter accounted for the other 2 complications. No bleeding complication resulted in death. Of interest, the median maximum dose of enoxaparin was significantly higher among patients with a bleeding complication.

We demonstrated that trauma and surgical patients had significant hypercoagulable risk factors. The CI and MA were in the hypercoagulable range for 82 (44.3%) and 99 (53.5%) patients, respectively, and were significantly higher in the control group. The G value was elevated in 123 patients (66.5%) and in 9 (75.0%) with a VTE. Previous authors[31] found that increased MA is associated with PE. Others have argued that trauma patients develop a hypercoagulable state despite adequate heparin-based therapy, likely due to increased platelet activation.[30] These data reinforce the importance of platelet contribution to VTE and the potential role for platelets as a target in future VTE prevention strategies.

Antithrombin III deficiency was prevalent in 35 of 185 patients (18.9%). Heparin-based anticoagulation relies on AT-III and has little pharmacologic activity with AT-III deficiency. Although our prevalence was lower than previously demonstrated, AT-III deficiency may contribute to persistent VTE incidence despite adequate heparin-based thromboprophylaxis.[13] In this study, 33.3% of patients with VTE were AT-III deficient. To further investigate the effects of AT-III deficiency, particularly in those patients receiving LMWH prophylaxis, we are conducting a prospective cohort trial powered to find differences in AT-III levels between patients with and without VTE.

The overall VTE rate in this trial was lower than we demonstrated previously (6.5% vs 15.0%).[13] One important difference is the time to enoxaparin administration. In this study, the median time to initiation was 1 day for both groups, whereas the mean time was 2 to 3 days in our previous study.[13] This observation suggests that an earlier time to enoxaparin administration may help lower VTE incidence. Another important observation is that median BMI was significantly higher in patients with VTE (30.6 vs 27.1; $P = .03$). In our prior trial,[13] with higher observed VTE rates, BMI ranged from 30.6 to 32.8. In a rat obesity model, McCully et al[32] demonstrated that obese rats do not develop the acute coagulopathy of trauma after hemorrhagic shock and are hypercoagulable at baseline. Other authors[21] suggest that obesity decreases the effectiveness of enoxaparin prophylaxis. These data suggest that the effects of obesity must be further evaluated and may contribute toward VTE formation.

This study has some limitations. First, only 185 patients were enrolled because of difficult enrollment logistics. Second, many patients in both study groups missed at least 1 enoxaparin dose. Because a missed dose is a demonstrated risk factor for DVT formation,[12] any effects of dose adjustment may have been absorbed by the high rate of missed doses. Next, the physiologic effects of the dose adjustment (ie, anti-Xa and Δ*R*) were not observed until the sixth measurement. It is possible that the time to achieve this difference was too late because VTE events had already occurred. Furthermore, only a marginal dosing difference and no significant difference in Δ*R* was achieved between groups. Also, few patients in the dose-adjusted group achieved Δ*R* greater than 1 minute because of the constraints of the dose-adjustment schedule. Therefore, conclusions about the role of Δ*R* remain hypothetical. Also, variable screening protocols at participating institutions and an 80% duplex completion rate may have contributed to the lower-than-expected VTE rate because some events may have been missed. Finally, overall VTE incidence was lower than anticipated in the power analysis. Therefore, this study was underpowered to detect differences in VTE rates between study groups or coagulation differences between patients with and without VTE.

## Conclusions

This multicenter, prospective randomized clinical trial compared TEG-adjusted vs standard prophylactic enoxaparin administration and VTE incidence in trauma and surgical patients. Few patients achieved a Δ*R* greater than 1 minute, and VTE rates were similar between groups. In addition, the difference in bleeding complications was not statistically significant. We conclude that TEG-adjusted enoxaparin administration based on Δ*R* is not supported by our current data in this study population. However, these data demonstrate that many trauma and surgical patients have hypercoagulation at baseline and that further investigations into the effects of platelet activation and obesity, time to enoxaparin administration, and AT-III deficiency are needed.

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**Author Contributions:** Drs Connelly and Schreiber had full access to all the data in the study and take

responsibility for the integrity of the data and the accuracy of the data analysis.
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**X-Chromosome Linked IRAK1 Polymorphism Is Strong Predictor Of Multiple Organ Failure And Mortality Post-Injury**

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**OBJECTIVE(S):** Clinical research characterizing the mechanisms responsible for gender based outcome differences post-injury remain conflicting. We sought characterize an x-chromosome linked IRAK1 polymorphism as an alternative mechanism responsible for gender differences post-injury. IRAK1 is key intermediate in the Toll Like Receptor (TLR) pathway thought to drive inflammation post-injury.
**METHODS:** A prospective cohort study was performed over an 18 month period. Blunt injured patients requiring ICU admission were enrolled while patients with isolated brain and spinal cord injuries were excluded. Outcomes of interest included Multiple Organ Failure (MOF, Mashall MODscore > 5) and mortality. Logistic regression was utilized to determine the independent risk of poor outcome associated with the IRAK1 variant after controlling for differences in injury and shock severity.
**RESULTS:** In an cohort of 272 patients, the prevalence of the IRAK1 variant was 12.5%. Patients with and without the variant were similar in age, injury severity and 24hr blood transfusion. After controlling for important confounders, the IRAK1 variant was independently associated with over a 6-fold (OR 6.4; 95% CI1.8-23) and 5-fold (OR 5.8; 95% CI1.4-24) greater risk of MOF and mortality, respectively. These differences were most prominent in males, while females heterozygous for the variant demonstrated worse outcome in a dose-dependent fashion.
**CONCLUSIONS:** The IRAK1 polymorphism is a strong independent predictor of MOF and mortality post-injury and represents a common variant with prognostic potential. These data demonstrate the importance of TLR signaling post-injury and supports that a genetic mechanism may drive gender outcome differences post-injury.

# The splenic injury outcomes trial: An American Association for the Surgery of Trauma multi-institutional study

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**BACKGROUND:** Delayed splenic hemorrhage after nonoperative management (NOM) of blunt splenic injury (BSI) is a feared complication, particularly in the outpatient setting. Significant resources, including angiography (ANGIO), are used in an effort to prevent delayed splenectomy (DS). No prospective, long-term data exist to determine the actual risk of splenectomy. The purposes of this trial were to ascertain the 180-day risk of splenectomy after 24 hours of NOM of BSI and to determine factors related to splenectomy.

**METHODS:** Eleven Level I trauma centers participated in this prospective observational study. Adult patients achieving 24 hours of NOM of their BSI were eligible. Patients were followed up for 180 days. Demographic, physiologic, radiographic, injury-related information, and spleen-related interventions were recorded. Bivariate and multivariable analyses were used to determine factors associated with DS.

**RESULTS:** A total of 383 patients were enrolled. Twelve patients (3.1%) underwent in-hospital splenectomy between 24 hours and 9 days after injury. Of 366 discharged with a spleen, 1 (0.27%) required readmission for DS on postinjury Day 12. No Grade I injuries experienced DS. The splenectomy rate after 24 hours of NOM was 1.5 per 1,000 patient-days. Only extravasation from the spleen at time of admission (ADMIT-BLUSH) was associated with splenectomy (odds ratio, 3.6; 95% confidence interval, 1.4–12.4). Of patients with ADMIT-BLUSH (n = 49), 17 (34.7%) did not have ANGIO with embolization (EMBO), and 2 of those (11.8%) underwent splenectomy; 32 (65.3%) underwent ANGIO with EMBO, and 2 of those (6.3%, $p = 0.6020$ compared with no ANGIO with EMBO) required splenectomy.

**CONCLUSION:** Splenectomy after 24 hours of NOM is rare. After the initial 24 hours, no additional interventions are warranted for patients with Grade I injuries. For Grades II to V, close observation as an inpatient or outpatient is indicated for 10 days to 14 days. ADMIT-BLUSH is a strong predictor of DS and should lead to close observation or earlier surgical intervention. (*J Trauma Acute Care Surg*. 2015;79: 335–342. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.)

**LEVEL OF EVIDENCE:** Prognostic/epidemiological study, level III; therapeutic study, level IV.

**KEY WORDS:** Spleen Injury; blunt spleen injury; blunt spleen injury splenectomy; blunt spleen injury angiography.

Approximately 39,000 adults with blunt splenic injury (BSI) are admitted to the hospitals in the United States every year.[1,2] Approximately 10% of these patients will be managed with urgent splenectomy.[2–4] The remaining patients are managed using nonoperative strategies that have developed during the last three decades.[2,5–13] This shift toward nonoperative management (NOM) may have unintended consequences, such as delayed splenic rupture, which is particularly worrisome in the outpatient setting.[14–16] Other risks may result from strategies aimed at splenic preservation, mainly the use of angiography (ANGIO) and embolization (EMBO). Patients may experience exposure to radiation, invasive procedures, and increased costs as a result of guidelines and treatment algorithms aimed at splenic preservation.[15,17,18]

There is wide debate in the literature regarding the optimal management algorithm for patients with BSI who do not need urgent operative intervention. Previous works studying various techniques aimed at splenic preservation are retrospective and primarily single-center studies.[11–13,19–25] Even the most recent guidelines published regarding the management of BSI are largely based on expert opinion and retrospective studies.[26,27] This lack of consensus extends to the American Association for the Surgery of Trauma (AAST), where a survey demonstrated variability in the optimal management of BSI.[28] Examples of the variation in treatment recommendations include the use of ANGIO, serial computed tomography (CT), serial

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From the AAST Multi-Institutional Trials Committee (B.L.B., R.K., J.G.M., J.A.C., T.M.S., T.A.N., A.A.M., L.A., A.C., A.K., R.X.); University of Tennessee Health Science Center (B.L.Z.), Memphis, Tennessee; Indiana University School of Medicine (B.L.Z.), Indianapolis, Indiana; University of Texas Health Science Center Houston (R.K.), Houston; and University of Texas Health Science Center San Antonio (J.G.M.), San Antonio, Texas; Case Western Reserve University School of Medicine (J.A.C.), Cleveland, Ohio; University of Maryland School of Medicine (T.M.S.), Baltimore, Maryland; Medical College of Wisconsin (T.A.N.), Milwaukee, Wisconsin; Yale University School of Medicine (A.A.M.), New Haven, Connecticut; University of Pennsylvania Medical Center–Presbyterian (L.A.); and University of Pennsylvania Medical Center–Mercy (A.C.), Philadelphia, Pennsylvania; University of Florida College of Medicine–Jacksonville (A.K.), Jacksonville, Florida; and University Of California San Diego Health Sciences (R.C.), San Diego, California.

This study was presented at the 73rd annual meeting of the American Association for the Surgery of Trauma September 10–13, 2014, in Philadelphia, Pennsylvania.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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ultrasonography, and prolonged bed rest for management of BSI.[11–13,19–25,29–31]

To begin to address the lack of prospective, multi-institutional data, we proposed a multicenter, prospective observational trial of patients with BSI. The aims of the trial were twofold. The first aim was to ascertain the 180-day risk of delayed splenic rupture after 24 hours of NOM of BSI. The second aim was to examine the role of ANGIO in the management of patients with BSI. Achieving the aims of this study is the first step in a continuum of research that is expected to lead to the development of management strategies that will result in subjecting adults with BSI to the least risk while preserving the most spleens.

## PATIENTS AND METHODS

### Participating Centers

The AAST multi-institutional trials committee approved this study, and participating centers were drawn from membership of the AAST. Eleven Level I trauma centers from across the United States participated. Principal investigators at each participating center were identified. Each participating center's institutional review board approved the study. Study related data were stored using the AAST online data collection service. To ensure that all centers used the same definitions for each data point, a standard data dictionary was developed and used throughout the study.

### Study Population

Adult patients (≥18 years) admitted to a participating center with a BSI managed for 24 hours without splenectomy were eligible for study enrollment. Patients who did not provide consent were excluded from the study. Other exclusion criteria included (1) more than 24 hours from the time of injury to hospital admission; (2) a history of a splenic injury; (3) history of surgery involving the spleen; (4) a history of a significant bleeding disorder (e.g., factor VII deficiency, factor VIII deficiency); (5) pregnant women (assessed by a urine pregnancy test); (6) or a history of any of the following: hereditary elliptocytosis, hereditary spherocytosis, sickle cell disease, thalassemia, Hodgkin's or non-Hodgkin's lymphoma, other lymphomas, leukemia, polycythemia vera, myelofibrosis, metabolic storage diseases, amyloidosis, splenic vein thrombosis, cirrhosis, splenic cysts, sarcoidosis, or systemic lupus erythematosus.

### Study Protocol

After enrollment and consent, demographic data, medical history, surgical history, and current medication use were obtained. Detailed injury, physiologic, and laboratory data were also recorded. Images and interpretations of the admission CT examinations of the abdomen were obtained. Patients were followed up while in the hospital and then as outpatients at 30, 90, and 180 days. Where possible, follow-up was performed face to face. If a face-to-face examination was not possible, a telephone follow-up was performed using a predefined standard script. The social security death index was used to determine if a patient had died after hospital discharge.

Initial spleen injury grading was obtained from the official radiology report from the admission CT using the AAST spleen injury grading scale. If a radiology report was not available or if the radiologist did not mention an AAST spleen injury score, the site principal investigator graded the injury. Standard definitions were used to define splenic pseudoaneurysm (PSA) and splenic blush. A splenic PSA was defined as an abnormal accumulation of contrast contained within the parenchyma of the spleen. A splenic blush was defined as any extravasation of contrast outside the parenchyma of the spleen.

### Spleen-Related Interventions and Outcomes

The main outcome was splenectomy. However, detailed data regarding other spleen-related interventions were also obtained. Spleen-related interventions were defined as any use of ANGIO (with or without EMBO) or any operation on the spleen that did not result in splenectomy. Indications for spleen-related interventions were also recoded. Secondary outcomes of interest were hospital and intensive care unit length of stay and mortality.

### Statistical Analysis

Bivariate analysis was performed to determine variables associated with splenectomy and the use of ANGIO and EMBO. Multivariable analysis was used to determine factors independently associated with splenectomy and ANGIO with EMBO. Variables that had a $p < 0.20$ or that were considered clinically significant were eligible for inclusion in multivariable models. A $p < 0.05$ was considered significant. All risks are reported relative to a time frame, and rates are reported with person-time in the denominator. SAS 9.2 (SAS institute, Cary, NC) was used for all statistical analyses.

## RESULTS

There were 1,002 patients screened, and 383 consented and were enrolled. Of those enrolled, 371 were discharged alive with a spleen. Follow-up was 95% at 30 days, 88% at 90 days, and 87% at 180 days. The median age was 36 years (interquartile range, 25–52), and 65.2% were male. The vast majority of patients were white, and the median Injury Severity Score (ISS) was 22 (interquartile range, 14–27). The AAST spleen injury grade was III to IV for 42.8% of the patients. Splenic PSA were present in 8.4% of the patients, and splenic blushes were present in 12.9% of the patients. ANGIO with EMBO was used in 18.7% of the patients. Overall mortality was 1.04%, and no deaths were spleen related (Table 1).

The flow of patients through the study is outlined in Figure 1. Of the 383 patients, 70 underwent ANGIO at admission. Of those, nine had no EMBO, and one went on to splenectomy. One patient underwent a second ANGIO with EMBO. This patient did not require a splenectomy. Of the 70 patients who underwent ANGIO at admission, 61 had EMBO. Forty-eight had no further angiographic intervention, and two required splenectomy. Thirteen patients underwent repeat ANGIO with five undergoing a second EMBO and eight requiring no further EMBO. None of the 13 patients who underwent repeat ANGIO had a subsequent splenectomy. Of the 313 patients who had no ANGIO at the time of admission, 21 underwent ANGIO in more than hours after admission. Ten

**TABLE 1.** Characteristics of Patients With BSI Who Did or Did Not Undergo Splenectomy Within 180 Days

| | | Splenectomy | | |
|---|---|---|---|---|
| | Entire Cohort | No | Yes | |
| Variable | n = 383 | n = 370 | n = 13 | *p* |
| Age, y | 36 (25–52) | 35 (25–52) | 47 (40–56) | 0.1217 |
| Male, % | 65.3 | 64.9 | 76.9 | 0.5552 |
| Body mass index, kg/m$^2$ | 26.7 (23.2–31.6) | 26.8 (23–2–316) | 25.1 (23.3–32.3) | 0.9099 |
| ISS | 22 (14–27) | 22 (14–27) | 22 (21–26) | 0.167 |
| Admission systolic blood pressure < 90 mm Hg, % | 5.5 | 5.5 | 8.3 | 0.5007 |
| Admission hematocrit, g/dL | 39 (35–42) | 39 (35–42) | 41 (32–42) | 0.7891 |
| Admission international normalized ratio, IU | 1.04 (1.00–1.12) | 1.00 (1.00–1.12) | 1.00 (0.95–1.05) | 0.2992 |
| Spleen injury grade, % | | | | 0.0502 |
| 1–2 | 57.2 | 58.1 | 41.9 | |
| 3–5 | 42.8 | 30.8 | 69.2 | |
| Admission PSA, % | 8.4 | 8.5 | 8.3 | 0.9889 |
| Admission blush, % | 12.9 | 12.2 | 33.3 | 0.0548 |
| Other solid organ injury, % | 28.5 | 27.8 | 46.2 | 0.2072 |
| Hollow viscus injury, % | 4.2 | 4.1 | 7.7 | 0.431 |
| ANGIO with EMBO, % | 18.7 | 3.5 | 2.8 | 0.7485 |
| Intensive care length of stay, d | 3 (1–6) | 3 (1–6) | 6 (3–13) | 0.0278 |
| Hospital length of stay, d | 6 (3–11) | 6 (3–10) | 12 (6–15) | 0.0304 |
| Mortality, % | 1.04 | 1.1 | 0 | 0.7063 |

of those had EMBO, and there were no splenectomies. Eleven had no EMBO, and three experienced a subsequent splenectomy. Of the 292 patients who were observed without ANGIO, 7 required a splenectomy.

Of the 61 patients who underwent ANGIO and EMBO within 24 hours of admission, 51 (84%) had a primary indication that was the presence of a blush or PSA or both on initial CT scan. For two patients (3%), the primary indication was hemodynamic instability. In the remaining eight patients (13%), the main indication was the appearance of the spleen on CT scan. Five of the eight had a Grade III injury, and one had a Grade IV injury. The remaining had Grade I and II injuries. Four of the eight had a

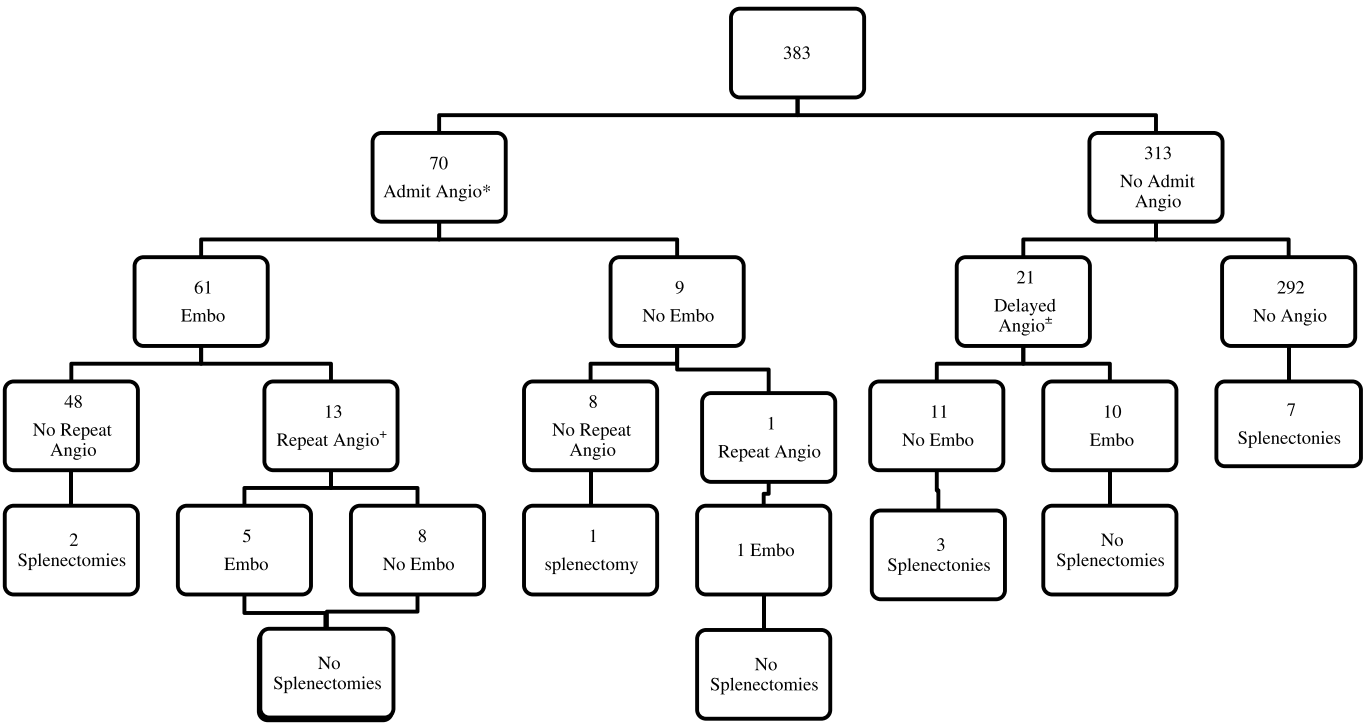


**Figure 1.** Flow chart of patient outcomes.

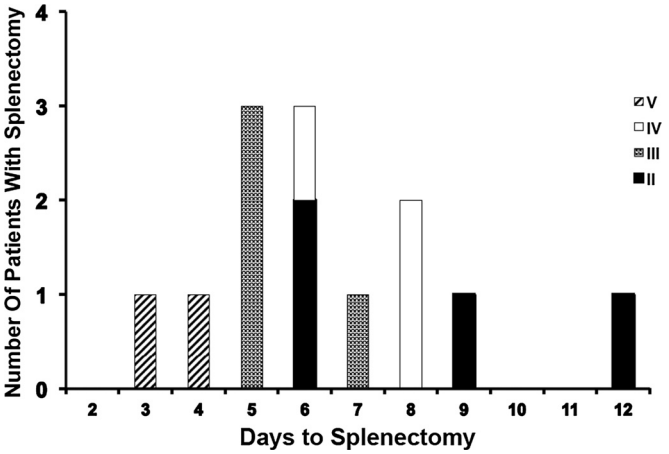


**Figure 2.** Absolute number of patients with splenectomy by AAST injury grade and by day of splenectomy.

repeat ANGIO, and one had a repeat EMBO. There were no splenectomies in the eight patients for whom the only indication for ANGIO and EMBO was the appearance of the spleen on CT scan. For the nine patients who had ANGIO with no EMBO within the first 24 hours of admission, the primary indication for ANGIO was the presence of a blush or PSA or both in eight patients. In one patient, the grade of the injury (Grade III) was the main indication. This patient went on to require an additional ANGIO and EMBO.

Overall, the risk of splenectomy while in the hospital was 3.1%. The risk of outpatient splenectomy was 0.24% within 180 days. The overall splenectomy rate after 24 hours of NOM was 1.5 splenectomies per 1,000 patient-days. The time course to splenectomy by injury grade is shown in Figure 2. The vast majority of splenectomies occurred within 10 days of injury. There were no statistical differences based on grade of injury and time to splenectomy. Furthermore, no Grade I injuries required a splenectomy. Factors associated with splenectomy on bivariate analysis are shown in Table 1. Increasing age, ISS, spleen injury grade, admission contrast blush, and other solid organ injury all met criteria for inclusion in multivariable models. Only extravasation outside the spleen parenchyma at the time of admission was associated with splenectomy (odds ratio, 3.6; 95% confidence interval, 1.4–12.4; area under the curve, 0.722; Hosmer-Lemeshow goodness-of-fit test $p$ = 0.1626) after controlling for other factors. However, intensive care unit and total hospital lengths of stay was significantly higher for those patients undergoing splenectomy.

In Table 2, those who underwent ANGIO and EMBO are compared with those who did not. This analysis was conducted for all spleen injury grades and for BSI Grades III to V. When considering all grades, the 180-day risk of splenectomy was 3.5% for those who did not undergo ANGIO with EMBO and 2.8% for those who did. The difference was not statistically significant. For Grades III to V, the 180-day risk of splenectomy was 6.9% for patients who did not undergo ANGIO with EMBO and was 3.2% for those who did. There was no statistical difference between the groups. When we limited the analysis to patients with only Grades 4 and 5 injures, the numbers were similar. There were 56 patients (50 Grade IV and 6 Grade V spleen injuries). Of those, 34 underwent ANGIO with EMBO. Of those, two failed (6%). Of the 22 who did not have ANGIO, 3 required splenectomy (14%). Again, the difference was not statistically significant.

Because admission contrast blush was associated with splenectomy, we examined the use of ANGIO and EMBO in these patients. Of patients with an admission contrast blush (n = 49), 17 (34.7%) did not have ANGIO and EMBO, and 2 of those (11.8%) underwent splenectomy; 32 (65.3%) underwent ANGIO and EMBO, and 2 of those (6.3%) required splenectomy. There was no statistical difference between those treated with ANGIO and EMBO and those not treated with ANGIO and EMBO.

## DISCUSSION

This study represents the first attempt to collect multi-institutional, long-term prospective data for patients with BSI. The results shed light on two issues in the management of BSI. The first is the risk and timing of inpatient and outpatient splenectomy. After the first 24 hours, the risk of splenectomy is relatively rare and occurs in 3.1% of patients while in the hospital. In the outpatient setting, the risk is even lower, 0.27% over 180 days. Overall, the vast majority of splenectomies occurred within 10 days of injury. Second, in this study, the benefits of ANGIO and EMBO in BSI are brought into question, highlighting the need for further multicenter trials.

Regarding the in-hospital risk of splenectomy after NOM for 24 hours, we observed a risk of 3.4%, which is consistent with the literature. Previously published retrospective studies estimate that the in-hospital risk of splenectomy after the first 24 hours ranges from 3% to 10%.[2,3,30,32] When turning to the outpatient setting, the literature is less clear. After hospital discharge, the risk for splenectomy is reported to range from 0.16% to 1.4%.[2,14,16,33,34] In a large retrospective, multi-institutional study, Peitzman et al.[2] noted that six splenectomies or 0.76% of their retrospective cohort occurred after hospital discharge. A higher risk of splenectomy after discharge was found after in two studies that linked trauma registry data to state discharge databases. Of patients discharged alive after a BSI, 1.1% to 1.4% were readmitted and had a splenectomy.[14,16] Our prospectively collected data revealed an outpatient splenectomy risk of 0.27% over 180 days.

The timing of splenectomy was also important. In the current study, 70% of all splenectomies occurred within 7 days of injury. These data are consistent with a study using the National

**TABLE 2.** Risk of Splenectomy With and Without ANGIO With EMBO

| | All Grades | | |
|---|---|---|---|
| | **No ANGIO and EMBO** | **ANGIO and EMBO** | |
| | **(n = 311)** | **(n = 72)** | ***p*** |
| Splenectomy | 3.5% | 2.8% | 1.0 |
| | All Grades | | |
| | No ANGIO and EMBO | ANGIO and EMBO | *p* |
| | (n = 102) | (n = 62) | |
| Splenectomy | 6.9% | 3.2% | 0.4851 |

Trauma Data Bank that showed that 96.5% of splenectomies occur within 5 days of BSI.[35] It is important to keep in mind that in the current study, many of the patients were severely injured and had a long hospital stay, increasing the chance that splenectomies would be observed while the patients were hospitalized.

Perhaps, the most controversial question in the management of BSI revolves around ANGIO use to increase splenic salvage. Some advocate ANGIO for essentially all nonoperatively managed high-grade BSI (AAST Injury Grade III–IV) and for lower-grade injuries (AAST Injury Grades I–II) that have evidence of active bleeding or parenchymal vascular lesions on admission CT scan.[9,12,24] Not all authors are in agreement with this management recommendation. Harbrecht et al.[3,36] outlined the arguments against the use of ANGIO and EMBO in the setting of BSI. The authors demonstrated in retrospective studies that there has been a significant increase in the detection of minor BSI over time. The authors argue that the success attributed to ANGIO with EMBO in studies using historical controls may be the result of time-dependent increase in the detection of relatively minor BSI (which are less likely to bleed in the first place) as opposed to the effect of ANGIO and EMBO. Furthermore, Peitzman et al.[15] argue that perhaps, some patients for whom splenectomy was delayed may have been inappropriately triaged. After reviewing the charts of 80 patients in a multi-institutional, retrospective study, the authors found that 25% of patients with BSI that ultimately failed were hemodynamically unstable up until the time of either splenectomy or death.

The findings in the current study also provide a note of caution regarding the use of delayed ANGIO. There were 21 patients who underwent delayed ANGIO. Of those, 10 had an EMBO and 11 had no EMBO. Of the 11 who had no EMBO, 3 had a splenectomy. Of the patients who required splenectomy, the indications for delayed ANGIO were transfusion of blood and hemodynamic instability. In no other patients who underwent delayed ANGIO was the indication for the delayed ANGIO hemodynamic instability or blood transfusion. Thus, in patients with spleen injuries who develop hemodynamic instability or who require blood transfusion, consideration should be given to proceeding directly to splenectomy and not obtaining ANGIO.

In the current study, ANGIO on admission was used in 18.3%, and EMBO was performed on 87.1% of patients who had ANGIO. When taking all injury grades into account, there was no statistically significant difference for patients managed with ANGIO and EMBO compared with those managed without ANGIO and EMBO. The same was true for Grade III to V BSI. Even when the highest-risk patients in the study (those with a contrast blush on admission CT) were examined, ANGIO and EMBO were not associated with splenic salvage.

The lack of statistical significance for the use of ANGIO and EMBO in the management of BSI, particularly high-grade BSI, is intriguing. One explanation is that the study may suffer from Type II error. To explore this possibility, we performed a power analysis. This power analysis revealed that 906 patients with Grade III to V BSI would need to be randomized to either management with ANGIO and EMBO or watchful waiting for 80% power to detect a statistical difference at the 0.05 $\alpha$ level. In a nonrandomized observational trial, the number of patients needed to detect a difference at the same levels is higher. Despite an aggressive recruitment campaign and funding for this prospective study that required patient consent and long-term follow-up, we still fell below expected enrollment targets. We also had a low proportion of patients enrolled of those who were screened. The low proportion of enrolled patients for this study was caused by variation in screening procedures at some study sites at the beginning of the study. Some sites reported all trauma patients admitted as "screened" even if they did not have a spleen injury. Some sites included patients who had a splenectomy within 24 hours as "screened." With standardization and education regarding screening and enrollment, the screen to enroll numbers was more in line with what was expected. These challenges offer lessons regarding resource allocation for future prospective studies in this patient population.

There are also public health implications of a weaker-than-expected effect of ANGIO and EMBO. Based on national estimates, 39,000 people will experience a BSI every year.[1,2] Of those, 10% will have splenectomy within 24 hours of admission, leaving 35,100 patients with BSI managed nonoperatively for at least 24 hours.[37] Based on data from the current study for all injury grades, 8,340 patients would have at least one ANGIO, and of those, 552 would have splenectomy. Of the 26,760 who would never get an ANGIO, 639 patients would require a splenectomy. The difference is only 87 potentially saved spleens. Similar calculations for the estimated 15,030 patients who would be expected to have Grade III to V BSI reveal that only 274 spleens would potentially be saved. Although three times as many spleens would be saved, it is possible that the high resource use for ANGIO and EMBO is not justified for such a limited number of saved spleens. Resource use versus patient outcomes is an area of debate, and it is likely that only large-scale, patient-centered, randomized controlled trials will help resolve these issues.

The results, while provocative, need to be viewed in light of this study's limitations. The definitions of splenic blushes and PSA may be inconsistent with previously published studies in the literature. This could limit the ability to compare this study to previous works and limit generalizability of this study. However, because of the lack of a clear consensus definition during the design of this study, the authors decided on the definition outlined in the Patients and Methods section of the article. The definition used in this study was applied consistently to all CT scans. Moreover, there was no protocol for the management of patients with BSI, and there was considerable variation in the types of patients for whom ANGIO and EMBO was used. This limits our ability to make management recommendations. There were limited data available regarding the amount and timing of blood transfusions; thus, we are unable to comment on blood transfusion in the setting of BSI. Furthermore, because the study focused on patients managed nonoperatively for the first 24 hours, we do not have information regarding patients who had splenectomy in the first 24 hours. It is well-known that there is significant variation in the use of early splenectomy and ANGIO.[37,38] A center with a liberal splenectomy policy on admission may enroll a different type of patient compared with a center with a more restrictive splenectomy policy on admission. This could influence the results of the analysis, particularly in reference to ANGIO and EMBO. Furthermore, the observed mortality in this study was low given the severity of injuries. This

could be a result of selection bias to exclude patients who were likely to die. It is also possible that the 24-hour cutoff for study inclusion may have also contributed to the low mortality by excluding patients who died early.

Despite good follow-up for the study, well above 80% for all time points, patients who were followed up could have been somehow different compared with those who were not, and this could bias the results. We also looked if the population lost to follow-up was examined to evaluate if they were significantly different from the study population. We found no statistical differences.

Resource use, complications, and cost are very important issues when trying to determine which treatment is optimal for patients with BSI. Intensive care unit length of stay, hospital length of stay, operating room costs, transfusion requirements, and the costs of ANGIO and EMBO are all important to consider. There is also the potential for complications from splenectomy such as subphrenic abscess, pancreatic tail injury, bleeding from short gastrics, enterotomy or fistula from bowel injury, adhesive bowel obstructions, and ventral hernias, to name a few. Complications from ANGIO and EMBO such as arterial injury, splenic abscess, and splenic infarction should also be considered. In this study, there is minimal information regarding complications of ANGIO, EMBO, or splenectomy, so we cannot comment on the risks or costs associated with any of these procedures.

Despite these limitations, there are important conclusions to be drawn from the data for patients with BSI managed nonoperatively during the first 24 hours. After the initial 24 hours, no additional interventions are warranted for patients with Grade I injuries as long as there are no concerning features on admission CT such as a splenic blush or a subcapsular hematoma. For Grade II to V BSI, observation is indicated for 10 days to 14 days because this is the time of greatest risk of splenectomy. Observation could occur in the hospital or as an outpatient with explicit instructions for signs and symptoms of bleeding. Furthermore, patients with Grade III to V BSI may benefit from ANGIO, but the effect may be small. Watchful waiting is also a viable strategy for these patients. Ultimately, a randomized study is needed to definitively make recommendations regarding ANGIO use and BSI. Any such study would require at least 450 patients per group, and a large multicenter trial is necessary to accrue these numbers. The AAST is well positioned to carry out such a trial, and this is the next step in the development of management strategies that will result in subjecting adults with BSI to the least risk while preserving the most spleens.

## AUTHORSHIP

B.L.Z., R.C., and R.K. designed this study. B.L.Z, R.C., R.K., J.G.M., J.A.C., T.M.S., T.A.N., A.A.M., L.A., A.C., A.K., and R.C. contributed to the data collection. B.L.Z. performed the data analysis, interpretation, and drafting of the manuscript. All authors contributed to critical revisions.

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## DISCLOSURE

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## DISCUSSION

**Dr. Andrew B. Peitzman** (Pittsburgh, Pennsylvania): As the authors have reported, late failure from non-operative management of blunt splenic injury is, fortunately, an uncommon event. As noted in our EAST study, 61% of the failures of non-operative management occurred within 24 hours and 90% by 72 hours.

The goals of this study, as stated, were to determine the risk of late splenic rupture and the role of angiography in management of blunt splenic injury. And I have several concerns and questions.

First, you screened over 1,000 patients and entered only 383. Why? Most studies consider Grades 4 and 5 splenic injury to be high-grade, generally not Grade 3. Failure of non-operative management in a review of several recent series ranges from 20%–30% for Grade 3, 33%–44% for Grade 4, and 50%–85% for Grade 5 injury with observation alone.

Tina Gaarder and our friends from Norway dropped Grade 3 splenic injury from their published protocols for angioembolization and they reported the fact that there was no benefit doing so for Grade 3 injuries but was of significant benefit in Grade 4 and 5 injuries.

With our friends from Norway, in addition to several nice studies from Jacksonville, they have suggested that failure of non-operative management of Grade 4 and 5 injury is so frequent-44% and 83%, respectively-and so diminished with angioembolization that we should embolize all Grade 4 and 5 injuries irrespective of the presence of active extravasation. These papers suggest that the natural history of a Grade 3 injury is different than a Grade 4 or 5.

In addition, in most series the splenic injuries are 25% Grade 3, 12% Grade 4, and only 5% Grade 5, so I worry that what you have taught us is true for Grade 3 splenic injury but probably not for Grade 5 splenic injury. Could we have learned more if you had separated the splenic injuries by grade?

I also worry that the degree of injury in your patient population is actually less than the EAST study as you reported a very low mortality, near 1%, and your mean ISS was only 21.

In the EAST study, ISS was 32 for the patients who went directly to OR, 27 in patients who failed non-operative management, and 20 in patients who were successfully managed non-operatively. Please comment.

Lastly, as you mention, you suggest close observation is indicated for 10 to 14 days for Grade 2 to 5 injuries. Again, could you clarify further exactly what you are recommending?

And, again, I compliment you on a very nice study. Thank you for the honor of the podium.

**Dr. Gregory J. "Jerry" Jurkovich** (Denver, Colorado): This is a very nice study and I congratulate the Program Committee for highlighting the multi-institutional trials group as well as the affiliation with the National Trauma Institute by honoring it with the first paper.

Ben, I have two questions and one comment. The two questions revolve around the patient population.

How often did the radiology report actually have or make use of the AAST grading system? And was the grading noted in this study doneby the PIs or was it done by the radiologists? I'm curious to see how penetrated into the lexicon of radiologists is the AAST grading system.

Secondly, how large was the exclusionary group? That group of patients that were excluded from the study, how big was that population? And do you have any idea of what happened to them? Ifthat is a significant percentage of the people

we are managing with splenic injuries, we probably should know what happens to them.

The last comment I have is about a paper by Lisa McIntyre—you weren't able to show it in your slides, I recognize that. But I would turn to that as the largest study: six years, 2,500 patients with splenic injuries from the state of Colorado followed over seven years.

In that study, which is significantly larger than this presented one, they had a 1.1% delayed splenectomy rate after discharge. So, while I do think it is unusual, I would caution the audience that following discharge there is a 1% rate of a non-operative splenic trauma patient presenting with signs and symptoms of a delayed splenic rupture. We should be cognizant of that when we are discharging people. Thanks.

**Dr. Christine Cocanour** (Sacramento, California): Very nice study. My question is a follow up on what Jerry just asked. Did you look at when patients were discharged from the hospital? Since that would affect if the splenic rupture occurred in the hospital or after they were discharged?

**Dr. Walter Biffl** (Denver, Colorado): Ben, can you use these data to help inform protocols for hospitals? A lot of people struggle with how long to keep the patient in-house. On one hand, you have Jim Davis saying when the hemoglobin is stable you can send them home; and, on the other, you've got the New England Consortium with 50% failure rate in Grades 4 and 5.

The Grade 2s and 3s, I think, are the big issue. Can you send them home after 24 hours? With a low rate of rupture it seems like we could.

**Dr. Samir Fakhry** (Charleston, South Carolina): Ben, that was a very nicely done study. I'm sure it was not easy to do.

My question has to do with the technique of the angiography. We have a member in our group (who will go unnamed) who won't use angiography because he is convinced that every time they do one of those the spleen dies.

Do you have any information on what approach was used? Was it a main splenic artery embolization? Was it a selective? And were there any subsequent problems that could be attributed to the technique or the embolization that you could glean from the study? Thank you.

**Dr. Reuven Rabinovici** (Boston, Massachusetts): We very recently analyzed NTDB data regarding cirrhotic patients with blunt splenic injury. Clearly, this group of patients is at high risk for almost everything. My question to you, did you include or exclude this group of patients? This may skew your data.

**Dr. Ben L. Zarzaur** (Indianapolis, Indiana): I would like to thank everyone for their comments and I will try to answer the questions as quickly and concisely as possible.

Regarding Dr. Peitzman's discussion and as well as Dr. Jurkovich's question about screening and enrolling, there was a large divergence. Early on in this study people were counting screened patients who were those who came in and had their spleen taken out in the first 24 hours.

If we exclude those patients this actually looks a lot better. And I don't have that information with me right now but I can certainly put that in our manuscript to explain that better.

But once we educated the sites about that amount of patients who were being screened for the study most of them were being excluded because of the non-operative management in 24-hours criteria. Also, we had to have consent. So there were some consent failures in there as well since we were going to contact the patients as outpatients.

Regarding high-grade and low-grade injuries, when I looked at grade, or when we looked at Grades 4 and 5 as a high-grade injury there was no difference in splenectomy rates statistically compared to-I mean with regard to embolization. I think that's probably a problem of power.

But we can go back and look at rates of splenectomy by grade and we can certainly report that information, which I think would be valuable, getting to Dr. Biffl's point, as well, about timing of discharge.

Regarding in-patient and out-patient management, I think I tried to address that in the conclusions. I don't think it's practical to keep people in the hospital for 10 to 14 days and wait for their spleen to rupture if it is going to. But I do think it is practical to send them out with specific instructions about signs and symptoms and to make sure that they have an appropriate place to go to. If they live out in the middle of nowhere they need to know how to get in contact to get back in if they do suffer symptoms of bleeding.

Regarding Dr. Jurkovich's question regarding who graded the CT scans, the PIs were the main ones who graded. The penetration of the use of the AAST grading system amongst radiologists was variable. It depended upon the institution, frankly. Institutions that see a lot of spleen injuries and have a lot of interest in it, they did a better job than probably other institutions who may not have as much trauma experience in their overall radiology population.

What happened to the other patients that were managed non-operatively? Well, frankly, we don't know for this study because we excluded patients that did not have successful non-operative management for 24 hours.

There is variation in the use of urgent splenectomy, which can certainly impact the success rates of angiography down the road. So I think that is something we should study. And we could certainly go back and ask our sites to look at that patient population over that study time period and we could get some more information about that.

Dr. Cocanour, the mean hospital stay was long. It was about eight days so we did have a greater chance to observe an in-patient splenectomy compared to an out-patient one. So that is true, basically because these patients were multiply injured.

Dr. Biffl, I think I addressed that question. Dr. Fakhry, the vast majority of the spleens were managed with regard to embolization by main splenic artery embolization. Selective embolization didn't work. They usually went on and had main splenic artery embolization.

There were no cysts. There were no splenectomies as a result of the embolization, at least in this cohort of patients.

And then, lastly, Dr. Rabinovici, to my knowledge there were no cirrhotic patients. We did not purposely exclude them but to my knowledge that was not part of the past medical history of any of the patients that were included in this study.

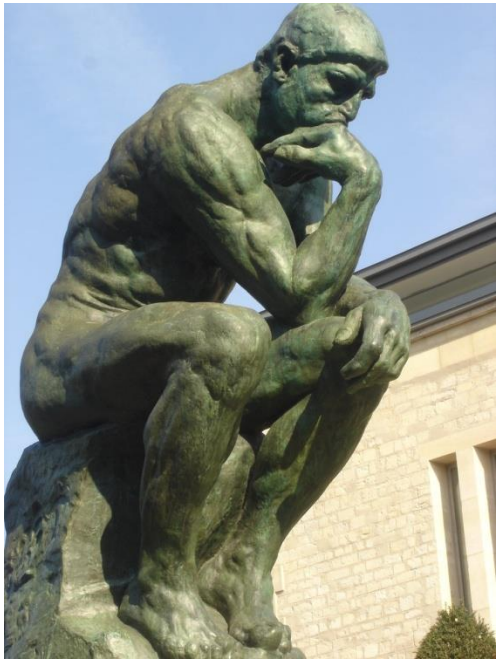
Again, I would like to thank the association for the privilege of the floor.

# Methicillin-Resistant Staph Aureus in a Trauma Population: Does Decolonization Prevent Infection?

Robert A. Maxwell
Professor of Surgery
University of Tennessee College of Medicine

# Subtitle

# Where Did Your MRSA Come From?



# Objectives

- Review what's known about MSSA vs. MRSA
- Review the evolution of MRSA from MSSA
- Discuss the differences between community acquired MRSA (CAMRSA) and hospital acquired (HAMRSA)
- Review the genetic classification of MRSA
- Discuss our findings of the MRSA decolonization study performed in the TICU and SICU

# IS MRSA Infection Worse Than MSSA?

- Mixed results when patients with MSSA outcomes were compared to MRSA
- Some studies have shown worse morbidity and survival for patients with HAMRSA pneumonia, bacteremia and surgical site infections
- Other literature has shown no difference between patients with MSSA and MRSA VAP or soft tissue skin infection
- No compelling evidence that MRSA is worse than MSSA

# MRSA History

- Methicillin first introduced in 1959/60
- Within a year the first strain of MRSA appeared in England in 1961
- Resistance emerged from the mec2A gene which encodes for the penicillin binding protein
- MRSA became a hospital acquired infection where patients were exposed to multiple antibiotic regimens-HAMRSA
- From 1997 to 1999 MRSA occurred outside of the health care setting-CAMRSA

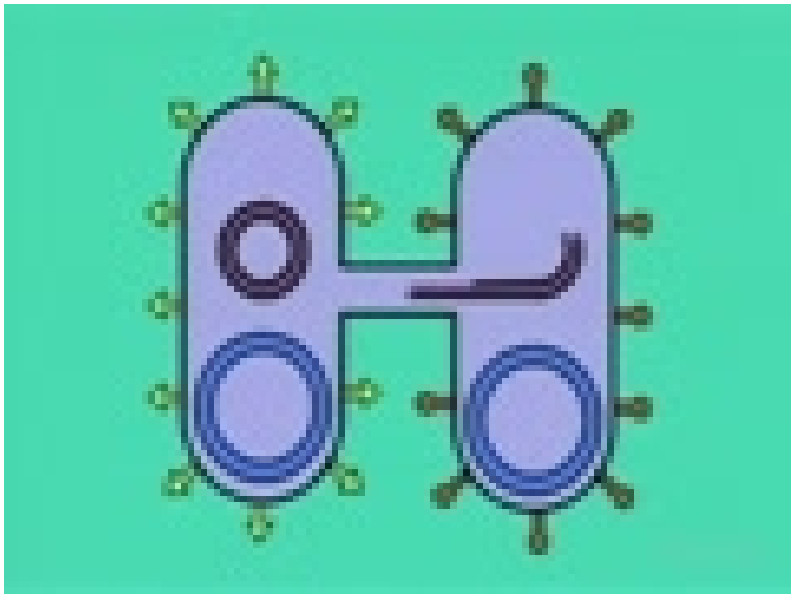
# CAMRSA History

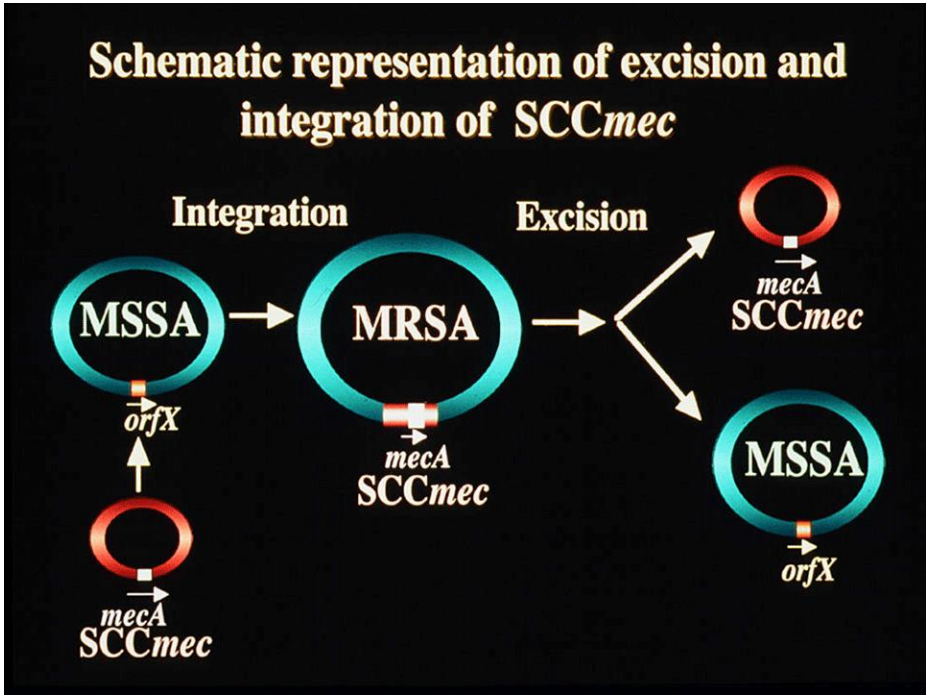
- USA400 caused necrotizing pneumonia in North Dakota and Minnesota in 4 children
- Fulminant infections that caused rapid death
- MRSA soft tissue infections were seen in inmates, homosexuals, athletes
- CAMRSA began to appear in the health care setting
- Difference between CA & HA MRSA has subsequently become less distinct

# SCC*mec* Makes MSSA MRSA

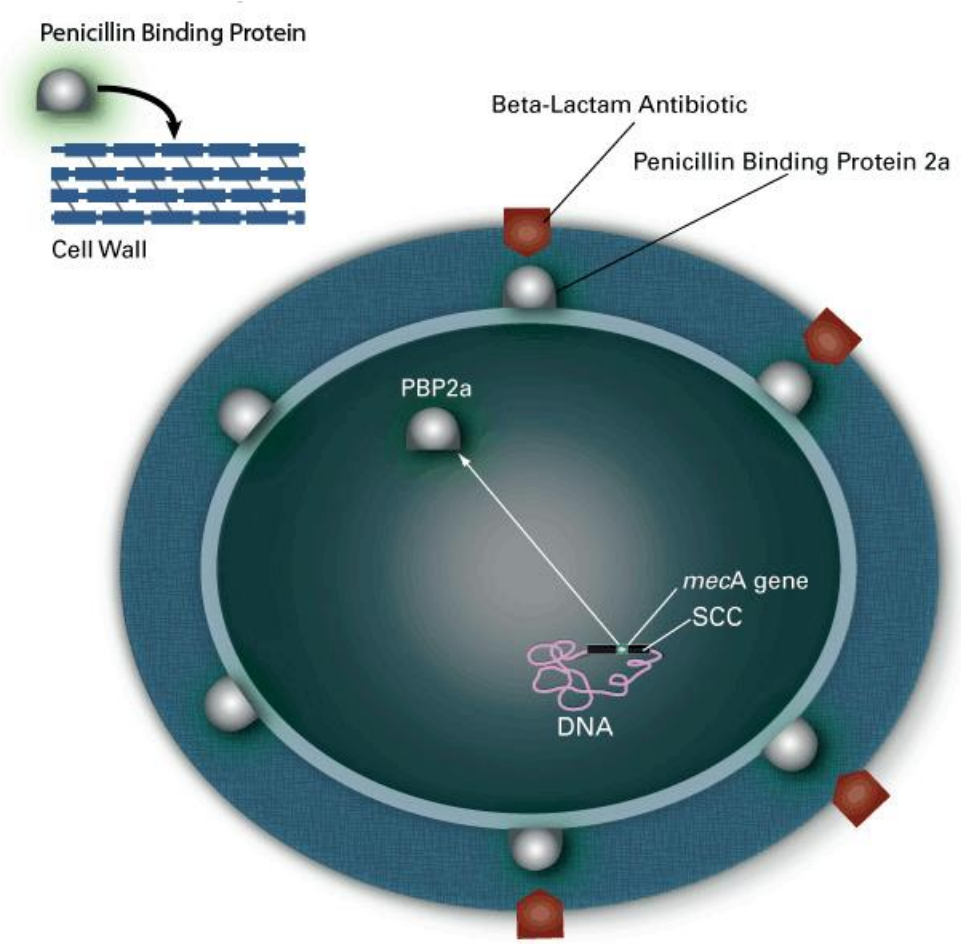
- “Promiscuous gene”
- SCCmec is the gene that causes resistance to methicillin
- Relatively small gene that can be passed between bacteria insighting antibiotic resistance

# Bacterial Congugation

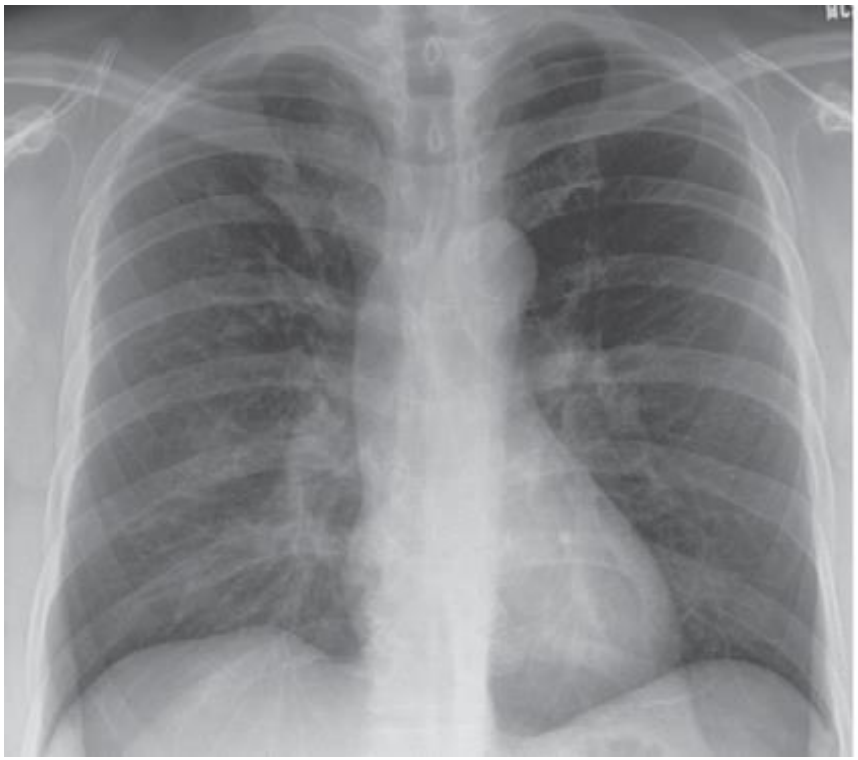


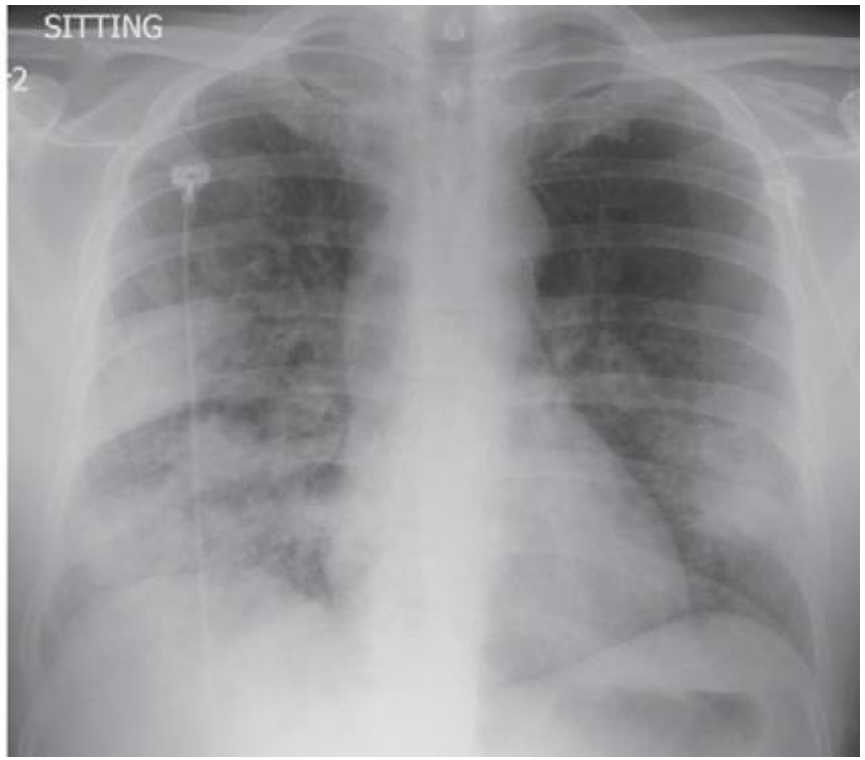


# Penicillin Binding Protein



# Rapidly Progressive CAMRSA Pneumonia

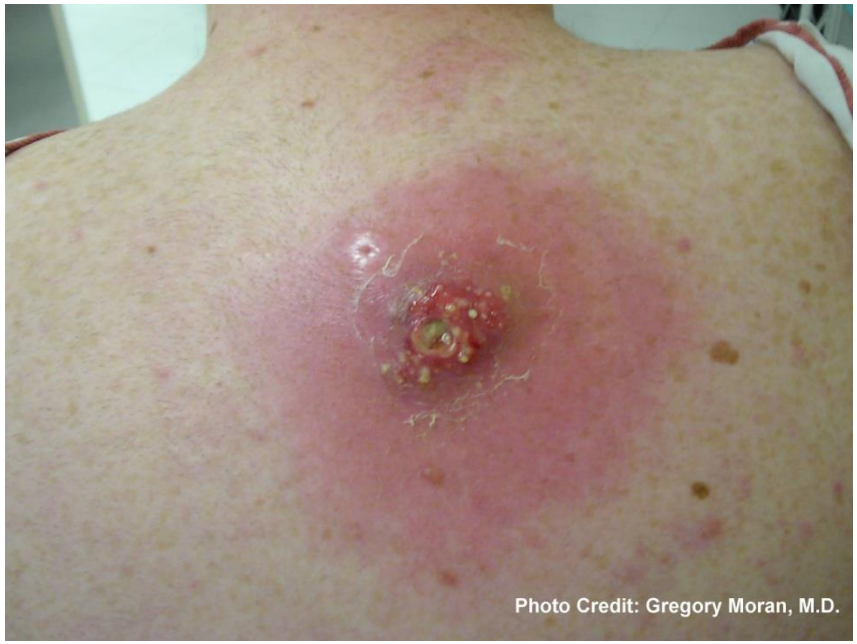





Presents initially with H1N1 that rapidly progressed to CAMRSA pneumonia

# Background of MRSA

- CDC reports that 33% people carry Staph aureus (SA) in their nasal passages
- 2% actually carry MRSA
- HAMRSA events are declining with 30,800 fewer infections between 2005 and 2011
- 9,000 fewer HAMRSA related deaths 2005 & 2011




http://www.cdc.gov/mrsa/tracking/index.html

# Background MRSA

- HAMRSA now being seen in the community
- HAMRSA outside the hospital known as “feral”
- Feral MRSA may be occurring from treating HAMRSA in the home setting

# Risk Factors For MRSA infection

recent hospitalization

indwelling line/catheter

liver, lung or vascular dz.

recent antibiotics

ICU admission

nursing home

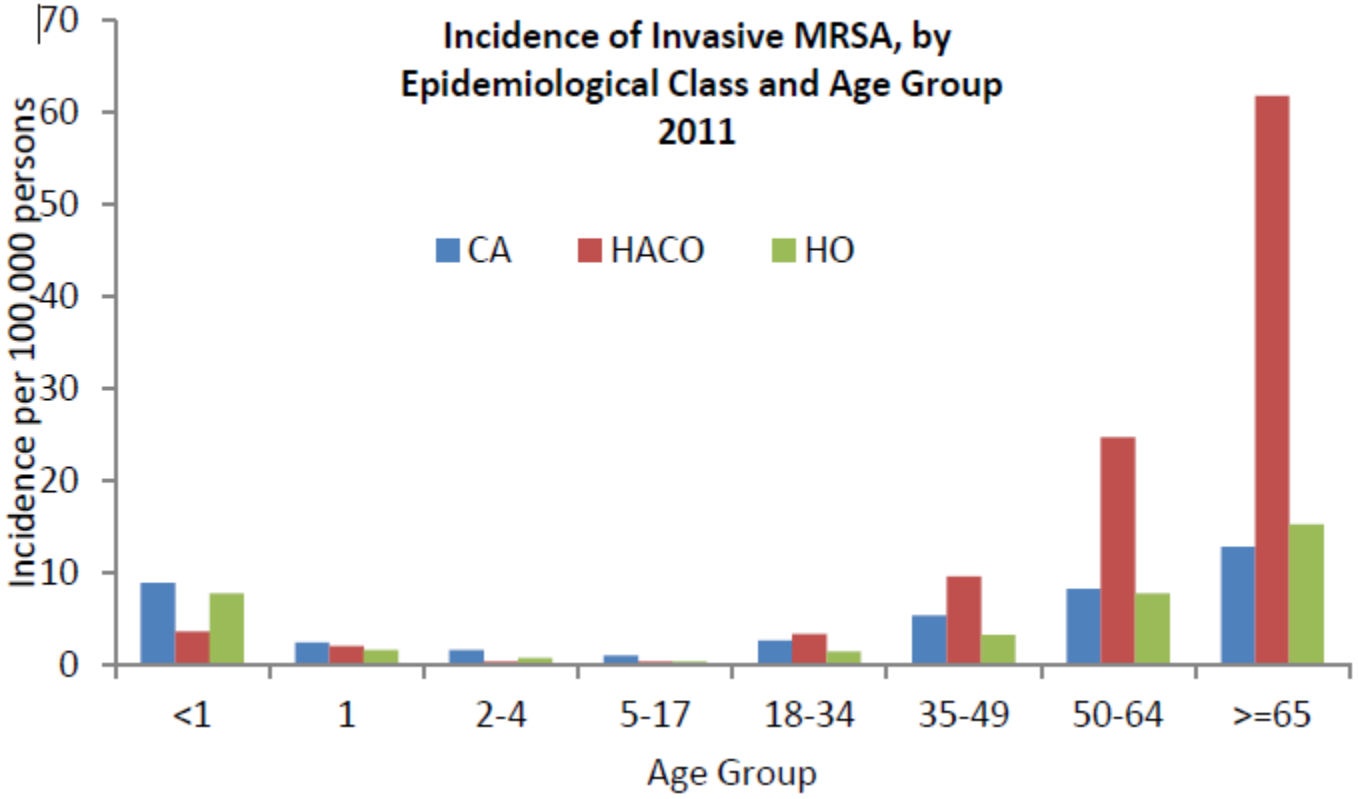
surgical wound

malignancy

IV drug abuse

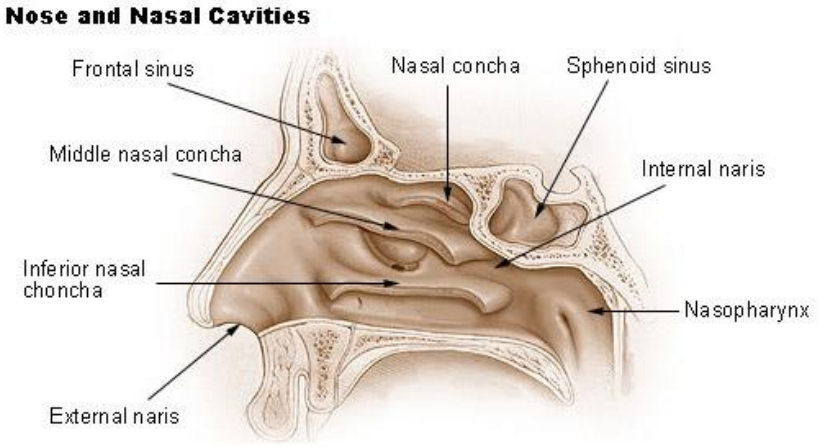
exposure to MRSA

# MRSA Age Related Incidence



# Colonization

- The nares provide a natural harbor for MRSA
- The axillae, groins and GI tract (throat/perirectal area) provide other reservoirs for MRSA
- When the host's immune barriers are breached infection subsequently develops
- Colonization increases the risk of infection*

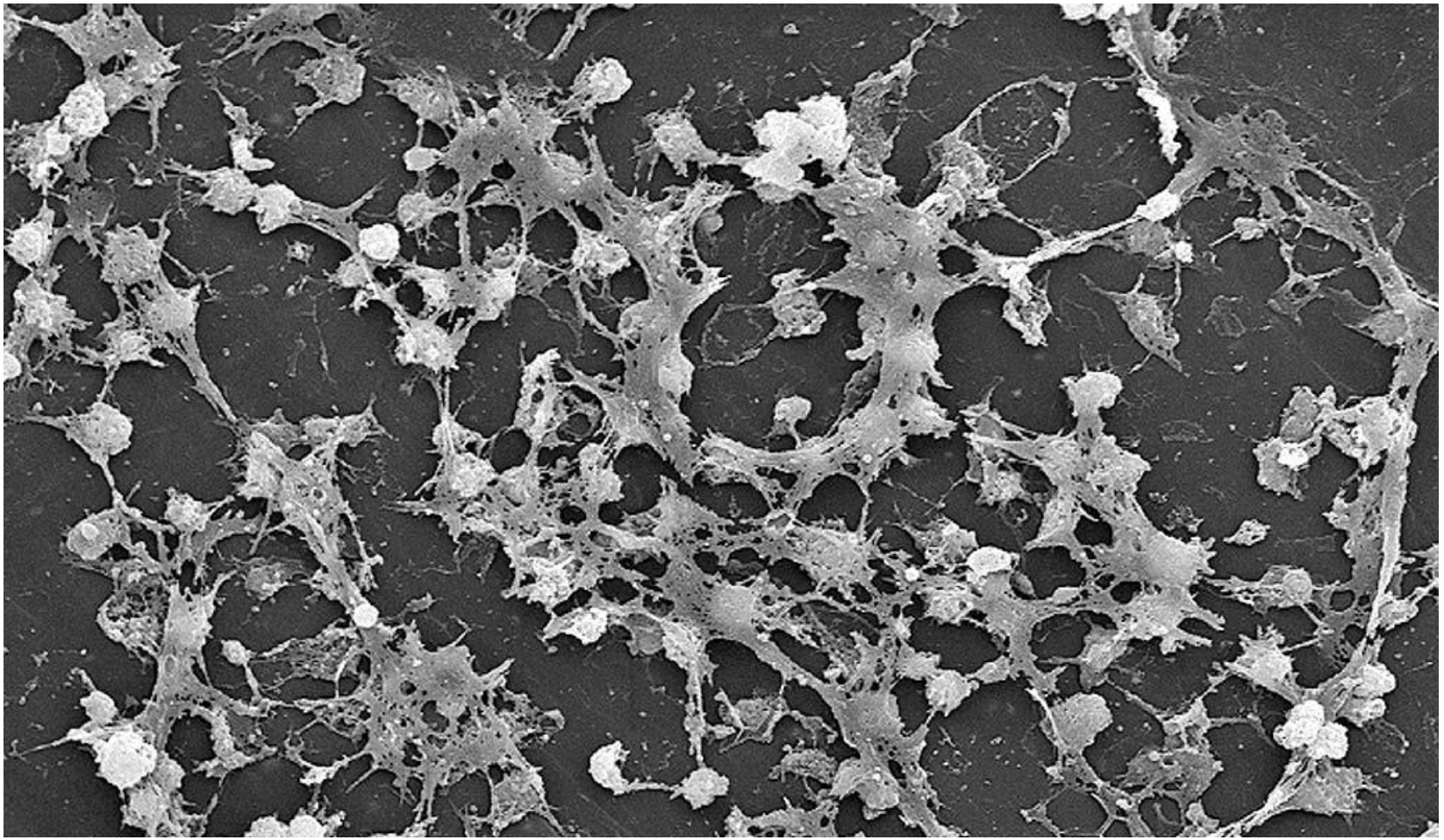



*Wertheim HF. *Lancet Infect Dis 2005;5:751-62.*

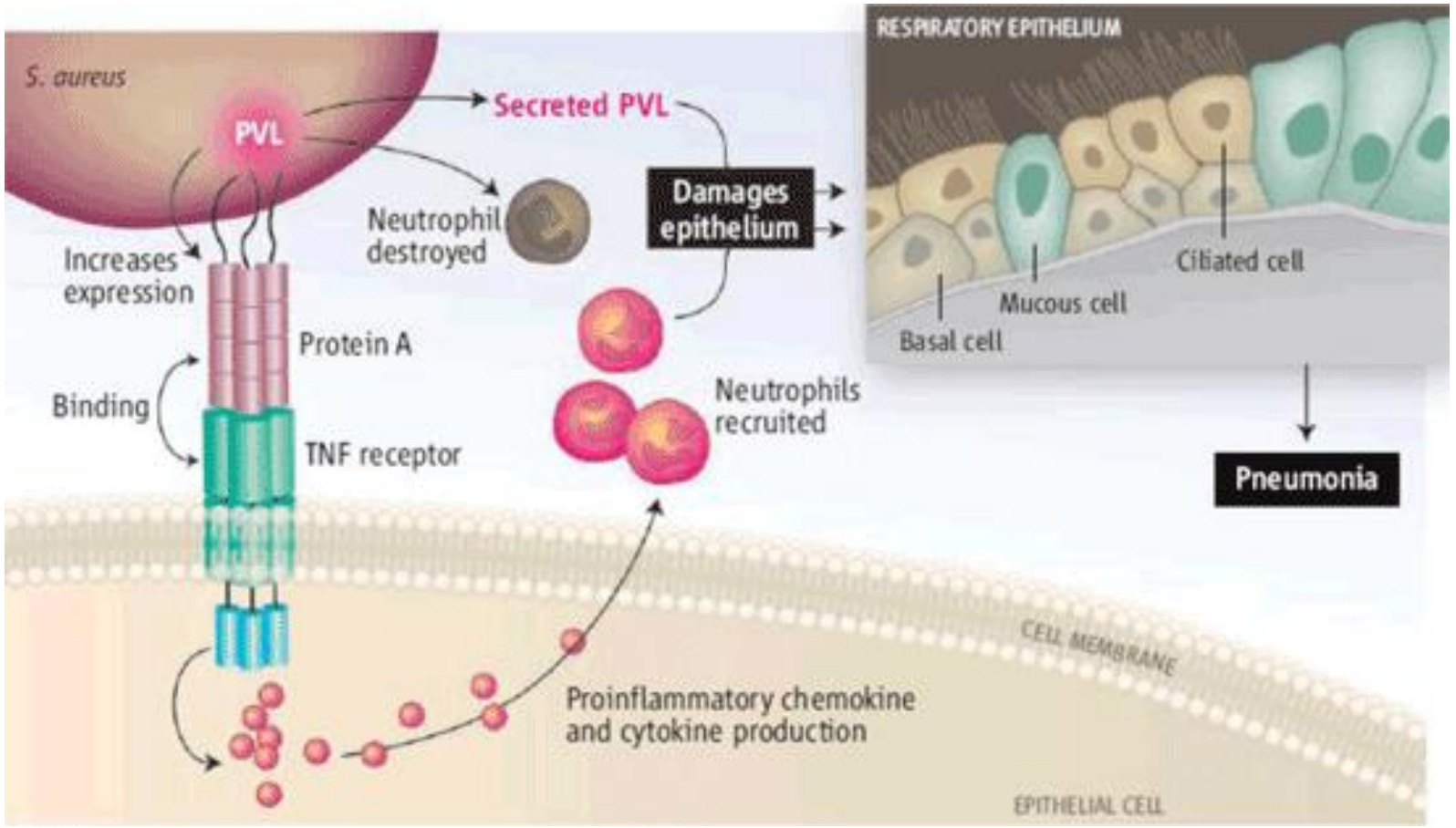
# Pathogenesis and Virulence

- MRSA produces virulence factors that give it different characteristics in the infectious state
- Secreted factors promote toxic effects and tissue invasiveness
- Structural factors provide resistance to antibiotics and biofilm
- Biofilm allows MRSA to cling to tissue and prosthetic material
- Subtypes can hide inside human epithelial cells unrecognized by the host (small colony variants)

# Biofilm



# Virulence Factors



# CAMRSA Versus HAMSSA

| Feature | CA-MRSA | HA-MRSA |
|---|---|---|
| Person affected | Young, healthy person with no recent health care exposure | Previous contact with health care settings (eg, hemodialysis center, nursing home) |
| Type of infection | More common mild to moderate skin and soft tissue infections | Severe, invasive disease in hospitalized patients or in persons in frequent contact with a health care facility |
| Areas commonly affected | Skin and soft tissue, lung | Bloodstream, lung, surgical site, prosthetic implant |
| SCC type | Type IV or V | Type II |
| PFGE type | USA300 or USA400 | USA100 or USA200 |
| PVL gene | Common | Rare |
| Antibiotic resistance pattern | Susceptible to many antibiotics except β-lactams | Multiresistant |

CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus;* HA-MRSA, health care–associated *S aureus*; SCC, staphylococcal cassette chromosome; PFGE, pulsed-field gel electrophoresis; PVL, Panton-Valentine leukocidin.

# MRSA Genetic Subtypes Community Vs. Hospital Acquired

- USA 100-prototypical HAMRSA
- USA 300-now the most common strain of CAMRSA in USA
- USA400/ST1-original CAMRSA probably MSSA that acquired SCC*mec*IV
- USA 1000- originally HAMRSA but now seen in the community contains SCCmecI-III and PVL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Gold Medal Forum Winner:

# *Methicillin-Resistant* Staphylococcus aureus *in a Trauma Population: Does Colonization Predict Infection?*

CHASEN A. CROFT, M.D., VICENTE A. MEJIA, M.D., DONALD E. BARKER, M.D., ROBERT A. MAXWELL, M.D., BENJAMIN W. DART, M.D., PHILIP W. SMITH, M.D., R. PHILLIP BURNS, M.D.

*From the University of Tennessee College of Medicine, Chattanooga Campus, Department of Surgery, Chattanooga, Tennessee*

- GeneOhm™ MRSA assay was used to test for nasal MRSA colonization on admission to the Trauma ICU from 4/07 to 5/08
- 10% of the patient population shown to be colonized with MRSA

Croft CA. Am Surg 2009; 75: 458-461

# Previous Results

- MRSA infections occurred more frequently in the colonized vs. noncolonizedpatients (33.3 vs. 6.6%, $p<0.001$)
- Mortality was higher in higher in colonized vs. noncolonized patients (22.2 vs 5.0%, $p<0.001$)

Croft CA. Am Surg 2009; 75: 458-461

# Decolonization Protocol

- All trauma patients admitted to the ICU at EMC, Chattanooga screened for MRSA using GeneOhm™ nasal swab
- Following positive assay, swabs were plated out and subsequently stored at -80°C
- Patients with positive assay randomized to chlorhexidine gluconate (CHG) bath and mupirocin (MUP) ointment to nares vs. soap and water bath and vaseline ointment to nares for five days
- Patients then underwent repeat nasal testing for MRSA with positive results again plated out and stored

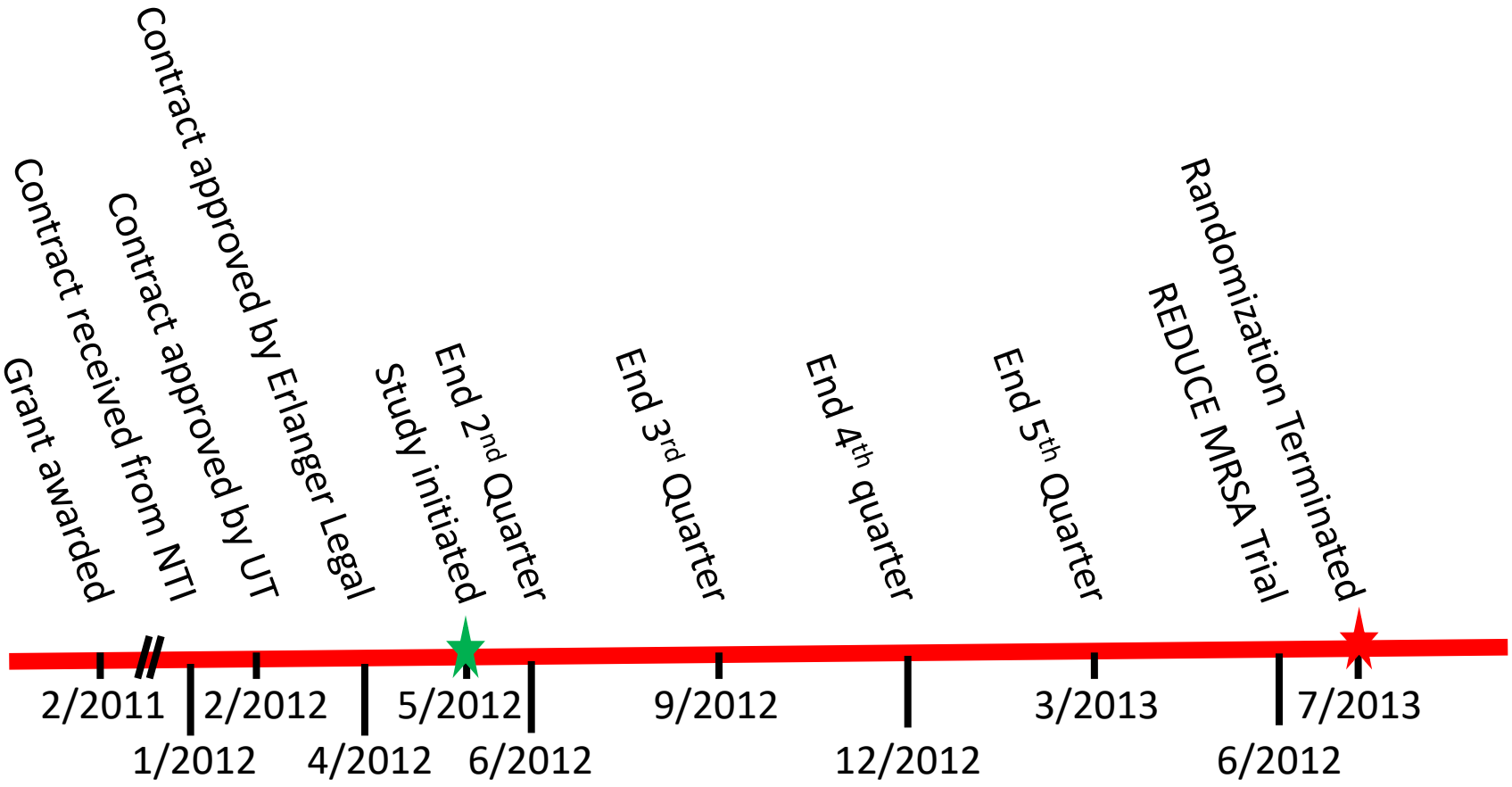
# Decolonization Protocol

- Patients then monitored subsequent infectious sequelae
- Positive MRSA nasal cultures and any subsequent MRSA clinical infection cultures were batched and shipped to Vanderbilt for genomic testing

# Power Analysis

Based on an MRSA infection rate of 33.3% in colonized patients, we predicted that decolonization would reduce the MRSA infection rate to 11%. This reduction predicted that it would require 64 patients per treatment arm to show a significant difference at $p < 0.05$ with 80% power.

# Time Line




**Study Duration = 13 months☹**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2013 VOL. 368 NO. 24

# Targeted versus Universal Decolonization to Prevent ICU Infection

Susan S. Huang, M.D., M.P.H., Edward Septimus, M.D., Ken Kleinman, Sc.D., Julia Moody, M.S., Jason Hickok, M.B.A., R.N., Taliser R. Avery, M.S., Julie Lankiewicz, M.P.H., Adrijana Gombosev, B.S., Leah Terpstra, B.A., Fallon Hartford, M.S., Mary K. Hayden, M.D., John A. Jernigan, M.D., Robert A. Weinstein, M.D., Victoria J. Fraser, M.D., Katherine Haffenreffer, B.S., Eric Cui, B.S., Rebecca E. Kaganov, B.A., Karen Lolans, B.S., Jonathan B. Perlin, M.D., Ph.D., and Richard Platt, M.D., for the CDC Prevention Epicenters Program and the AHRQ DECIDE Network and Healthcare-Associated Infections Program*

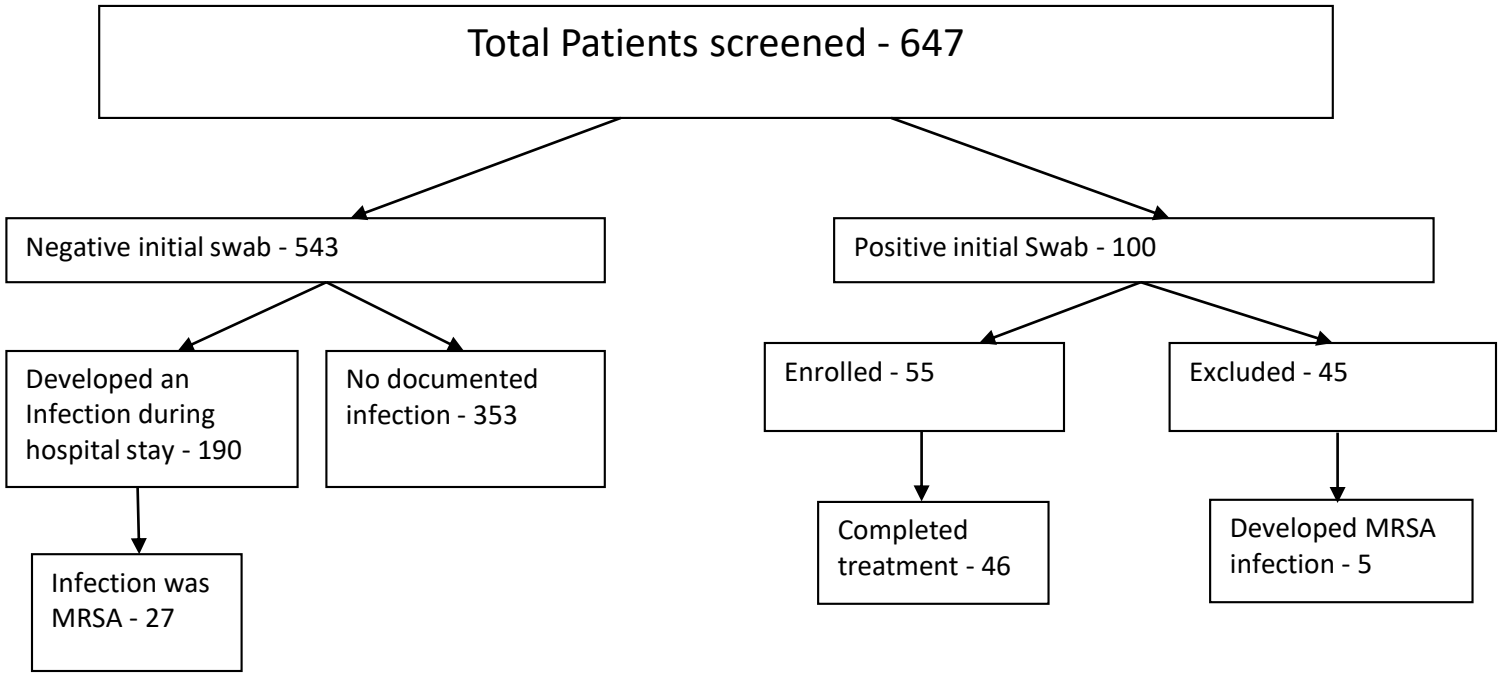
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2013 VOL. 368 NO. 24

# Targeted versus Universal Decolonization to Prevent ICU Infection

- Universal decolonization reduced incidence of positive MRSA cultures and bacteremia from all cause organisms better than screening and decolonization or screening and contact precautions
- Ushered in universal decolonization with CHG as standard of care for all patients admitted to the ICU

# Results


Total Patients screened - 647
Negative initial swab - 543
Positive initial Swab - 100
Developed an Infection during hospital stay - 190
No documented infection - 353
Enrolled - 55
Excluded - 45
Infection was MRSA - 27
Completed treatment - 46
Developed MRSA infection - 5

# Overall Incidence of MRSA Infection

Analysis of all nasal swab(+) patients compared to all nasal swab(-) patients confirmed a strong association between carrier status and subsequent MRSA infection

| MRSA Infection | Swab(+) | Swab(-) | P value |
|---|---|---|---|
| Yes | 32*(32) | 27*(5.2) | <0.001 |
| No | 68 | 516 | |
| Total | 100 | 543 | |

# Reasons for Exclusion

| Reason Excluded | No MRSA Infection | MRSA Infection |
|---|---|---|
| Declined | 7 | 1 |
| ICU < 72° | 18 | 1 |
| Institutionalized | 7 | 1 |
| Age | 1 | NA |
| Previous MRSA | NA | 2 |
| Withdrawal/Expired | 7 | NA |
| Total (%) | 40 (89) | 5 (11) |

# Demographic Data

| | Soap/Vaseline | CHG/MUP | P -value |
|---|---|---|---|
| Total | 20 | 34 | NS |
| Age (SD) | 47.9±16.4 | 47.6±17.4 | NS |
| Intubated ER/EMS (%) | 16 (80) | 22 (64.7) | NS |
| Blunt (%) | 19 (95) | 31 (91.2) | NS |
| ISS (SD) | 30.4 ± 10.8* | 24.7 ± 11.0* | 0.032 |
| APACHE II (SD) | 19.3 ± 5.4 | 16.9 ± 5.9 | 0.20 |
| GCS (SD) | 7.9 ± 5.1 | 8.2 ± 5.0 | NS |
| Total Length of Stay | 13.7 ± 11.2 | 15.3 ± 13.5 | NS |
| Days to 1st MRSA Infection | 9.1 ± 7.4 | 9.8 ± 11.6 | NS |
| MRSA Infection (%) | 6(30) | 8 (23) | NS |

# Second Swab Positive (after decolonization procedure)

| Group | Negative | Positive | Not Applicable |
|---|---|---|---|
| Soap & Vaseline (%) | 5 (35) | 9 (65) | 6 |
| CHG/MUP (%) | 15 (50) | 15 (50) | 4 |

# Patients with MRSA Infections

| # Pt's | Group | Subtype Swab 1 | Swab 2 MRSA | Subtype Swab 2 | MRSA infection |
|---|---|---|---|---|---|
| 1 | CHG | USA 300 | Negative | n/a | USA100/300 |
| 2 | CHG | MSSA | Negative | n/a | Pending |
| 1 | CHG | USA 1000 | Positive | USA 1000 | USA 1000 |
| 1 | CHG | USA 1000 | Positive | USA 300 | Pending |
| 1 | CHG | USA 300 | Positive | USA 1000 | USA 300 |
| 2 | CHG | Pending | Negative | n/a | Pending |
| 4 | Soap | USA 1000 | Positive | USA 1000 | USA 1000 |
| 1 | Soap | USA 100 | Positive | USA 100 | USA 100 |
| 1 | Soap | USA 300 | Positive | USA 300 | USA 300 |

# ALL Cause Gram(-) AND Gram(+) Infections

| Infection | Soap/Vaseline | CHG/MUP | P value |
|---|---|---|---|
| Total patients | 20 | 34 | NS |
| # Completed TX | 14 | 30 | NS |
| Pneumonia (%) | 5 (25.0) | 11 (32.3) | NS |
| UTI (%) | 2 (10.0) | 3 (8.8) | NS |
| Wound (%) | 2 (10) | 1 (2.9) | NS |
| Blood (%) | 2 (10) | 1 (2.9) | NS |
| Total (%) | 11 (55.0) | 16 (47.0) | .184 |

# Discharge Status

| Place | Soap/Vaseline | CHG/MUP | P value |
|---|---|---|---|
| Home (%) | 2 (10.0) | 14 (41.0) | NS |
| Rehab (%) | 7 (35.0) | 12 (35.0) | NS |
| SNF (%) | 4 (20.0) | 4 (12.0) | NS |
| Other | NA | 1 (3.0) | NS |
| Mortality | 7 (35.0)* | 3 (8.8)* | 0.028 |
| Cause | | | |
| TBI (%) | 6 (85.0) | 2 (66.7) | NS |
| ARDS (%) | NA | 1 (33.3) | NS |
| MSOF (%) | 1 (15.0) | NA | NS |

# Conclusions

- First attempt to look at MRSA decolonization exclusively in a trauma population.
- Trauma volumes were lower than anticipated, study duration was shortened by almost 50%, and exclusion rates were higher than predicted limiting number of patients eligible for enrollment.
- Randomization terminated after a larger study showed that universal decolonization with CHG is effective in reducing MRSA and all cause ICU bloodstream infections.

# Conclusions

- Colonization rates are higher (15.4%) than our previous study (10.0%) reflecting possible growing incidence of MRSA in the community
- MRSA infection rates in patients colonized with MRSA at admission are higher (32%) than non-carriers (5.0%) and may be lowered by decolonization

# Conclusions

- Decolonization with CHG/MUP in this study eliminated MRSA from the nasal passages approximately 50% of the time
- There was a trend that decolonization with CHG and MUP reduces subsequent all cause infection in trauma patients but did not reach significance due to small sample size

# Conclusions

- Growing concern now exists for CHG and MUP resistance
- Some MRSA subtypes have genes that may confer resistance to CHG or MUP
- Plasmid encoded efflux pump genes known as qac A/B and smr have been reported in up to 18.5% of randomly selected MRSA isolates

Johnson JG. Infect Cont Hosp Epidemiology. 2013; 34: 1325-27.

# CHG Resistance Patterns in MRSA

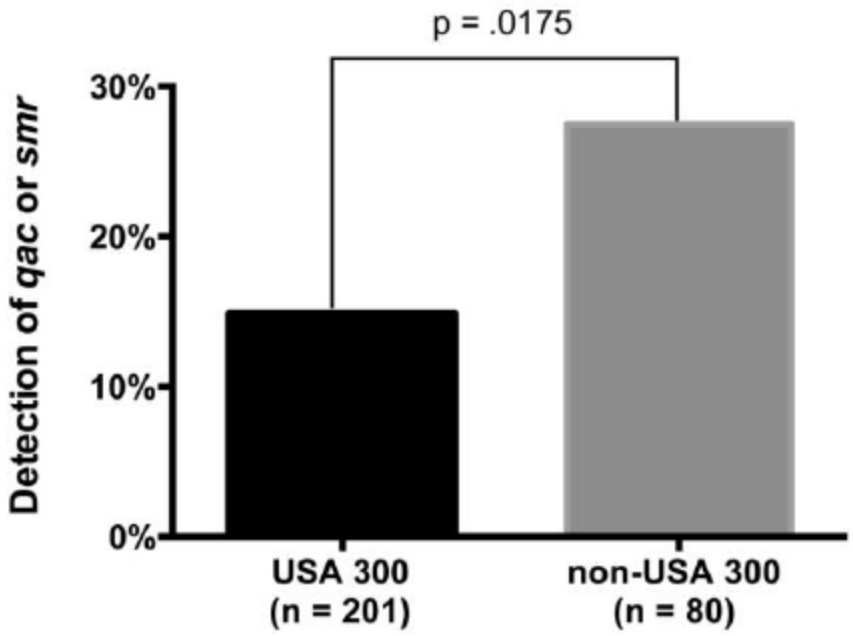



FIGURE 1. Presence of disinfectant resistance genes *smr* and *qac A/B* by methicillin-resistant *Staphylococcus aureus* pulse type. Non-USA300 isolates were more likely than USA300 isolates to harbor *smr* or *qacA/B* ($P = .0175$).

# Future Directions

- Further research efforts should focus on:
  - the utility of MUP in clearing the nasal passages of MRSA perhaps with an aerosolized route
  - Further surveillance of CHG and MUP resistance patterns
  - Areas that harbor MRSA such as the anorectal area, axillae and deeper within the areodigestive tract need further evaluation
- A randomized trial studying the efficacy of MUP seems like the next step to take

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# CDC's Five "C's" of MRSA Transmission

- **Crowding**
- Frequent skin to skin **Contact**
- **Compromised** skin integrity
- **Contaminated** surfaces
- Lack of **Cleanliness**

# Previous Results

TABLE 2. *Rates of Methicillin-Resistant* Staphylococcus aureus *Infections by Location*

| | Noncolonized | Colonized | *P* |
|---|---|---|---|
| Total umber infected (%) | 21 (6.6) | 12 (33.3) | <0.001 |
| Pneumonia (%) | 12 (57.1) | 8 (66.7) | NS |
| Urinary tract infection (%) | 1 (4.8) | 0 (0) | NS |
| Bacteremia (%) | 1 (4.8) | 0 (0) | NS |
| Skin/soft tissue (%) | 4 (19) | 1 (8.3) | NS |
| Intra-abdominal (%) | 2 (9.5) | 0 (0) | NS |
| Multisite (%) | 1 (4.8) | 3 (25.0) | NS |

NS, not significant.

# Filtration lesions impair functional coagulation in banked whole blood

**UCLA Department of Surgery, Hematology and Laboratory Medicine**

**Sigrid Burruss M.D., Terry Gruber M.S., Alyssa Ziman M.D., Victor Marder M.D., Gill Cryer M.D. Ph.D**

# Haemostatic Resuscitation

- **Current massive transfusion protocols utilize red blood cells, plasma, and platelets in a 1:1:1 ratio**
- **Reconstituted whole blood has been used in the military with remarkable results**
- **Whole blood is not routinely available in US blood banks**

# Warm Whole Blood

- **Advantages**
  - **More equivalent to lost blood**
  - **Smaller volume**
  - **More functional product**
  - **Decreased number of donor exposures**
- **Disadvantages**
  - **Short shelf life**

# Specific Aims

- **Determine if coagulation impairment occurs over time in filtered whole blood**
- **Determine if there are differences in levels of coagulation parameters between filtered and unfiltered units of blood**

# Methods

- Volunteer blood donors
- Seven units of filtered and seven units of unfiltered whole blood
- Stored at 4ºC
- Tested samples on day 0 (day of collection) 1, 2, 3, 4, 5, 6, 7, 10, 14, 21, 28, and 35

# Analysis

- Coagulation markers (Fibrinogen, Factor II, V, VII, VIII, IX, and X)
- Thromboelastogram (TEG)
- Calibrated Automated Thrombogram (CAT)
- t-test and mixed model regression analysis

# Fibrinogen

| 200-400 mg/dL | Filtered | Unfiltered |
|---|---|---|
| Day 0 | 188±82 | 244±150 |
| Day 2 | 188±10 | 256±142 |
| Day 10 | 232±92 | 277±134 |
| Day 28 | 202±50 | 265±100 |
| Day 35 | 231±46 | 252±124 |

- No significant difference between filtered and unfiltered whole blood (p=0.5)
- No significant difference over time in both filtered (p=0.2) and unfiltered (p=0.8) whole blood

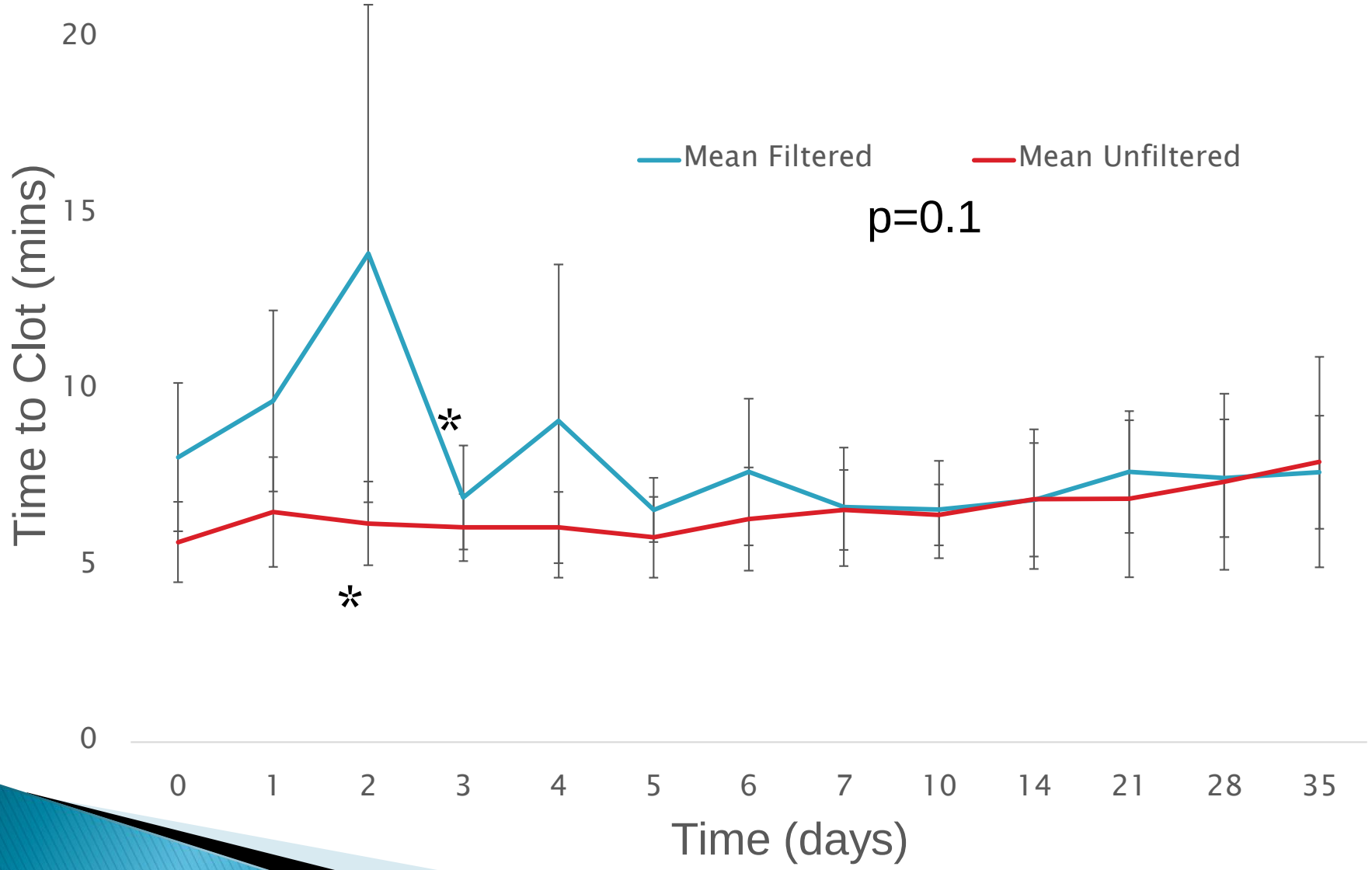
# Mean Changes in Coagulation Factors

| | Filtered | Unfiltered | p |
|---|---|---|---|
| **Factor II 70-120%** | | | |
| day 0 | 69±8 | 65±21 | 0.9 |
| day 35 | 60±7 | 58±7 | |
| **Factor VII 55-170%** | | | |
| day 0 | 55±18 | 68±28 | 0.2 |
| day 35 | 45±12 | 65±29 | |
| **Factor IX 60-150%** | | | |
| day 0 | 74±15 | 76±40 | 0.7 |
| day 35 | 67±19 | 51±13 | |
| **Factor X 70-120%** | | | |
| day 0 | 74±24 | 69±20 | 0.7 |
| day 35 | 58±8 | 65±14 | |

# Mean Changes in Coagulation Factors

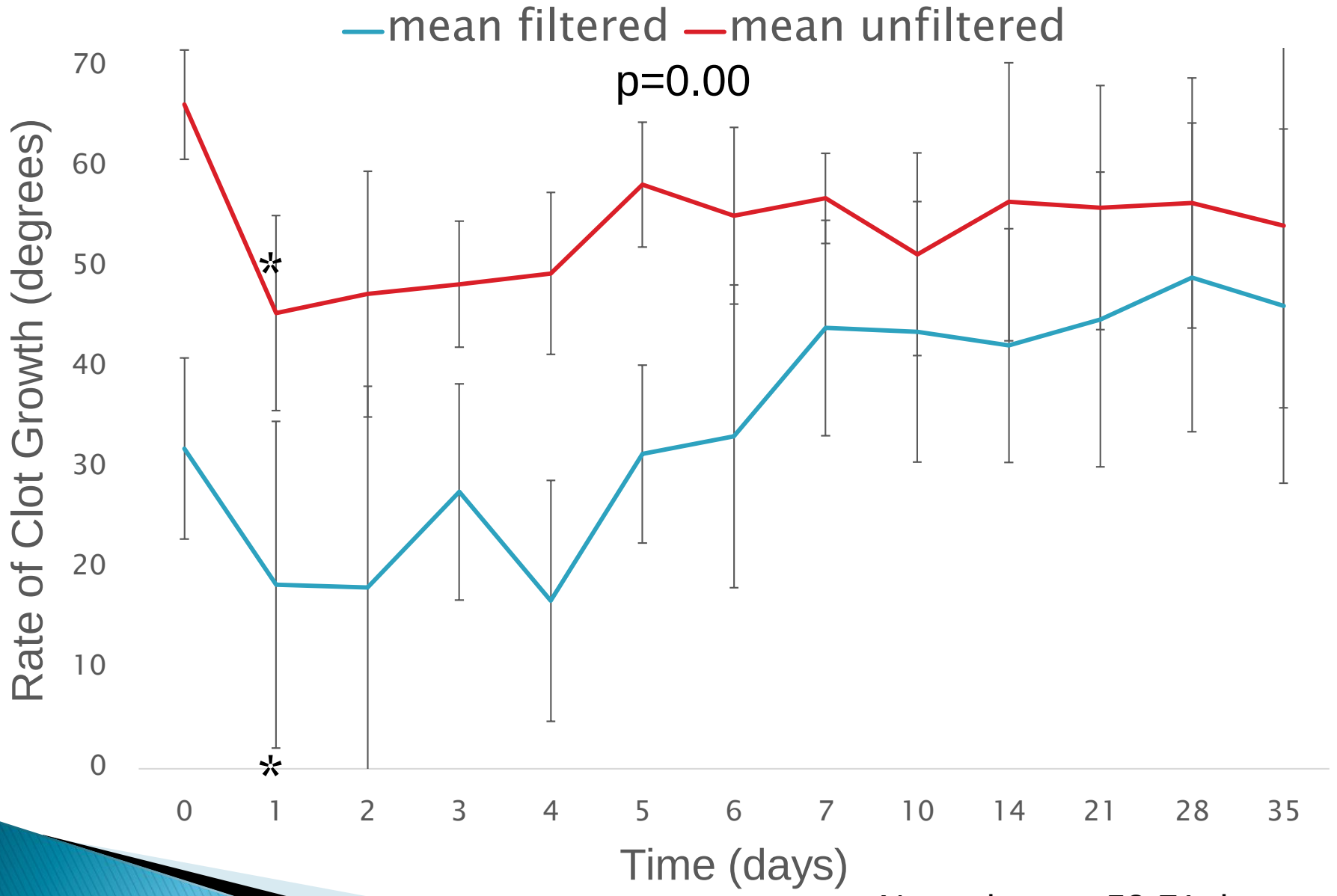
| | Filtered | Unfiltered | p |
|---|---|---|---|
| Factor V 70-120% | | | |
| day 0 | 63±46 | 71±20 | 0.5 |
| day 35 | 54±20 | 16±7 | |
| Factor VIII 60-150% | | | |
| day 0 | 97±39 | 80±59 | 0.5 |
| day 35 | 50±31 | 21±16 | |

# TEG R: Filtered blood has a clinically significant increase in R at day 2



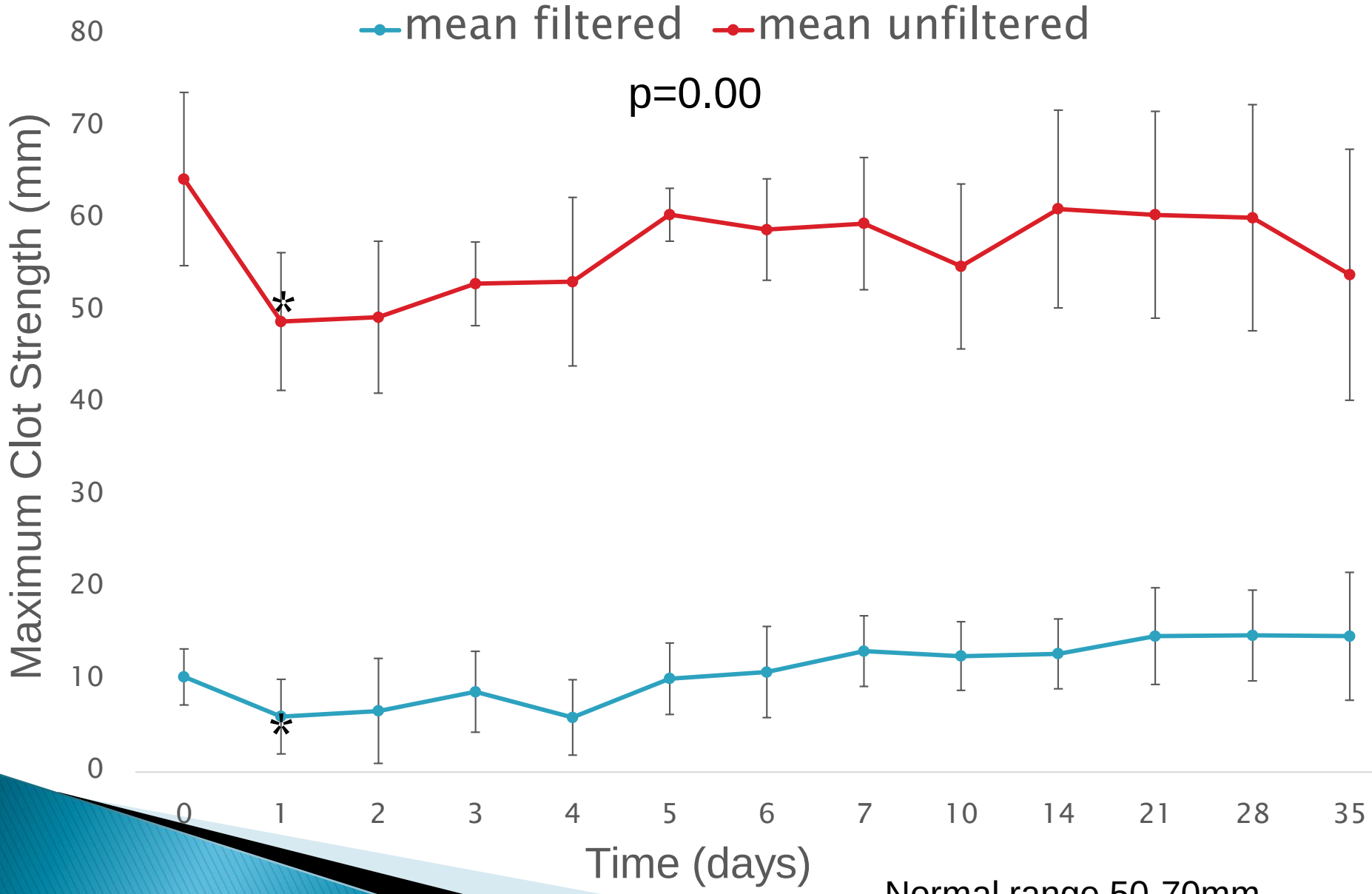

Normal range 5-10mins

# TEG Angle: Filtered blood is below normal range



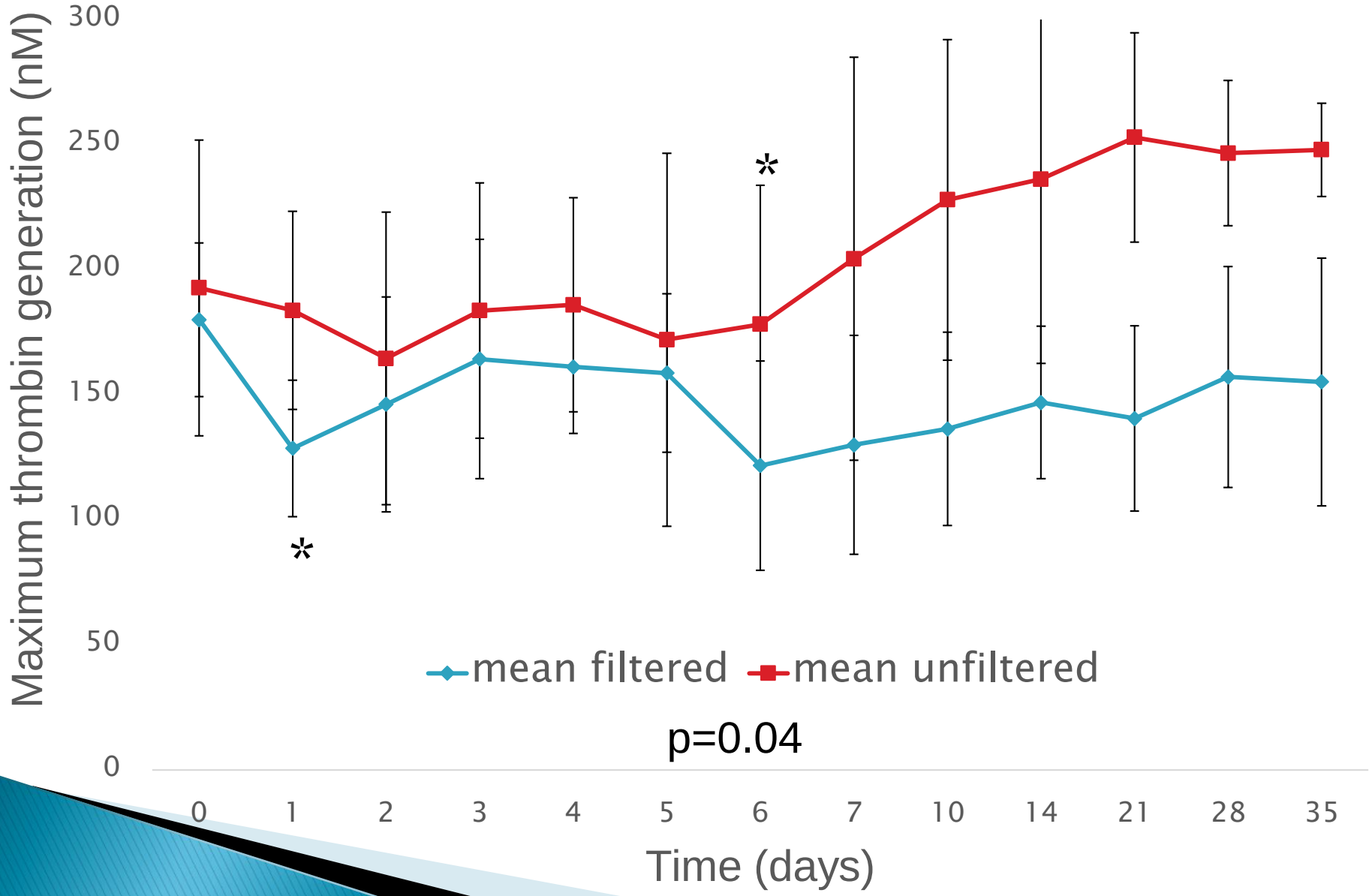

Normal range 53-71 degrees

# TEG MA: Filtered blood is below normal range

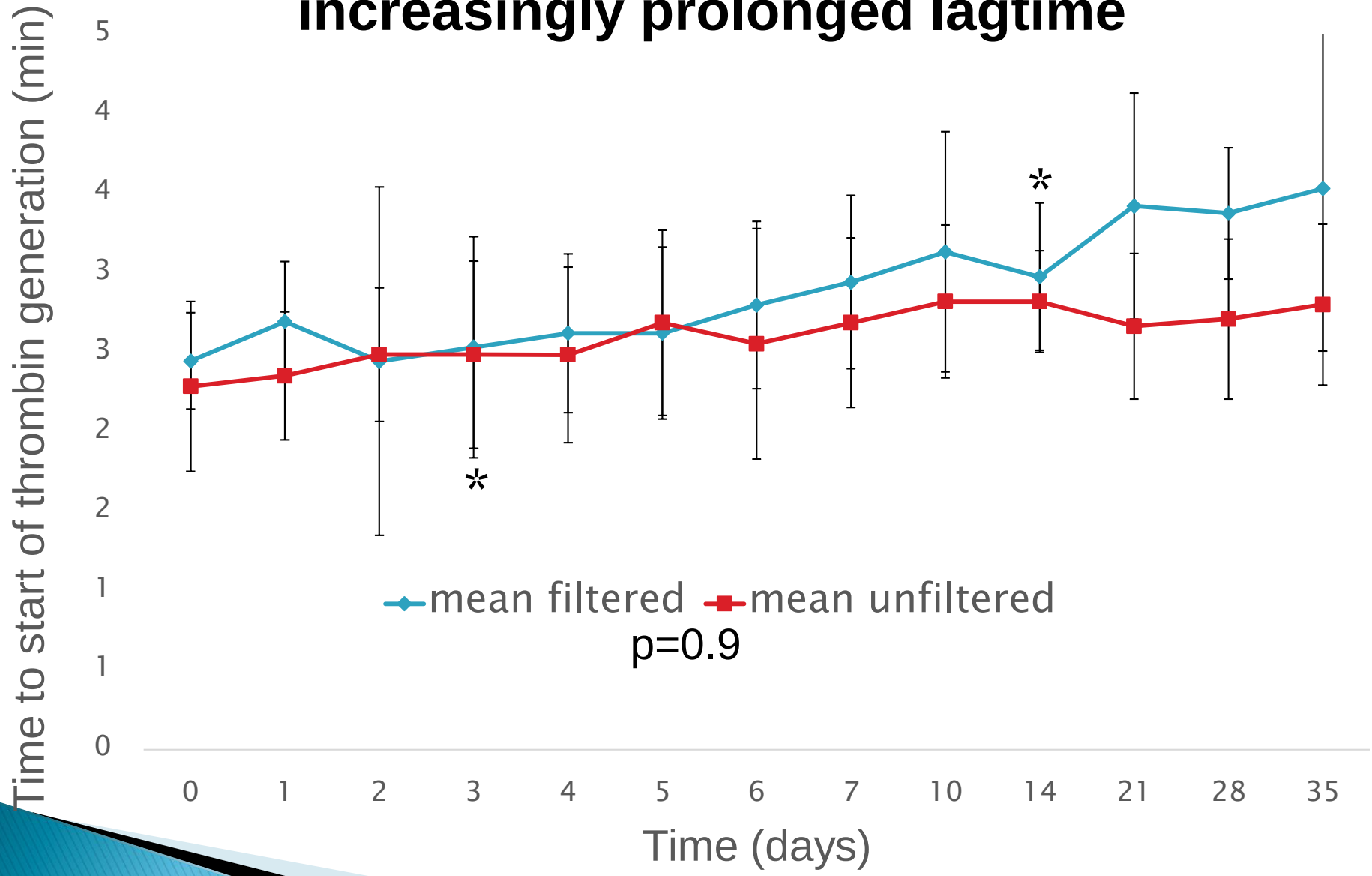



Normal range 50-70mm

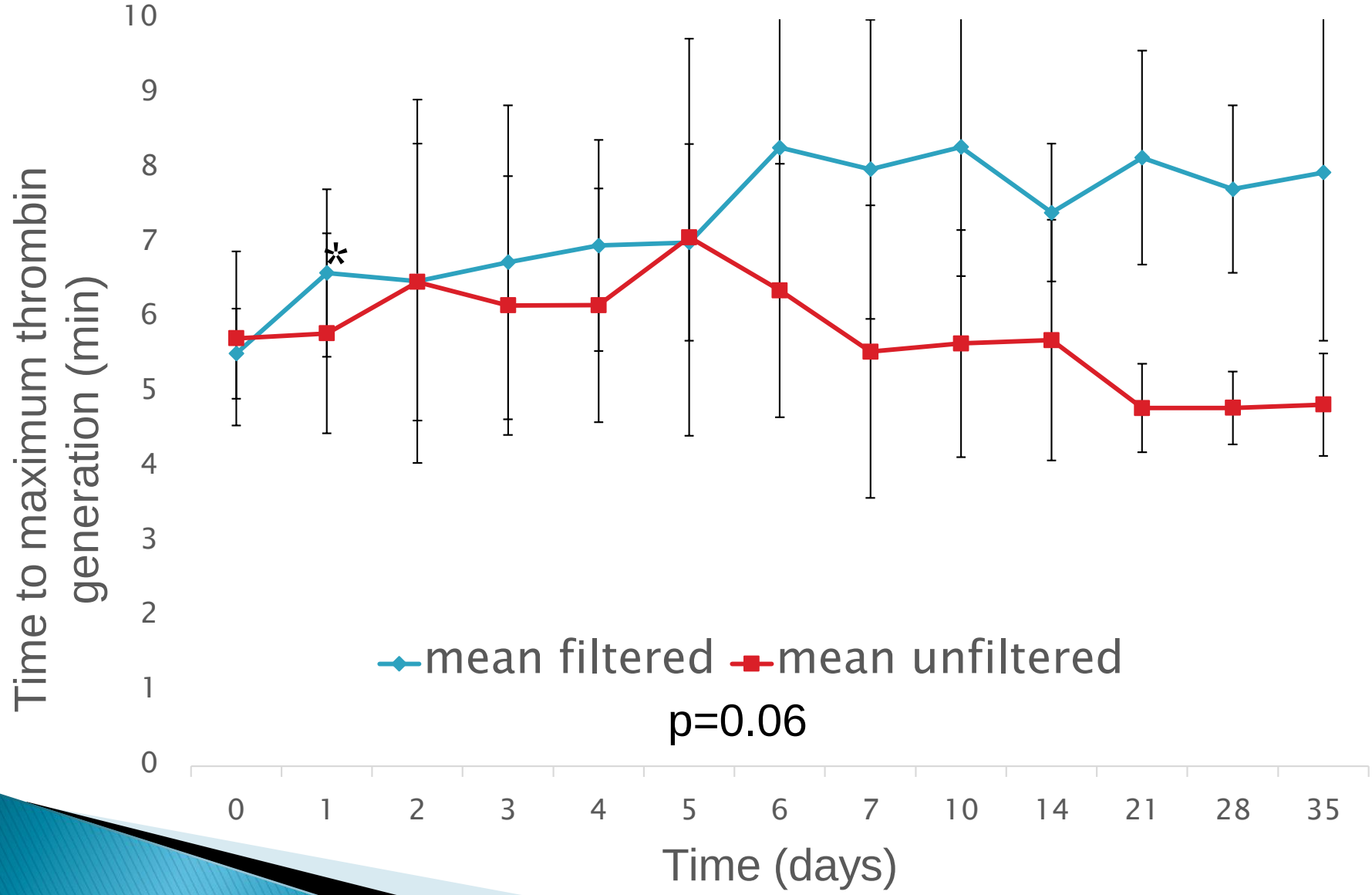
# CAT Cmax: Filtered blood has a statistically significant drop in Cmax at day 1



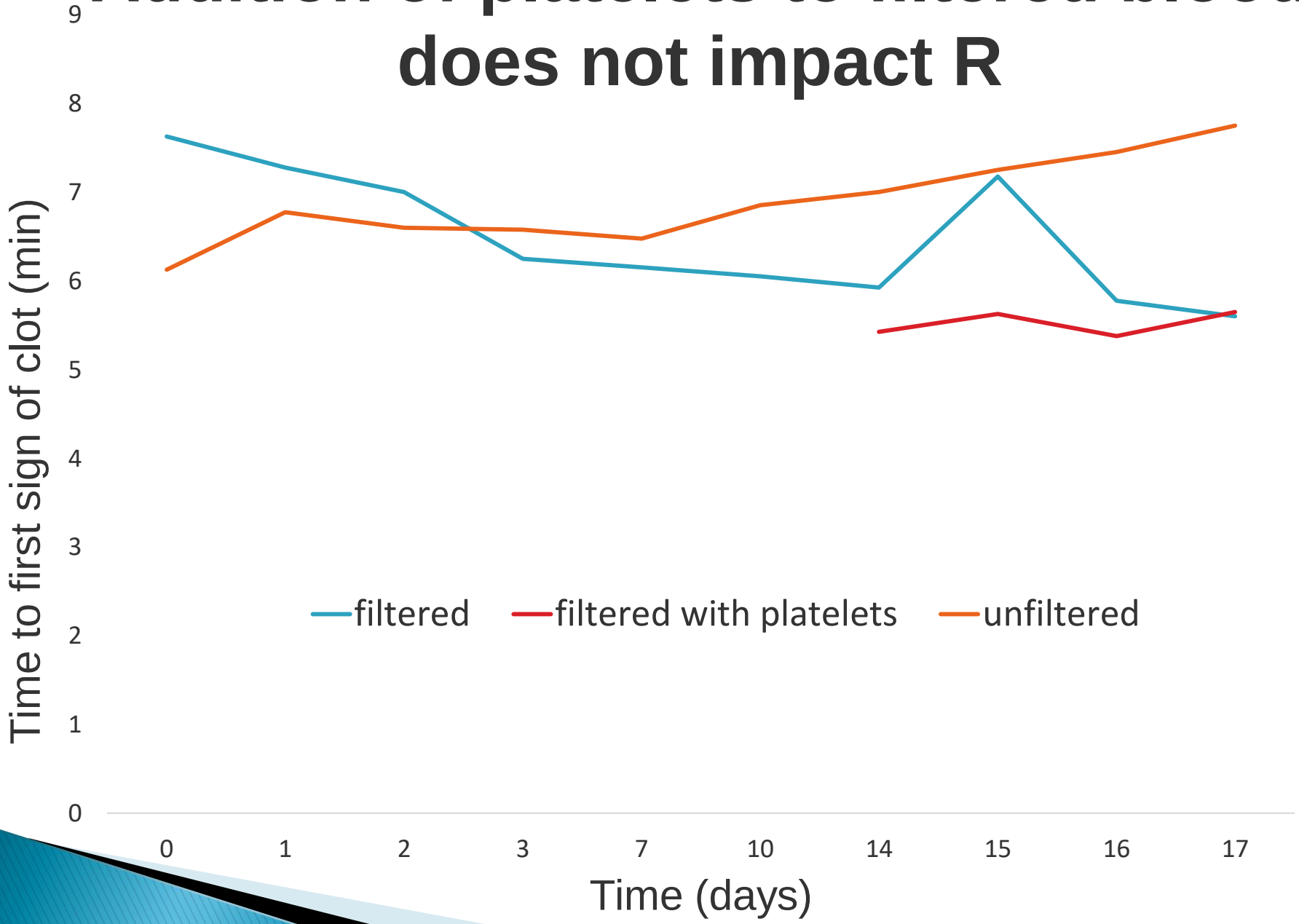
# CAT lagtime: Filtered blood has an increasingly prolonged lagtime



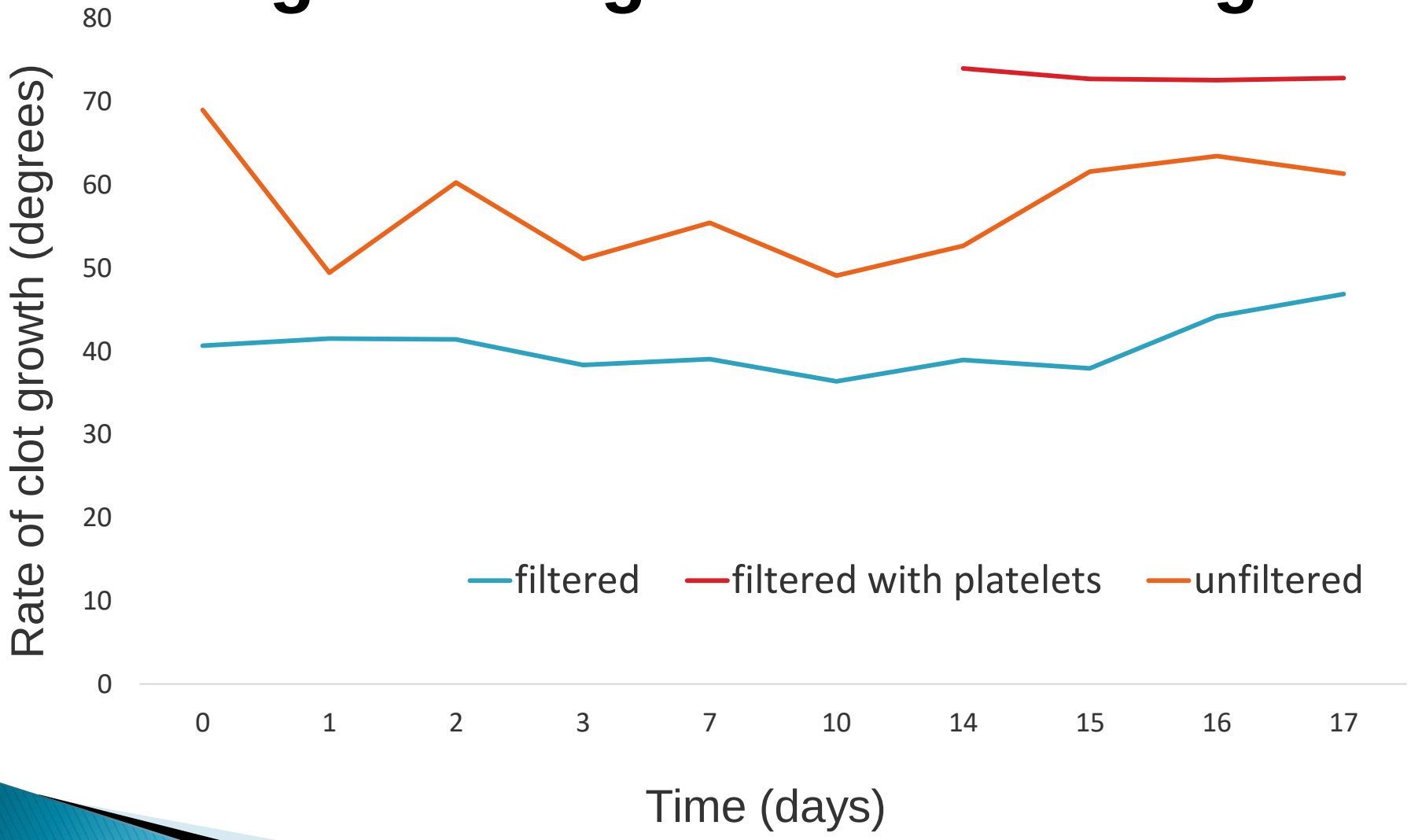
# CAT Tmax: Filtered blood has a significant increase in Tmax starting at day 1



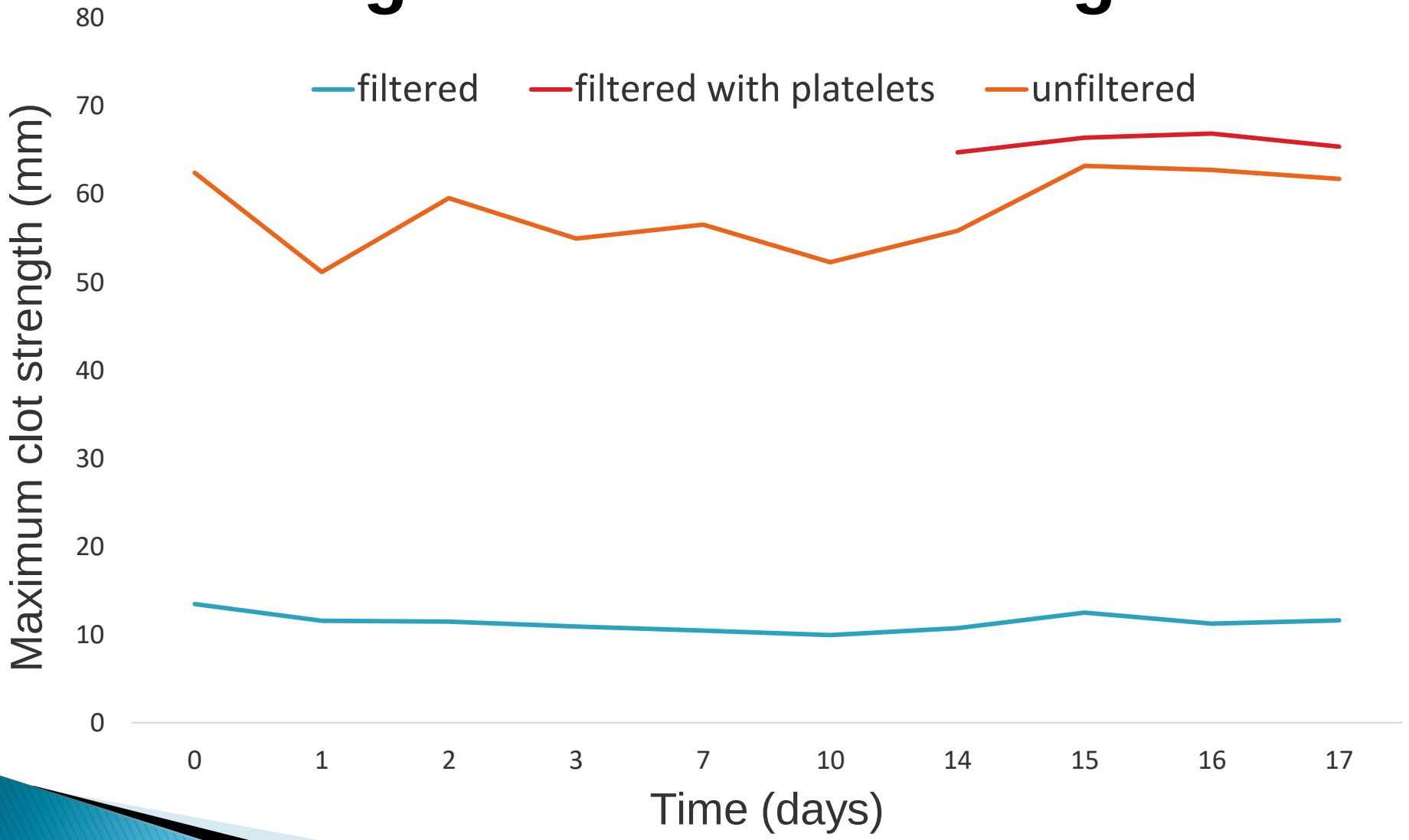
# Addition of platelets to filtered blood does not impact R



# Addition of platelets to filtered blood brings the angle to normal range



# Addition of platelets to filtered blood brings MA to normal range



# Summary of Results

- **Fibrinogen levels are low normal with no difference over time or between filtered and unfiltered**
- **Coagulation factor levels are similar between filtered and unfiltered but are better preserved in filtered units**
- **Filtered blood has significantly lower maximum clot strength, smaller rate of clot growth, and lower maximum thrombin generation**
- **Filtered blood has an increased time to maximum thrombin generation at day 1 and increased time to start of thrombin generation at day 14**

# Stored Whole Blood

- **Counts 1979: Clotting factors in modified whole blood remain >50% at 21 days of storage at 4º C except for Factor V and VIII**
- **Nillson 1983: Little deterioration over 2 weeks in coagulation factors in whole blood stored at 4º C with the exception of Factor VIII**
- **Jobes 2010: TEG does not change until after day 14 in refrigerated whole blood.**

# Conclusion

- **Filtered blood has a filtration lesion resulting in a coagulopathic product**
- **Filtered whole blood has some decrease in clotting capability over 35 days with individual parameters changing as early as day 1**
- **Platelet transfusion may correct the filtration lesion seen in filtered stored whole blood**
- **Additional studies are needed to determine the exact timing and ratio of platelet transfusion required**

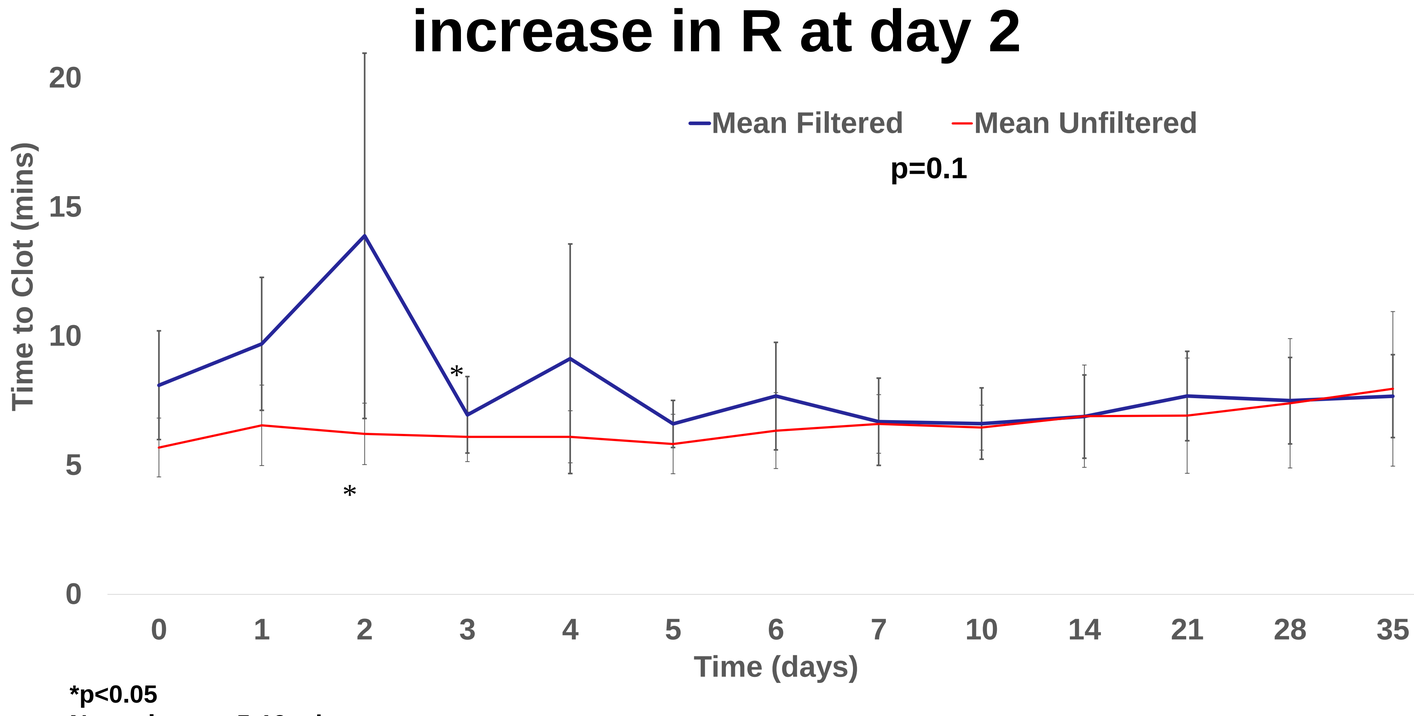
# Filtration lesions impair functional coagulation in banked whole blood

H Cryer, S Burruss, T Gruber, V Marder

**INTRODUCTION:** Whole blood (WB) has been proposed as the ideal product for hemostatic resuscitation, but the shelf life and coagulation function have not been determined in leukoreduced banked whole blood. We hypothesized that coagulation impairment occurs during storage in filtered and unfiltered refrigerated WB.
**METHODS:** Seven donated WB units underwent leukocyte filtration and 7 did not. Units were stored at 4°C and sampled for 35 days for thromboelastogram (TEG) and centrifuged and stored at -80°C for later Calibrated Automated Thrombogram (CAT) and coagulation factor tests. Results were analyzed using t-test and mixed model regression analysis.
**RESULTS:** K-dependent factors and fibrinogen were low normal, and decreased slightly over 35 days but were similar between groups. Labile factors were better preserved in filtered units. CAT studies showed that thrombin production is largely preserved in both filtered and unfiltered units for 35 days. TEG studies showed that unlike unfiltered blood, filtered blood had significantly decreased clot strength (MA) and rate of clot generation (angle) as seen in the graph. Time to first sign of clot (TEG R) did not differ between filtered and unfiltered units over time.
**CONCLUSION:** Remarkably, unfiltered banked WB had no impairment of coagulation function over 35 days of storage. However, filtered WB had significantly decreased rate of clot growth, and clot strength and does not appear to be suitable for hemostatic resuscitation as a stand alone product.

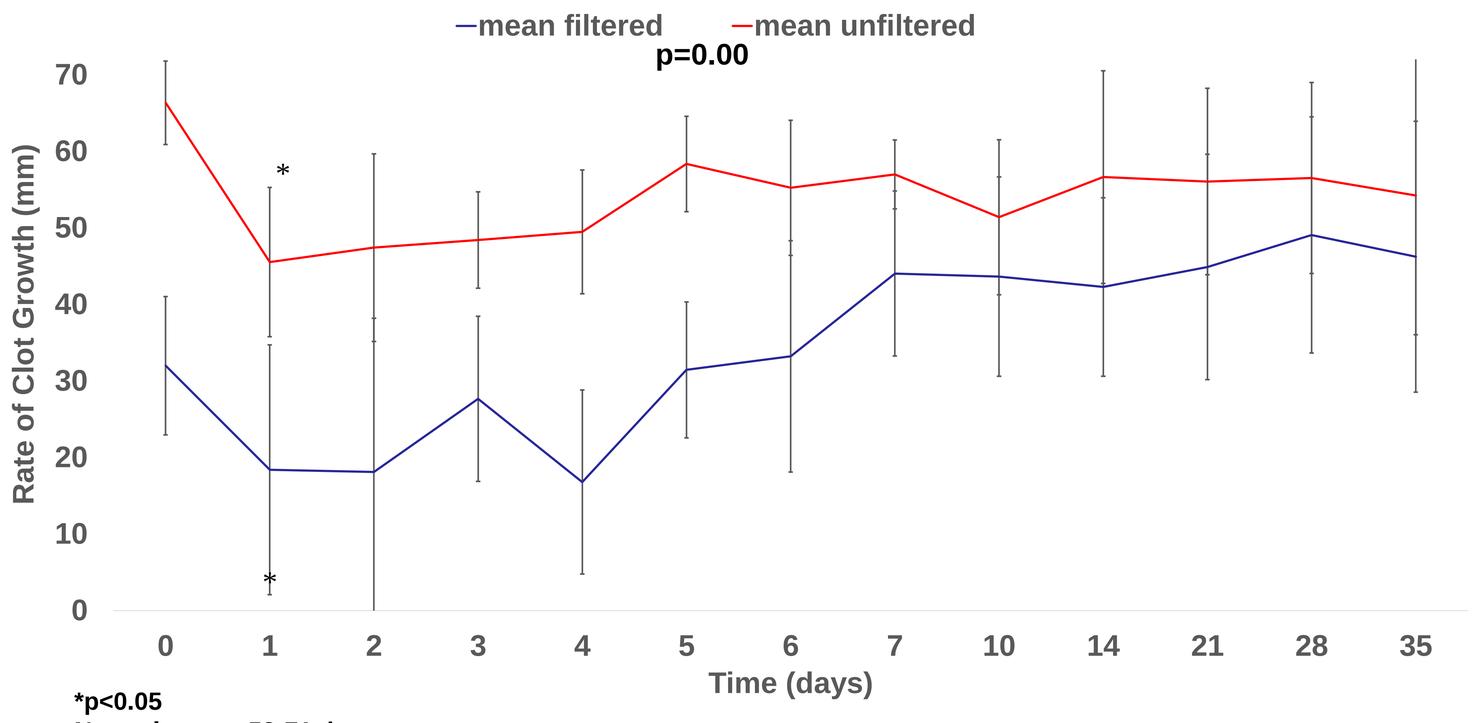
| Mean Changes in Coagulation Factors | | | |
|---|---|---|---|
| | Filtered | Unfiltered | p |
| Fibrinogen 200-400 mg/dL | | | |
| day 0 | 188 | 244 | |
| day 35 | 231 | 252 | 0.5 |
| Factor II 70-120% | | | |
| day 0 | 69±8 | 65±21 | 0.9 |
| day 35 | 60±7 | 58±7 | |
| Factor VII 55-170% | | | |
| day 0 | 55±18 | 68±28 | 0.2 |
| day 35 | 45±12 | 65±29 | |
| Factor IX 60-150% | | | |
| day 0 | 74±15 | 76±40 | 0.7 |
| day 35 | 67±19 | 51±13 | |
| Factor X 70-120% | | | |
| day 0 | 74±24 | 69±20 | 0.7 |
| day 35 | 58±8 | 65±14 | |
| Factor V 70-120% | | | |
| day 0 | 63±46 | 71±20 | 0.5 |
| day 35 | 54±20 | 16±7 | |
| Factor VIII 60-150% | | | |
| day 0 | 97±39 | 80±59 | 0.5 |
| day 35 | 50±31 | 21±16 | |

## TEG R: Filtered blood has a clinically significant increase in R at day 2



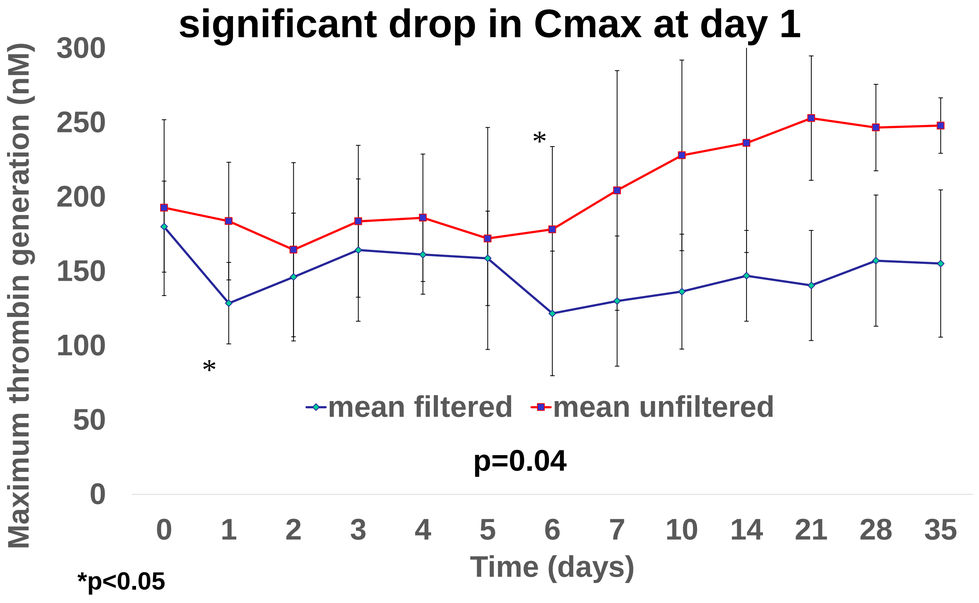

*p<0.05
Normal range 5-10 mins

## TEG MA: Filtered blood is below normal range



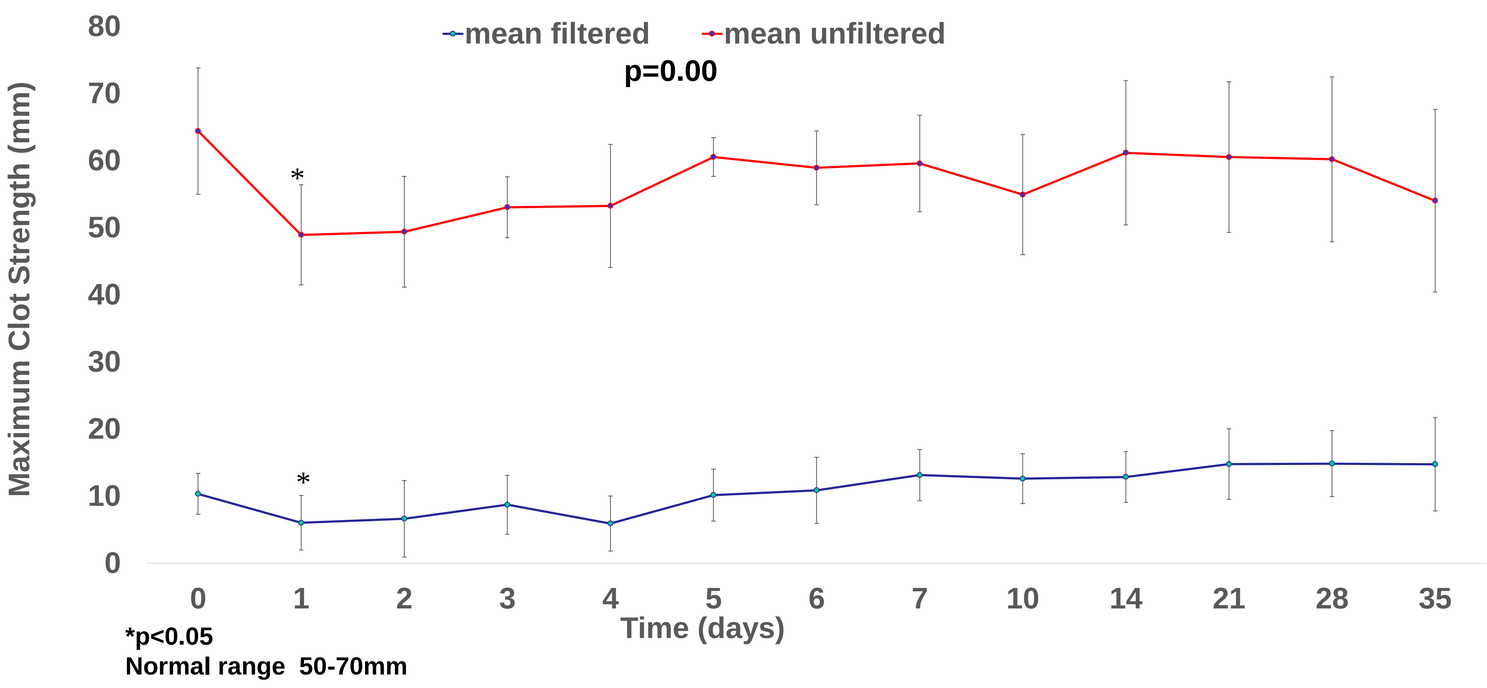

*p<0.05
Normal range 53-71 degrees

## CAT Cmax: Filtered blood has a statistically significant drop in Cmax at day 1




*p<0.05

## TEG MA: Filtered blood is below normal range




*p<0.05
Normal range 50-70mm

- Filtered blood has a filtration lesion resulting in a coagulopathic product
- Filtered whole blood has some decrease in clotting capability over 35 days with individual parameters changing as early as day 1
- Platelet transfusion may correct the filtration lesion seen in filtered stored whole blood
- Additional studies are needed to determine the exact timing and ratio of platelet transfusion required

Journal of Trauma and Acute Care Surgery

# Leukocyte Filtration Lesion Impairs Functional Coagulation in Banked Whole Blood

--Manuscript Draft--

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Cover Letter

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Dear Editor,

It is our pleasure to submit for consideration our original research article entitled, "Leukocyte Filtration Lesion Impairs Functional Coagulation in Banked Whole Blood" for your consideration for publication in the Journal of Trauma and Acute Care Surgery.

Expanding on data originally presented at the ACS Committee on Trauma 2013 Resident Competition and at AAST 2014, this important work demonstrates impairment in coagulation potential in banked whole blood that has undergone standard leukocyte reduction filtration. As the interest in banked whole blood for civilian trauma resuscitation grows, it is necessary to define processes and storage conditions that will preserve the apparent benefits of whole blood compared to component therapy that have been established in military settings. This paper defines the functional coagulation potential and factor concentrations in filtered and unfiltered whole blood units stored under standard blood banking conditions over 35 days. We believe this data is important to the development of effective and efficient systems to provide whole blood for civilian traumatic resuscitation, and as such, will be of broad interest to readers. We appreciate your consideration for publication in the Journal of Trauma and Acute Care Surgery, and look forward to your reply.

Sincerely,

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Type of paper: Original Article

Section Category: Poster presentations at: ACS Committee on Trauma 2013 Resident Competition; AAST, 2014.

Other than poster presentations listed above, we confirm that the data in this manuscript has not been published elsewhere.

# Leukocyte Filtration Lesion Impairs Functional Coagulation in Banked Whole Blood


## Abstract

Background: Whole blood (WB) transfusion is a promising alternative to component therapy in hemostatic resuscitation. Use of banked WB requires filtration of white blood cells (leukoreduction) and an established shelf life during which WB retains coagulant capacities. The goal of this study was to define the time course of coagulation stability in leukoreduced compared to unfiltered WB under standard refrigeration conditions.

Methods: Twelve WB units were donated by healthy volunteers after routine screening. Five units underwent standard leukocyte filtration and five did not. Two units were aliquoted into filtered and unfiltered samples, with platelets added to each sample on Day 14. Units were stored at 4°C and sampled on days 0, 1, 2, 3, 4, 5, 6, 7, 10, 14, 21, 28, and 35 for immediate thromboelastogram (TEG) analysis, and centrifuged and stored at -80°C for later Calibrated Automated Thrombogram (CAT) and coagulation factor assays.

Results: K-dependent factors and fibrinogen were low normal, decreased slightly over 35 days, and were similar between unfiltered and filtered units. Labile factors were better preserved in filtered units, although unfiltered units did not show impaired coagulation over 35 days. Filtered blood had delayed clot initiation on days 0, 1, and 2 as measured by TEG R ($p<0.021$); slower clot progression (TEG α-angle) on days 0, 1, 2, 3, 4, 5, and 6 ($p<0.023$); weaker final clot (TEG MA) on all days ($p<0.0001$). Thrombin generation

was delayed on day 28 ($p=0.046$) and decreased on days 10, 21, 28, and 35 ($p<0.034$). Addition of platelets to filtered WB rescued TEG MA.

Conclusions: Filtered WB had decreased functional clotting capacity and thrombin generation and may not be suitable for hemostatic resuscitation as the sole blood product.

Level of Evidence: Laboratory study

Key words: “whole blood”, “stored whole blood”, “thromboelastography”, “hemostatic resuscitation”

Title Page

# Leukocyte Filtration Lesion Impairs Functional Coagulation in Banked Whole Blood

Short Title: Filtration Lesion in Banked Whole Blood

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The authors declare that they have no conflicts of interest.

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# Leukocyte Filtration Lesion Impairs Functional Coagulation in Banked Whole Blood

## Short Title: Filtration Lesion in Banked Whole Blood

Anaar Siletz, M.D. Ph.D.*[1], Sigrid Burruss M.D. *[2], Terry Gruber M.S. [3], Alyssa Ziman M.D.[4], Victor Marder M.D. [3], Henry Magill Cryer M.D. Ph.D.[1]

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## Background

Hemorrhage from traumatic injury is the leading cause of preventable death in trauma. (1, 2) The pathophysiology of hemorrhage includes loss of both oxygen carrying capacity and clotting ability (3, 4). Along with the loss of clotting components due to bleeding, tissue hypoperfusion results in an intrinsically coagulopathic state in the remaining blood, characterized by activation of protein C, hyper-fibrinolysis, and platelet dysfunction. This state is known as acute traumatic coagulopathy (ATC) (3, 5, 6). Coagulopathy is exacerbated by acidemia, hypothermia and dilution of clotting factors via excess administration of products such as crystalloid solution or packed red cells (pRBCs) (6). Accordingly, transfusing plasma and platelets in addition to pRBCs is associated with improved mortality rates in traumatic resuscitation. (7-10) The current treatment of hemorrhage attempts to address coagulopathy by transfusing pRBCs, plasma, and platelets in an approximately 1:1:1 ratio. (2) Taken together, transfusion of pRBCs, plasma, and platelets approximates reconstituted whole blood (WB). (11)

Prior to the mid-1970s, there was no need to "reconstitute" WB for the treatment of traumatic resuscitation, as WB was the FDA-approved product used for traumatic resuscitation. (5, 12) Subsequently, the technology to separate WB into its components and store each separately became widespread in both civilian and military use due to the improved storage capability. (12, 13) This practice was also a more efficient means of providing blood products to patients who only required one component (*i.e.*, for cytopenia from impaired bone marrow function). (12) However, patients requiring resuscitation for traumatic hemorrhage may not have been well served by this change. (14) No studies were performed during the transition to component therapy that demonstrated equivalence with whole blood for traumatic resuscitation. Recent data from military operations in Iraq and Afghanistan demonstrated improved survival in

patients receiving warm fresh whole blood (FWB) as compared to component therapy. (14) Possible benefits of WB over component therapy include a more physiologic product, in part due to a smaller volume of preservative solution transfused; closer approximation of the concentrations of shed blood, resulting in a more functional hemostatic product, and exposure to blood from a smaller number of donors. (4, 14, 15) Military data has sparked civilian interest in reintroducing WB for traumatic resuscitation. (15)

Whole blood is considered "fresh" if it is used within 48 hours of donation, which while feasible in a military setting with a walking donor base, is extremely difficult in the civilian setting where 48 hours is the typical time required for processing and testing of donated units. (4, 16) WB is still used in pediatric cardiac surgery, and WB not used after 48 hours is processed for pRBCs with the plasma component wasted. (16) For WB use in civilian trauma resuscitations, storage conditions for refrigerated WB that preserve both oxygen carrying and hemostatic properties must be determined. (17) An appropriate shelf life for refrigerated WB must take into account typical turnaround times for infectious disease testing.

The study hypothesis was that filtered stored WB would have decreased coagulation potential compared to unfiltered units. The stability of coagulation over time and the differences in coagulation properties between filtered and unfiltered units of WB were investigated using thromboelastography (TEG), which provides measures of clot functionality (18); calibrated automated thromboelastgraphy (CAT), which measures thrombin generation (19, 20); and measurement of the concentration of clotting factors in WB samples filtered with a standard leukocyte filter (non-platelet-sparing) versus unfiltered samples.

## Methods

*Sample collection and processing:*

This study was approved by the UCLA IRB. Through the UCLA Blood and Platelet Center, ten healthy male blood donor volunteers were identified, consisting of five A+ and five O+ blood type donors. Consent for collection of the units was obtained from the blood donors per routine blood bank protocol. Only units unsuitable for transfusion due to insufficient collection volume were used for the study, so further consent specific to the study was waived by the IRB. Whole blood (WB) units were stored at 4°C. For tests involving the addition of platelets to filtered samples, two additional whole blood units were similarly collected along with one platelet unit. The two additional blood samples were aliquoted into filtered and unfiltered fractions, and on Day 14 of storage, platelets were added to whole blood units for a final a concentration of 200,000/mL. Platelets had been collected approximately 48 hours prior and stored at 20-24°C under gentle agitation until addition.

Leukocyte reduction of whole blood containing the preservative CPDA-1 was performed using the Sepacell RS-2000 in-line leukocyte reduction filter set (Fenwal, Lake Zurich, IL). In accordance with blood bank regulation, all pre-storage units at ambient temperature (20-24°C) started filtration within 8 hours of collection end-time. Units stored at 1°C to 6°C were filtered up to 72 hours from collection end-time. All units were filtered on the same day as collection. Units were agitated to thoroughly mix the unfiltered whole blood, and allowed to filter by gravity. 5 units were not filtered prior to storage at 4°C.

Each sample day, 1 mL aliquots of WB were collected for TEG analysis. Additional test samples were obtained using five 5mL aliquots of WB centrifuged at 2500x*g* for ten minutes. The resulting plasma was stored at -80°C for calibrated automated thromboelastography (CAT) and coagulation factor (factors II, V, VII, VIII, IX, X, and fibrinogen) tests. Samples were tested on days 0, 1, 2, 3, 4, 5, 6, 7, 10, 14, 21, 28, and 35. These time points were selected based on the average storage time of transfused pRBCs at our institution, and on previous studies suggesting that clotting potential begins to deteriorate after 14 to 21 days (16, 21).

*Coagulation Tests:*

TEG was performed using a hemostasis analyzer (TEG 5000 Thromboelastograph, Haemonetics, Braintree, MA) in accordance with the manufacturer's instructions. TEG measures coagulation parameters by sensing resistance to rotation of a sample of clotting blood. (18) The TEG R value measures time to the first clot formation. A one mL blood sample was pipetted into a vial containing pre-warmed Kaolin and mixed thoroughly by inversion. Citrated blood mixture and calcium chloride solution were added to the TEG analyzer cup and tests were run until R (a measure of time to first sign of clot), K (measuring rate of clot progression), α-angle (measuring rate of clot progression), and MA (a measure of overall clot strength) were recorded.

CAT was performed using a Calibrated Automatic Thrombogram (Diagnostica Stago, Inc., Parsipanny, NJ) according to the manufacturer's instructions to measure thrombin-generating capacity in plasma (20, 22). In this technique thrombin generation is measured using a fluorogenic substrate so that the presence of fibrinogen and platelets does not disturb measurement. Briefly, 5 mL of the 20-30 mL centrifuged plasma was further centrifuged at

10000x*g* to yield platelet-poor plasma (PPP) and stored at -80°C until testing. On the day of testing, all thawed samples were loaded onto one plate for testing.

*Assays of coagulation factors:*

Assays of fibrinogen and factor II, V, VII, VIII, IX, and X concentration were performed using the STA Compact apparatus (Diagnostica Stago, Inc., Parsipanny, NJ) according to the manufacturer's instructions. Briefly, plasma centrifuged at 2500x*g* was stored at -80°C until testing. On the day of testing, undiluted thawed samples were loaded into the instrument and the relevant test selected for analysis.

*Statistical Analysis:*

Values for filtered versus unfiltered units were compared using Student's t-test (unpaired) and mixed model regression analysis (a statistical model taking into account fixed and random effects on repeated measurements) as appropriate.

## Results

*TEG Results* (**Figure 1**): The R value for days 0,1, and 2 showed a significant delay in time to first sign of clot in filtered WB compared to unfiltered WB. Filtered WB showed a delay to the first sign of clot (normal range of R 5-10 min; **Figure 1A**) on sample day 0 (8.7 vs 5.5 min, p = 0.021), day 1 (11.5 vs 6.4 min, p = 0.008), and day 2 (17.1 vs 6.4 min, p = 0.011) as compared to unfiltered WB. There were no significant differences on days 3 to 35, with all times to the first sign of clot within the normal range.

Filtered WB had a smaller α-angle, indicating a slower rate of clot progression than unfiltered WB on sample days 0 (25.4° vs 65.3°, p <0.0001), 1 (6.8° vs 43.9°, p <0.0001), 2 (9.8° vs 42.3°, p = 0.007), 3 (22.3° vs 47.3°, p = 0.001), 4 (16.8° vs 49.5°, p = 0.002), 5 (31.4° vs 58.3°, p = 0.001), and 6 (33.2° vs 55.2°, p = 0.023), (normal α-angle 53°-71°; **Figure 1B**). The filtered WB samples did not display a normal rate of clot progression on any day. The unfiltered WB sample was within a normal range on day 0, dropped to just below the normal range for days 1 to 4 and day 10, and then returned to a low-normal range for the remaining days (**Figure 1B)**.

Filtered WB had a lower MA indicating a weaker clot strength (normal MA 50-70 mm; **Figure 1C**) than unfiltered WB on all days (p<0.0001 for all days). The filtered WB clot strength range was never near normal, with ranges from 3.3-15.2 mm. The clot strength of unfiltered WB was in the low-normal range (52.3-65.2 mm), except for days 1 and 2 (48.0 and 45.3 mm, respectively).

*CAT Results* (**Figure 2**): There were no differences in maximum thrombin generated between filtered and unfiltered WB on days 0-7 (**Figure 2A**). However, filtered WB had significantly less thrombin generation than unfiltered WB on days 10 (136.3 vs 228.0, p = 0.026), 14 (146.9 vs 236.2, p = 0.037), 21 (140.5 vs 253.0, p = 0.002), 28 (157.1 vs 246.7, p = 0.005), and 35 (155.2 vs 248.0, p = 0.004). There were no differences between the two groups in the time to the start of thrombin generation (CAT Lag; **Figure 2B**). There were no differences between filtered and unfiltered WB in the time to reach the maximum thrombin generated on days 0-7 and 14 (**Figure 2C**). For days 10 (8.3 min vs 5.7 min, p= 0.034), 21 (8.2 min vs 4.8 min, p = 0.001), 28 (7.7 vs 4.8 min, p= 0.001), and 35 (8.0 vs 4.8 min, p = 0.018), filtered WB had significantly longer times to reach maximum thrombin than unfiltered WB.

*Coagulation factor levels*:

K-dependent coagulation factors II, VII, IX, and X (**Figure 3A-D**) were low normal initially, tended to decrease slightly over 35 days, and were similar between groups (p>0.05 for all days).

Labile factors (**Figure 4A-B**) were better preserved over time in filtered samples, with Factor V significantly higher on days 14 (51.7% vs 28.2%, p = 0.030), 21 (59% vs 20.4%, p =0.43), 28 (48.5% vs 19.1%, p = 7.8) and 35 (53.7% vs 16.3%, p = 0.004).

Although not significantly different, Factor VIII decreased continuously in unfiltered samples from day 0 to 35, declining to approximately one quarter of the day 0 value by day 35 (79.8% on day 0 vs 21.1 % on day 35 in filtered units, compared with 96.8% on day 0 vs 50.2% on day 35 in filtered units). Fibrinogen levels were low normal in all samples (**Figure 4C**). There was no

significant difference between filtered and unfiltered whole blood fibrinogen levels at any time point and no significant difference over time in both filtered and unfiltered WB.

*TEG profiles of filtered and unfiltered blood with additional platelets:*

Addition of platelets to filtered blood did not significantly impact R or α-angle (**Figure 5A-B)**. Addition of platelets to filtered blood brought MA back to the normal, unfiltered range (**Figure 5C**).

## Discussion

This study describes the effects of storage on filtered and unfiltered cold stored whole blood coagulation function. Unfiltered banked whole blood has decreased labile clotting factors without impairment of coagulation potential over 35 days. However, unfiltered blood is not appropriate for resuscitation because it contains donor leukocytes, putting recipients at risk for febrile nonhemolytic transfusion reactions, increased rates of alloimmunization, and transmission of viruses such as EBV and CMV. (23) Despite improved levels of labile clotting factors, filtered blood had delayed first sign of clot growth, rate of clot formation, clot strength, and thrombin generation, at various time points. Clot strength was rescued by the addition of platelets on day 14. Future resuscitation strategies using whole blood will need to include either additional platelet transfusions, or use of a platelet-sparing filter in the WB leukoreduction process. (15) Testing of the properties of WB leukoreduced with a platelet-sparing filter is ongoing in our laboratory.

Similar to our findings that clotting potential is largely preserved in unfiltered cold stored WB, Jobes et al (16) studied functional clotting capacity, platelet function and storage lesion in stored refrigerated WB over 35 days and found that global clotting functions as measured by TEG did not change until after day 14. Decreased TEG α-angle and MA, indicating defective platelet contribution to clot development, did not occur until day 14. Nilsson et al (22) in a study of stored WB also similarly found that storage for 2 weeks had minimal effect on the level or function of most coagulation factors. The exception was Factor VIII, which decreased to 50% of its initial value after 24 hours; Factor V was not tested. In a clinical study of patients undergoing massive transfusion of whole blood that had been processed to remove cryoprecipitate and platelets, Counts et al (21) found that all stable clotting factors were present in modified stored blood for greater than 21 days at levels comparable to that in fresh frozen plasma, remaining at levels that are considered to be well within the hemostatic range. Labile Factor V levels in WB remained >50% after two weeks of storage at 4°C, and Factor VIII fell below 50% rapidly. Pidcoke et al (24) compared WB units stored for 21 days at 4°C versus 22°C. Half of the units underwent treatment with UV light; filtration was not used. Measures of coagulation factor activity (PT and PTT), platelet aggregation, lactate accumulation and glucose depletion worsened over time, but these effects were attenuated by refrigeration. TEG parameters including reaction time, rate of clot formation, clot strength, and fibrinolysis were also somewhat preserved by refrigeration. This study also demonstrated relatively stable levels of fibrinogen, von Willebrand factor, and antithrombin III, with decreased Factor V and VIII over time. Although levels of inflammatory mediators interleukin-6 (IL-6), tumor necrosis factor α (TNF)

and heat shock protein 70 (HSP-70) were investigated, levels were not reliably detectable (data not shown).

It should be noted that the shortened shelf life for WB might be partially responsible for the benefits seen in WB transfusion versus component therapy. Increasing age of transfused pRBCs beyond 14 days has been associated with increasing risk of multiple organ failure in trauma patients and the critically ill, possibly related to increased buildup of inflammatory mediators. (25, 26) The shelf-life of pRBCs is based primarily on the requirement that 70% of cells have intact membranes 24 hours after transfusion, and there is a paucity of evidence that older RBCs have adequate oxygen delivery. (12) Further studies of the oxygen carrying capacity and inflammatory mediator concentrations of cold stored WB are needed to determine the appropriate shelf life to preserve all functions of the product.

## Conclusions

Unfiltered WB retains clotting capacity over 35 days despite decreased labile clotting factors. Filtered WB has a filtration lesion resulting in a coagulopathic product and may not be suitable as the sole transfusion product for hemostatic resuscitation. Addition of platelets to filtered WB restores clot strength as measured by TEG. Additional studies are needed to determine the exact timing and ratio of platelet transfusion requirements, and to investigate the coagulation parameters of cold stored WB leukoreduced with a platelet-sparing filter.

## Author Contributions

Anaar Siletz, M.D. Ph.D.: Wrote paper, literature search, contributed to data analysis.

Sigrid Burruss M.D.: Study design, data collection and analysis, literature search, edited paper.

Terry Gruber M.S.: Data collection and analysis, study design.

Alyssa Ziman M.D.: Study design and implementation, edited paper.

Victor Marder M.D.: Study design and implementation.

Henry Magill Cryer M.D. Ph.D.: Senior author. Study design and implementation, edited paper.

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## Figure Legends

**Figure 1. Thromboelastography values for filtered and unfiltered units.** Five filtered and five unfiltered units were analyzed.

Figure 1A. Mean thromboelastography R values. Normal range of R 5-10 min. Values for filtered and unfiltered units were significantly different on days 0, 1 and 2.

Figure 1B. Mean thromboelastography α-angle. Normal α-angle 53-71 degrees. Values for filtered and unfiltered units were significantly different on days 0-6.

Figure 1C. Mean thromboelastography maximum amplitude (MA). **(**Normal MA 50-70 mm.) Values for filtered and unfiltered units were significantly different on all days.

**Figure 2. Thrombin generation measured by calibrated automated thrombogram (CAT).** Five filtered and five unfiltered units were analyzed.

Figure 2A. Maximum thrombin generation. Values for filtered and unfiltered units were significantly different on days 10, 14, 21, 28 and 35.

Figure 2B. Time to start of thrombin generation (CAT lag time). Values for filtered and unfiltered units were not significantly different on any day.

Figure 2C. Time to reach maximum thrombin (CAT Tmax). Values for filtered and unfiltered units were significantly different on days 10, 21, 28, and 35.

**Figure 3. K-dependent coagulation factor levels in filtered and unfiltered units.** Five filtered and five unfiltered units were analyzed.

Figure 3A. Mean factor II levels. Values for filtered and unfiltered units were not significantly different on any day. Normal range: 70-120%.

Figure 3B. Mean factor VII levels. Values for filtered and unfiltered units were not significantly different on any day. Normal range: 55-170%.

Figure 3C. Mean factor IX levels. Values for filtered and unfiltered units were not significantly different on any day. Normal range: 60-150%.

Figure 3D. Mean factor X levels. Values for filtered and unfiltered units were not significantly different on any day. Normal range: 70-120%.

**Figure 4. Non-K-dependent coagulation factor levels in filtered and unfiltered units.** Five filtered and five unfiltered units were analyzed.

Figure 4A. Mean factor V levels**.** Values for filtered and unfiltered units were significantly different on days 14, 21, 28, and 35. Normal range: 70-120%.

Figure 4B. Mean factor VIII levels. Values for filtered and unfiltered units were not significantly different on any day. Normal range: 60-150%.

Figure 4C. Mean fibrinogen levels. Values for filtered and unfiltered units were not significantly different on any day. Normal range: 200-400 mg/dL.

**Figure 5. Thromboelastography values for filtered and unfiltered units with addition of platelets.** Two filtered and two unfiltered units, each with platelets added on Day 14, were analyzed.

Figure 5A. Mean TEG R values. Values for different filtration conditions were not significantly different on any day. Normal range of R 5-10 min.

Figure 5C. Mean TEG MA. Values for filtered and unfiltered units were significantly different until addition of platelets. Normal MA 50-70 mm.

**Figure 1. Thromboelastography values for filtered and unfiltered units.** Five filtered and five unfiltered units were analyzed.

Figure 1A. Mean thromboelastography R values. Normal range of R 5-10 min. Values for filtered and unfiltered units were significantly different on days 0, 1 and 2.

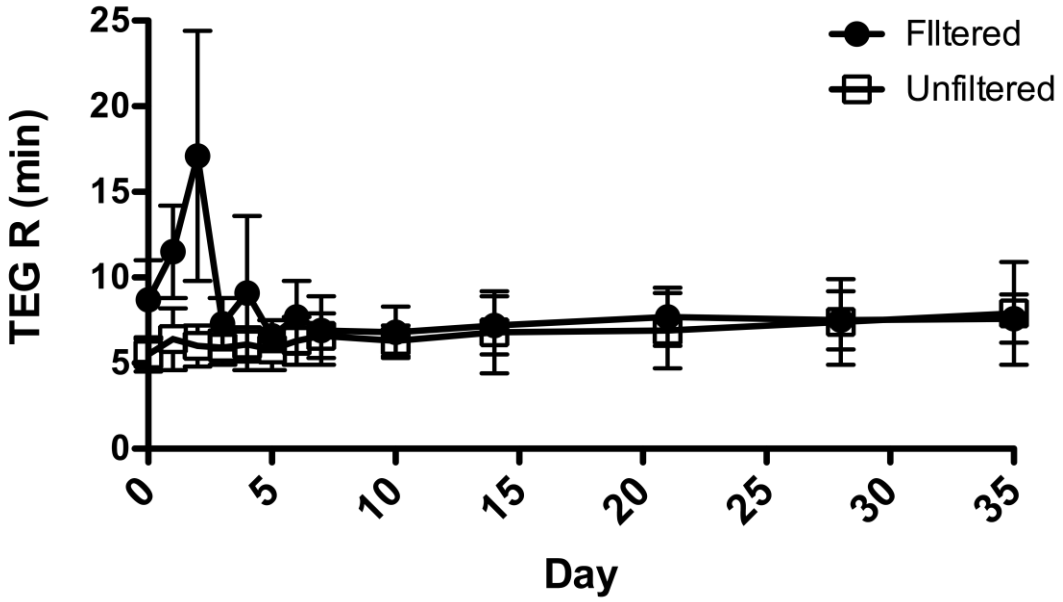

FIltered
Unfiltered
TEG R (min)
25
20
15
10
5
0
0
5
10
15
20
25
30
35
Day

Figure 1B. Mean thromboelastography α-angle. Normal α-angle 53-71 degrees. Values for filtered and unfiltered units were significantly different on days 0-6.

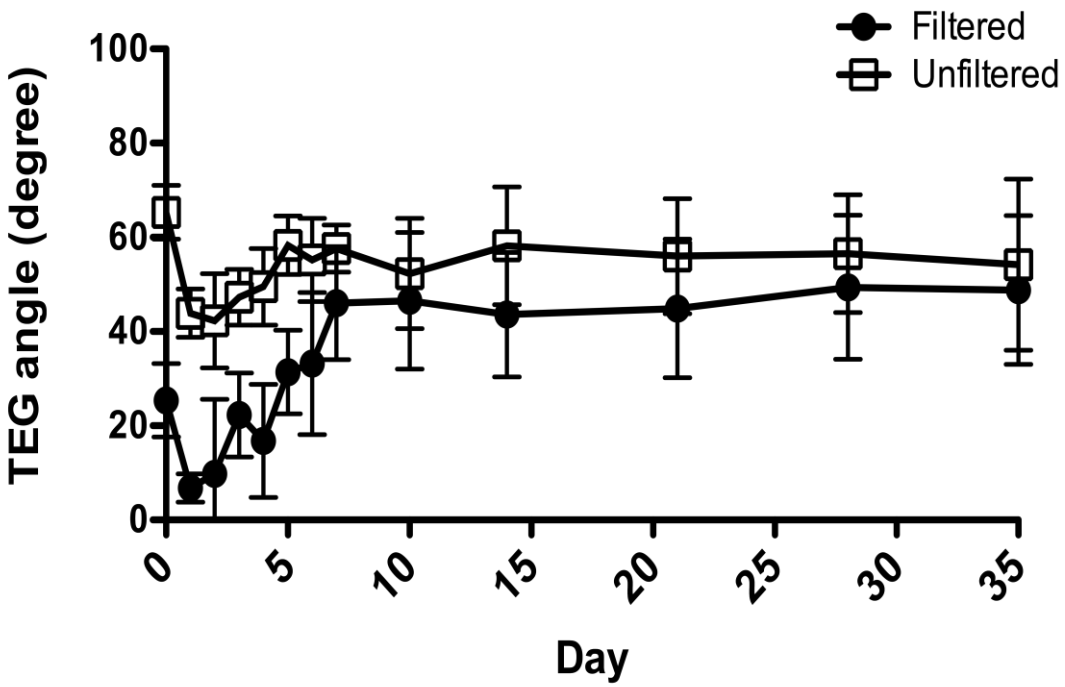

Filtered
Unfiltered
TEG angle (degree)
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Day

Figure 1C. Mean thromboelastography maximum amplitude (MA). **(**Normal MA 50-70 mm.) Values for filtered and unfiltered units were significantly different on all days.

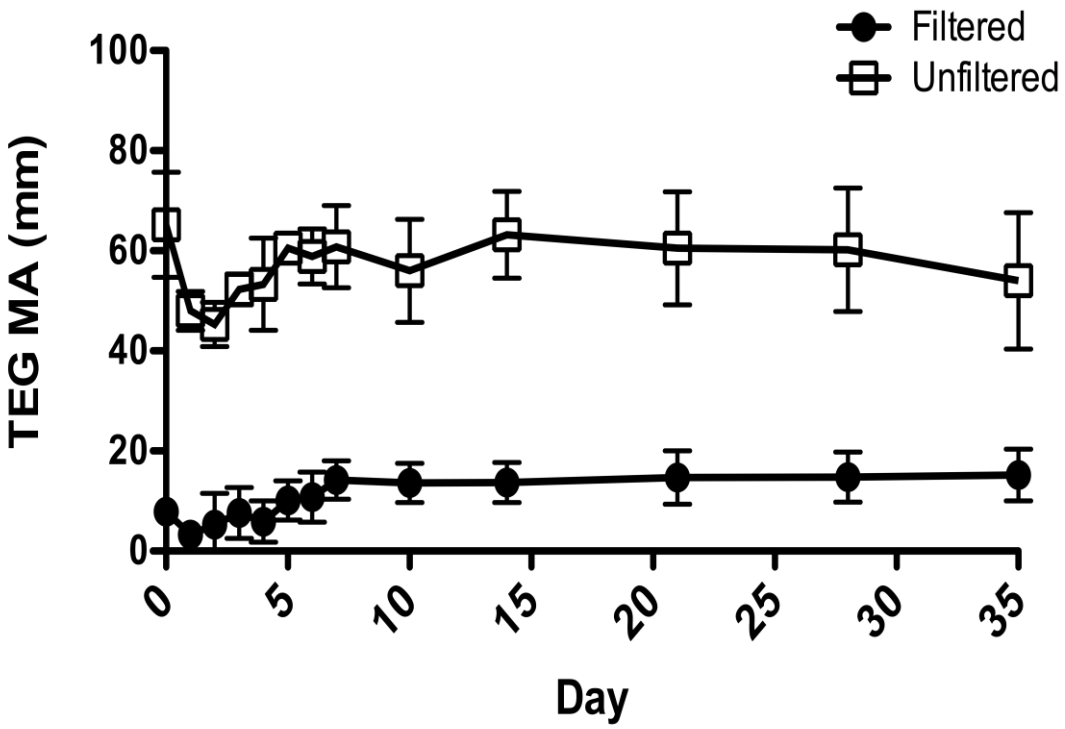

Filtered
Unfiltered
TEG MA (mm)
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Day

**Figure 2. Thrombin generation measured by calibrated automated thrombogram (CAT).** Five filtered and five unfiltered units were analyzed.

Figure 2A. Maximum thrombin generation. Values for filtered and unfiltered units were significantly different on days 10, 14, 21, 28 and 35.

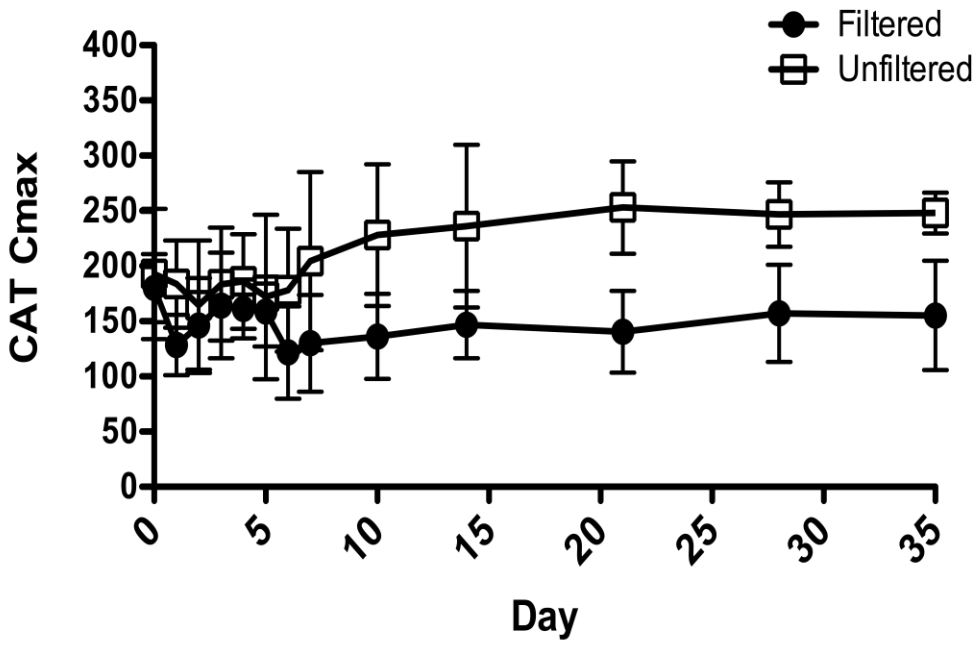

Filtered
Unfiltered
CAT Cmax
400
350
300
250
200
150
100
50
0
0
5
10
15
20
25
30
35
Day

Figure 2B. Time to start of thrombin generation (calibrated automated thrombogram lag time, CAT lag). Values for filtered and unfiltered units were not significantly different on any day.

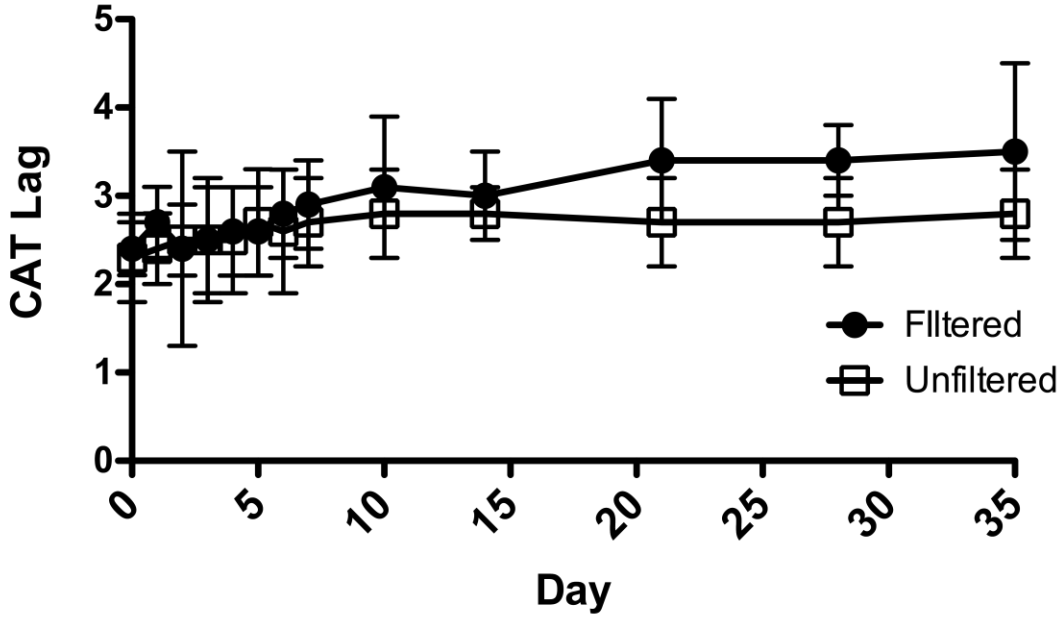

CAT Lag
5
4
3
2
1
0
0
5
10
15
20
25
30
35
Day
FIltered
Unfiltered

Figure 2C.  Time to reach maximum thrombin (CAT Tmax). Values for filtered and unfiltered units were significantly different on days 10, 21, 28, and 35.

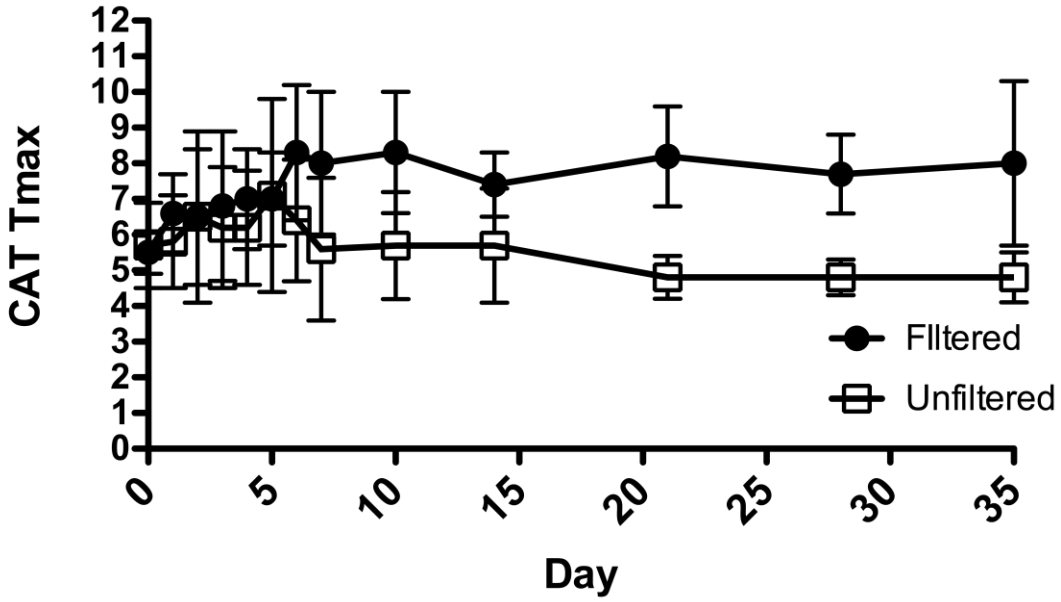

CAT Tmax
12
11
10
9
8
7
6
5
4
3
2
1
0
0
5
10
15
20
25
30
35
Day
FIltered
Unfiltered

**Figure 3. K-dependent coagulation factor levels in filtered and unfiltered units.**

Five filtered and five unfiltered units were analyzed.

Figure 3A. Mean factor II levels. Values for filtered and unfiltered units were not significantly different on any day. Normal range: 70-120%.

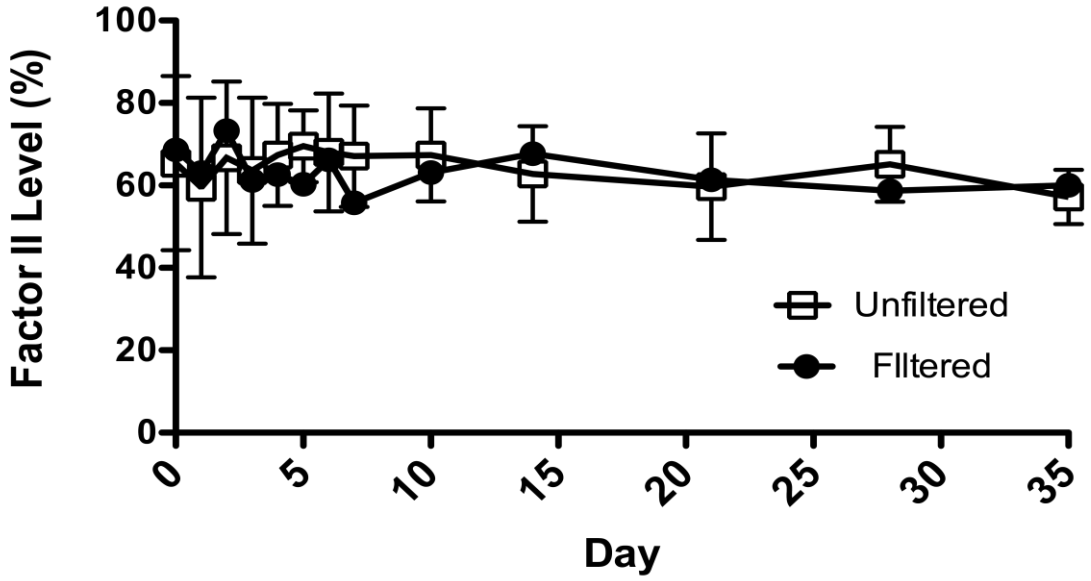

Factor II Level (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Day
Unfiltered
FIltered

Figure 3B. Mean factor VII levels. Values for filtered and unfiltered units were not significantly different on any day. Normal range: 55-170%.

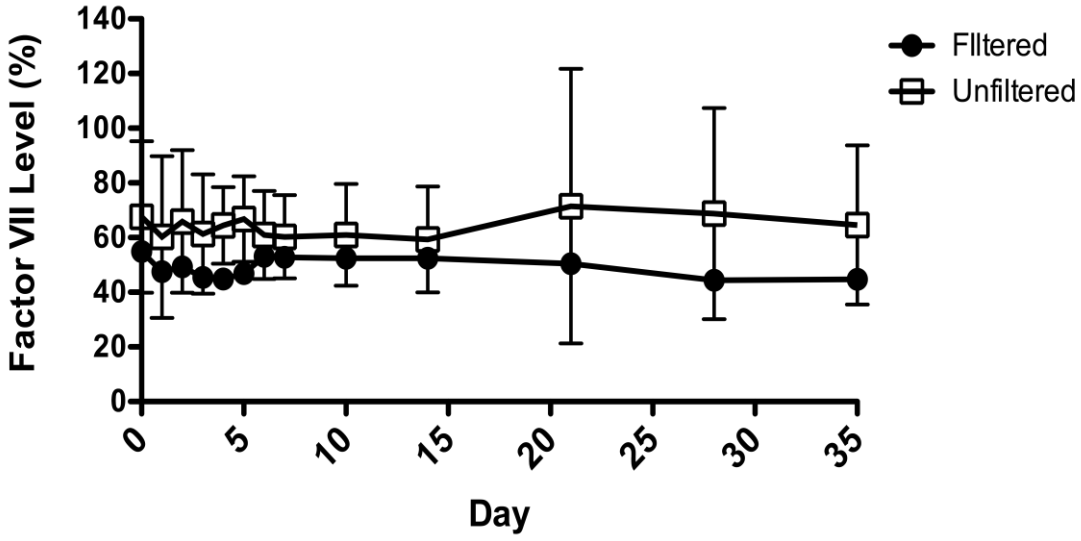

Factor VII Level (%)
140
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Day
FIltered
Unfiltered

Figure 3C. Mean factor IX levels. Values for filtered and unfiltered units were not significantly different on any day. Normal range: 60-150%.

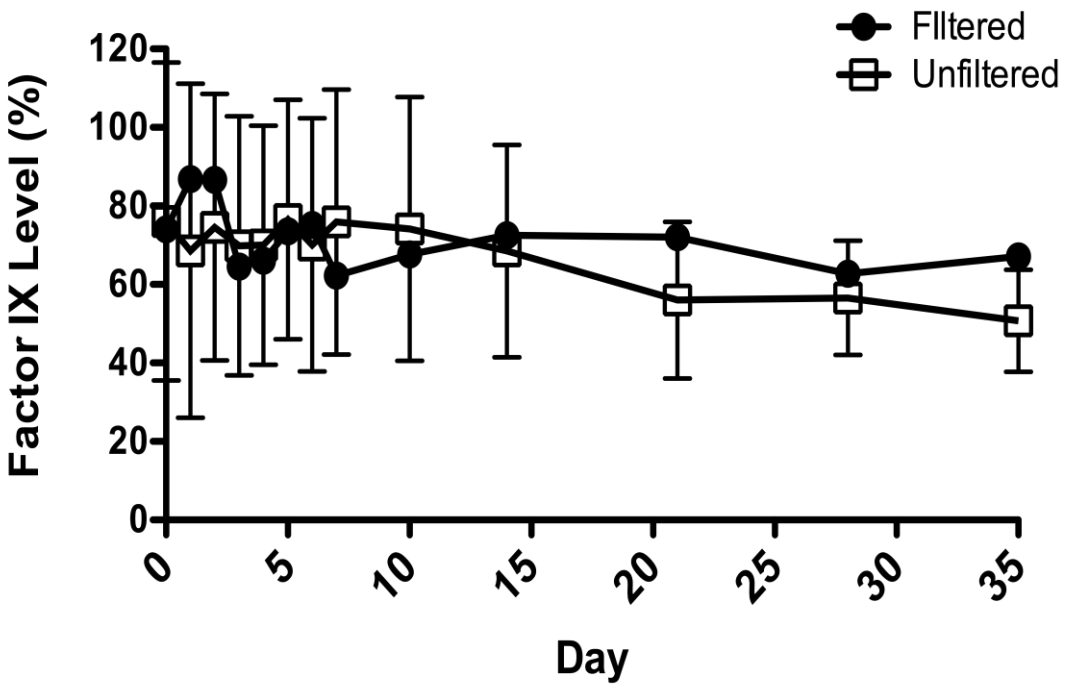

FIltered
Unfiltered
Factor IX Level (%)
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Day

Figure 3D.  Mean factor X levels. Values for filtered and unfiltered units were not significantly different on any day.  Normal range: 60-150%.

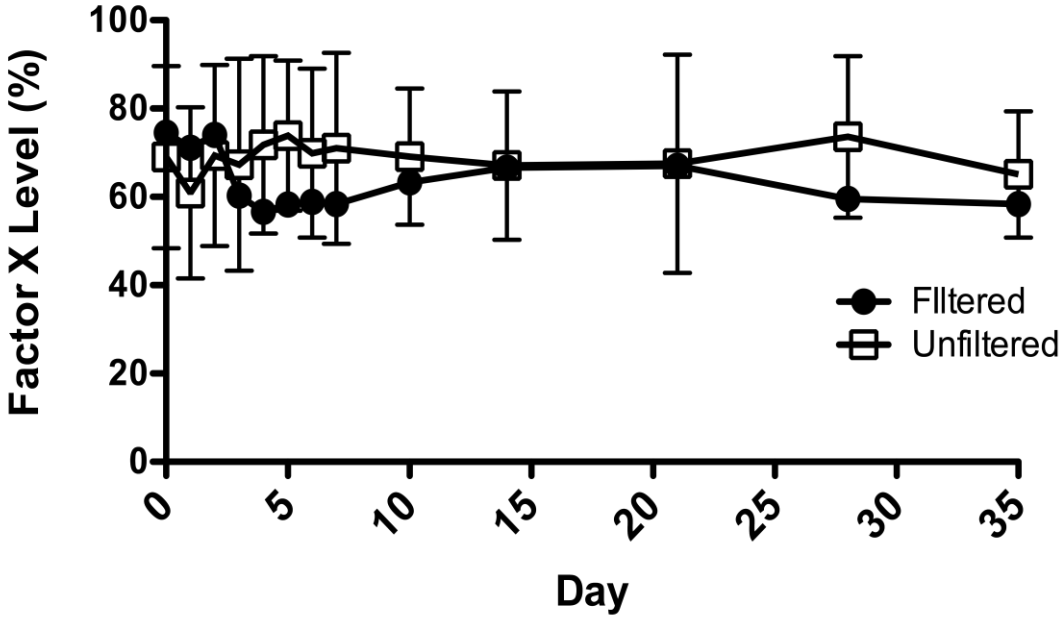

Factor X Level (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Day
FIltered
Unfiltered

**Figure 4. Non-K-dependent coagulation factor levels in filtered and unfiltered units.**

Five filtered and five unfiltered units were analyzed.

Figure 4A. Mean factor V levels**.** Values for filtered and unfiltered units were significantly different on days 14, 21, 28, and 35. Normal range: 70-120%.

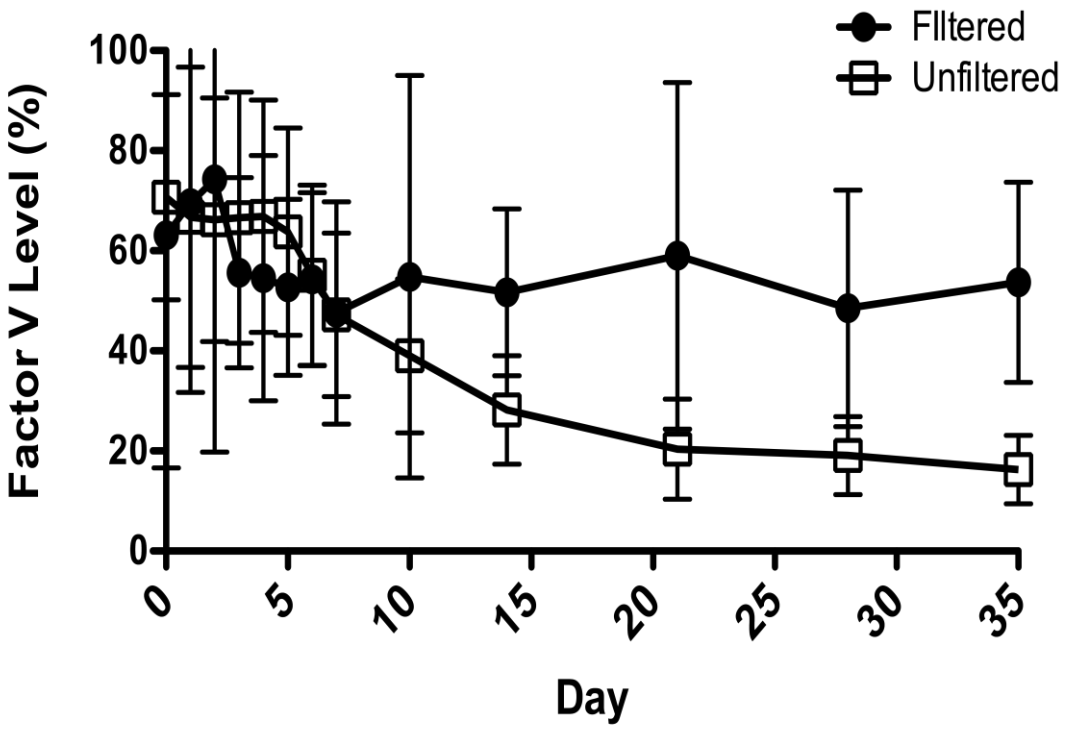

FIltered
Unfiltered
Factor V Level (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Day

Figure 4B. Mean factor VIII levels. Values for filtered and unfiltered units were not significantly different on any day. Normal range: 60-150%.

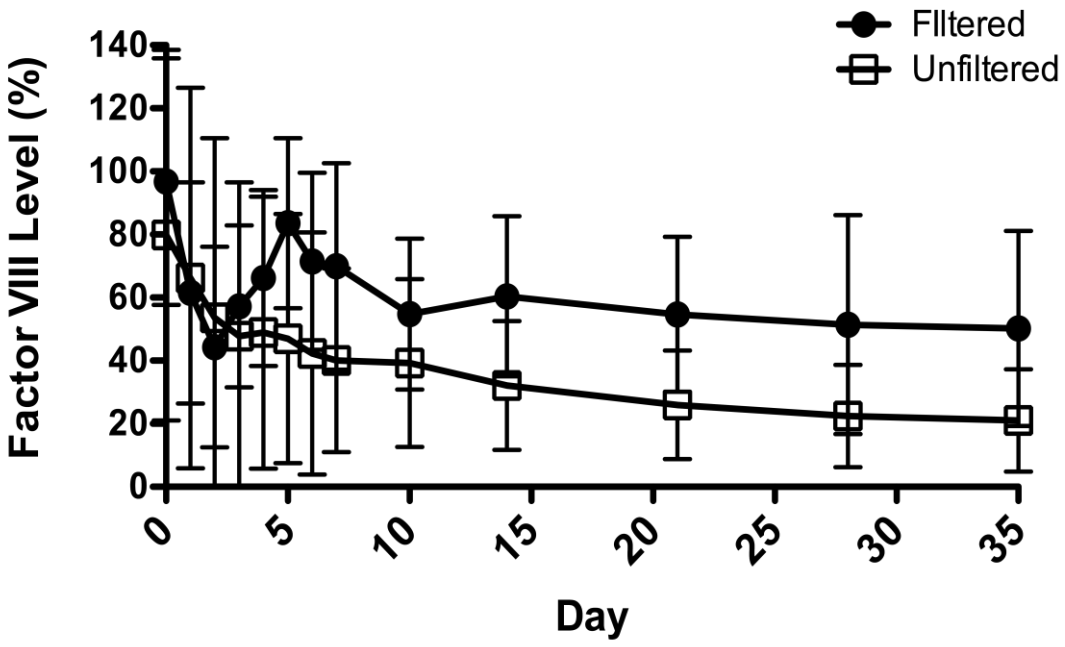

FIltered
Unfiltered
Factor VIII Level (%)
140
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Day

Figure 4C. Mean fibrinogen levels. Values for filtered and unfiltered units were not significantly different on any day. Normal range: 200-400 mg/dL.

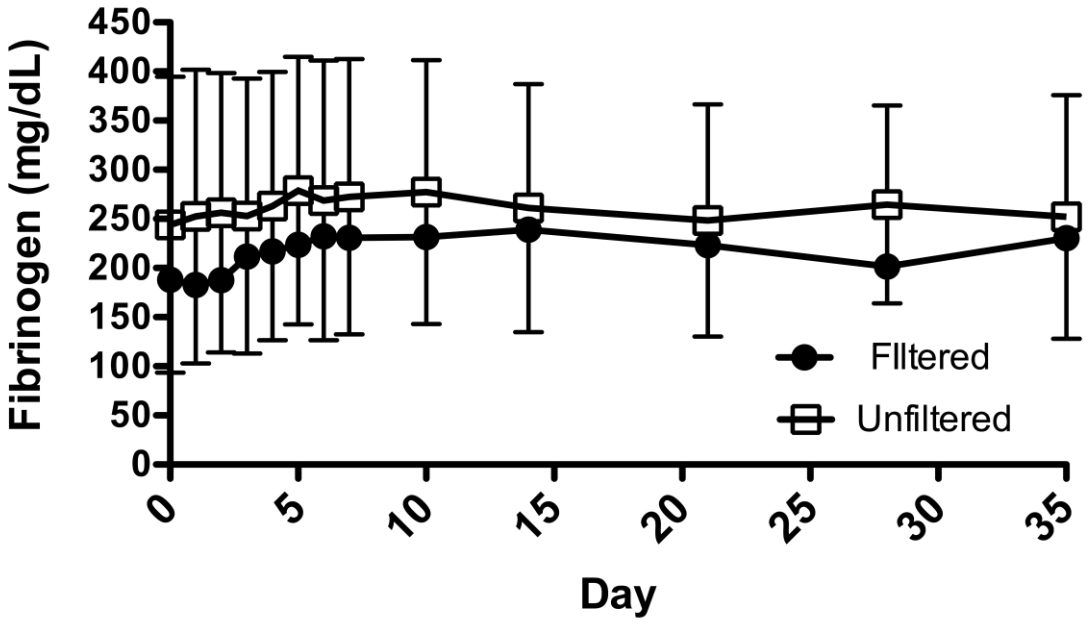

Fibrinogen (mg/dL)
450
400
350
300
250
200
150
100
50
0
0
5
10
15
20
25
30
35
Day
FIltered
Unfiltered

**Figure 5. Thromboelastography values for filtered and unfiltered units with addition of platelets.** Two filtered and two unfiltered units, each with platelets added on Day 14, were analyzed.

Figure 5A. Mean TEG R values. Values for different filtration conditions were not significantly different on any day. Normal range of R 5-10 min.

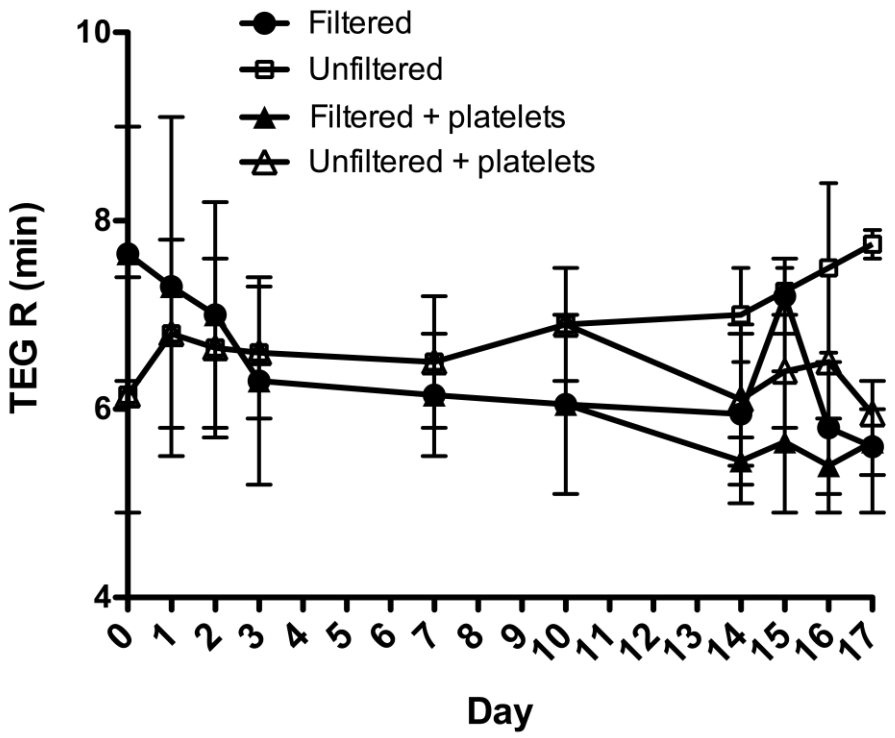

Filtered
Unfiltered
Filtered + platelets
Unfiltered + platelets
TEG R (min)
10
8
6
4
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Day

Figure 5B. Mean TEG α-angle. Values for different filtration conditions were not significantly different on any day. Normal α-angle 53-71 degrees.

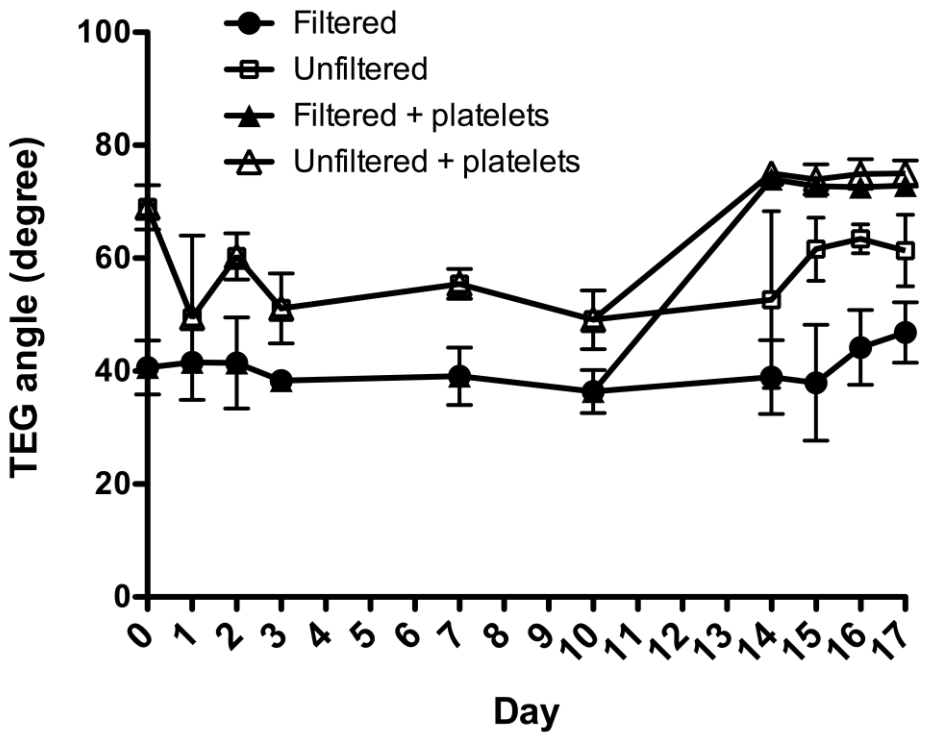
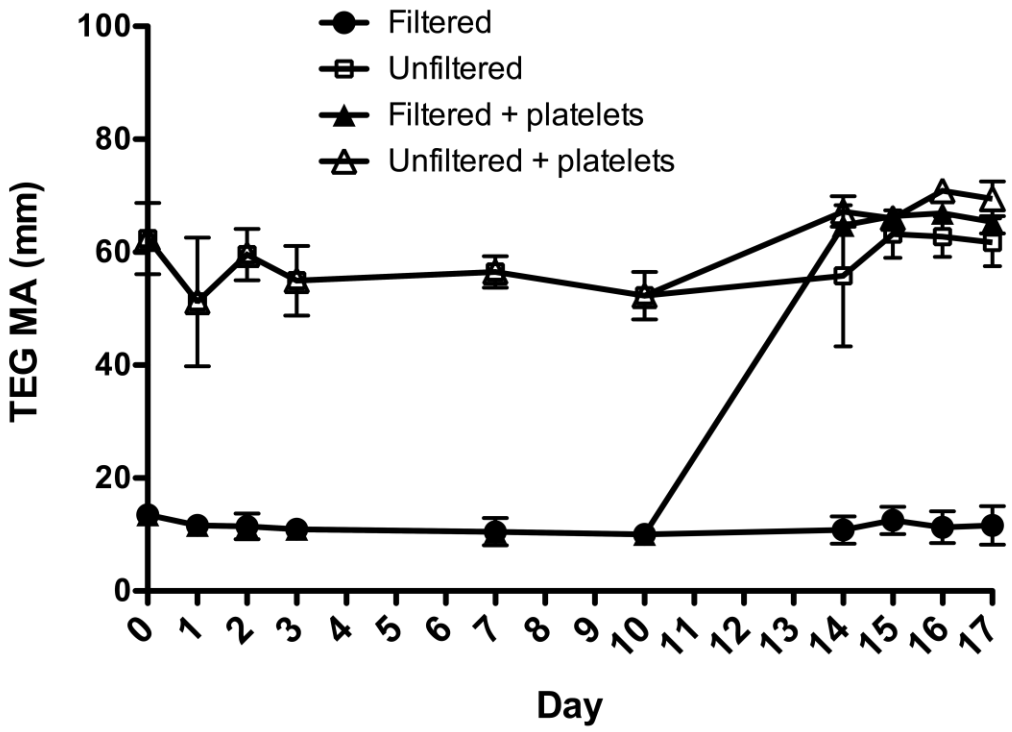
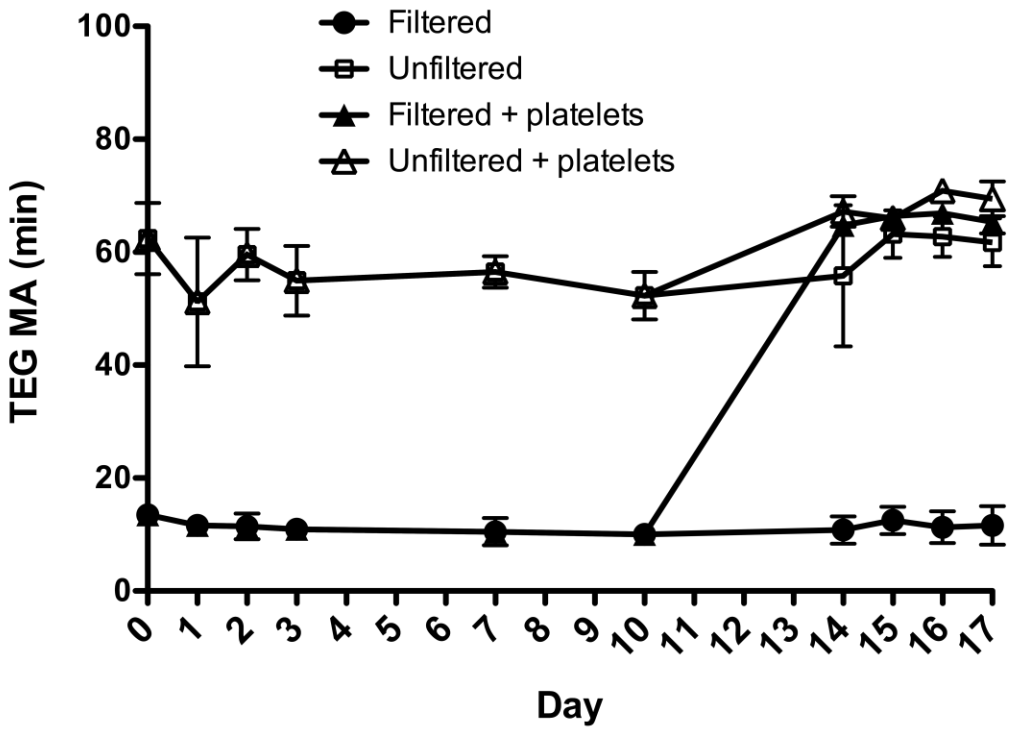

Filtered
Unfiltered
Filtered + platelets
Unfiltered + platelets
TEG angle (degree)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Day

Figure 5C.  Mean TEG MA. Values for filtered and unfiltered units were significantly different until addition of platelets . Normal MA 50-70 mm.


Filtered
Unfiltered
Filtered + platelets
Unfiltered + platelets
TEG MA (mm)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Day


Filtered
Unfiltered
Filtered + platelets
Unfiltered + platelets
TEG MA (min)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Day

**X-Chromosome Linked IRAK1 Polymorphism Is Strong Predictor Of Multiple Organ Failure And Mortality Post-Injury**

Jason Sperry*, **Brian Zuckerbraun***, Samuel Zolin*, Yorum Vodovotz*, Rami Namas*, Andrew Peitzman, Robert Ferrell*, Timothy Billiar
*University of Pittsburgh, Pittsburgh, PA*

**OBJECTIVE(S):** Clinical research characterizing the mechanisms responsible for gender based outcome differences post-injury remain conflicting. We sought characterize an x-chromosome linked IRAK1 polymorphism as an alternative mechanism responsible for gender differences post-injury. IRAK1 is key intermediate in the Toll Like Receptor (TLR) pathway thought to drive inflammation post-injury.
**METHODS:** A prospective cohort study was performed over an 18 month period. Blunt injured patients requiring ICU admission were enrolled while patients with isolated brain and spinal cord injuries were excluded. Outcomes of interest included Multiple Organ Failure (MOF, Mashall MODscore > 5) and mortality. Logistic regression was utilized to determine the independent risk of poor outcome associated with the IRAK1 variant after controlling for differences in injury and shock severity.
**RESULTS:** In an cohort of 272 patients, the prevalence of the IRAK1 variant was 12.5%. Patients with and without the variant were similar in age, injury severity and 24hr blood transfusion. After controlling for important confounders, the IRAK1 variant was independently associated with over a 6-fold (OR 6.4; 95% CI1.8-23) and 5-fold (OR 5.8; 95% CI1.4-24) greater risk of MOF and mortality, respectively. These differences were most prominent in males, while females heterozygous for the variant demonstrated worse outcome in a dose-dependent fashion.
**CONCLUSIONS:** The IRAK1 polymorphism is a strong independent predictor of MOF and mortality post-injury and represents a common variant with prognostic potential. These data demonstrate the importance of TLR signaling post-injury and supports that a genetic mechanism may drive gender outcome differences post-injury.

# The early evolving sex hormone environment is associated with significant outcome and inflammatory response differences after injury

**Samuel J. Zolin, Yoram Vodovotz, PhD, Raquel M. Forsythe, MD, Matthew R. Rosengart, MD, MPH, Rami Namas, MD, Joshua B. Brown, MD, Andrew P. Peitzman, MD, Timothy R. Billiar, MD,** *and* **Jason L. Sperry, MD, MPH,** *Pittsburgh, Pennsylvania*

**BACKGROUND:** Clinical research characterizing the mechanisms responsible for sex-based outcome differences after injury remains conflicting. Currently lacking is an understanding of the early sex hormone milieu of the injured patient and the effects these early hormone differences have on clinical outcomes and the innate immune response following injury.

**METHODS:** A prospective cohort study was performed over a 20-month period. Blunt injury patients requiring intensive care unit admission were enrolled. Samples were collected within 6 hours and at 24 hours after injury and were analyzed for total testosterone (TT) and estradiol concentrations. Outcomes of interest included multiple-organ failure (MOF; Marshall Multiple Organ Dysfunction Score [MODScore] > 5), nosocomial infection (NI), mortality, and serial cytokine/chemokine measurements. Multivariate logistic regression was used to determine the independent risks associated with early sex hormone measurements.

**RESULTS:** In 288 prospectively enrolled patients, 69% were male, with a median Injury Severity Score (ISS) of 16 (interquartile range 10–21). Elevated TT levels at 6 hours were associated with elevated interleukin 6 levels and cytokine/chemokine measurements (18 of 24 measured). Rising TT levels were significantly associated with more than a fivefold and twofold higher independent risk of MOF and NI, respectively (odds ratio [OR], 5.2; $p = 0.02$; 95% confidence interval [CI], 1.2–22.3; and OR, 2.1; $p = 0.03$; 95% CI, 1.02–4.2). At 24 hours, TT levels were no longer associated with poor outcome, while estradiol levels were significantly associated with nearly a fourfold higher independent risk of MOF (OR, 3.9; $p = 0.04$, 95% CI, 1.05–13).

**CONCLUSION:** Early elevations and increasing testosterone levels over initial 24 hours after injury are associated with an exaggerated inflammatory response and a significantly greater risk of MOF and NI. High estrogen levels at 24 hours are independently associated with an increased risk of MOF. The current analysis suggests that an early evolving testosterone to estrogen hormonal environment is associated with a significantly higher independent risk of poor outcome following traumatic injury. (*J Trauma Acute Care Surg*. 2015;78: 451–458. 

**LEVEL OF EVIDENCE:** Prognostic/epidemiologic study, level II.

**KEY WORDS:** Testosterone; estrogen; multiple-organ failure; nosocomial infection; regression.

An important and persistent finding has been that males and females respond differently following traumatic injury and hemorrhagic shock, with a relative protection afforded to females.[1,2] An increasing body of evidence from animal models has revealed that sex hormones and or their derivatives play an intricate role in the pathologic response to trauma hemorrhage. Estrogen and testosterone in disparate ways have been shown to influence the hemodynamic, immunologic, organ system, and cellular responses to traumatic insult in animals.[1–10]

The hormonal milieu of the proestrus female rodent has been shown to be protective following trauma and hemorrhage, while male sex steroids are associated with deleterious effects.[11–13] The strength of these laboratory findings has even led some to consider estrogen-based therapy as a possible therapeutic intervention following traumatic injury in human patients.[12,14]

Despite this mounting evidence, clinical studies have been unable to consistently reproduce these laboratory findings.[15–22] Recent prospective evidence, where sex hormone levels were measured 48 hours following injury, provides compelling evidence for estrogen (17β-estradiol [EST]) levels being associated with a greater risk of mortality, a conclusion which contradicts the majority of the experimental animal literature.[23] Similar findings for noninjured but critically ill patients have also been reported.[24,25] It remains unknown whether elevated endogenous estrogens out from the time of injury (>48 hours) are simply a

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This study was presented at the annual meeting of the American Association for the Surgery of Trauma, September 9–13, 2014, in Philadelphia Pennsylvania.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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marker or play a causal role for poor outcome.[23–25] Currently lacking is an understanding of the early sex hormone milieu of the injured patient (<6 hours from injury through 24 hours after injury) and the effects early sex hormones have on clinical outcomes and the immune response trajectory soon after injury.

In the present study, we sought to characterize the early sex hormone environment and its independent association with important clinical outcomes and the early innate immune response after injury. We hypothesized that estrogen would be associated with beneficial effects, while testosterone moieties would be associated with poor outcome.

## METHODS

A prospective observational cohort study was performed over a 20-month period (February 2011 to October 12) with the overarching goal of characterizing the mechanisms responsible for sex (male vs. female)–based outcome differences following traumatic injury. Inclusion criteria for the overall cohort study included blunt injury patients 17 years or older requiring intensive care unit (ICU) admission who arrived within 6 hours of injury to obtain early blood samples. Patients older than 90 years, those with isolated traumatic brain injury (no other injury identified other than brain injury), those with preexisting immunosuppression, those with an anticipated survival of less than 24 hours, or those patients where consent was unable to be obtained were excluded from enrollment. Blood samples were collected within 6 hours and again at 24 hours after injury and were analyzed for sex hormones (total testosterone [TT] and estradiol) and serial cytokine concentrations by specifically trained staff.[26] Clinical outcomes assessed included the development of multiple-organ failure (MOF, Marshall Multiple Organ Dysfunction Score [MODScore] > 5), nosocomial infection (NI), and in-hospital mortality.

Under the auspices of a waiver of initial consent (up to 48 hours), blood was obtained from enrolled patients upon arrival or soon after within 6 hours from the time of injury and again at 24 hours after injury in most patients. A 48-hour window was approved to obtain consent for the use of samples from the time of admission. All samples and data were destroyed if consent was unable to be obtained within the 48-hour widow. Plasma was separated from whole blood and stored at −70°C for batched analysis. TT and EST levels were measured using high sensitivity ELISA kits following the manufacturer's directions (Testosterone ELISA kit, catalog #ADI-900-176; 17β-estradiol ELISA kit, catalog # ADI-900-174; ENZO Life Sciences, Inc., Farmingdale, NY). Human inflammatory MILLIPLEX MAP Human Cytokine/Chemokine Panel-Premixed kits (catalog # HCYTOMAG-60K and # HCYTOMAG-60K; Millipore Corporation, Billerica, MA) and Luminex 100 IS (Luminex, Austin, TX) were used to measure plasma levels of cytokines and chemokines (interleukin 1β [IL-1β], IL-1RA, IL-2, sIL-2Rα, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-13, IL-15, IL-17, interferon γ, IP-10, MIG, MIP-1α, MIP-1β, MCP-1, GM-CSF, Eotaxin, tumor necrosis factor α, NO2/NO3, and interferon α) per the manufacturer's directions.

Sex hormone variables for TT and EST were first dichotomized at their median values into high and low groups. Sex hormone levels were further categorized over time into groups of less than 6 hours (<6HR), 24 hours (24HR), and additionally a group where hormone measurements were increasing between 6HR and 24HR measurements (rising). Finally, EST/TT ratios were also characterized and used for the cytokine and outcome analyses.

MOF was evaluated using the well-validated Marshall MODScore.[27–29] A MODScore greater than 5 beyond 48 hours from injury was classified as MOF. Primary nosocomial infectious outcomes of interest included ventilator-associated pneumonia, blood stream infection (excluding those associated with an intra-abdominal abscess), and urinary tract infections.[30] These were selected in attempts to use those infectious outcomes, which can be used as a marker for the degree of relative immune dysregulation/suppression. The development of these NIs was based on positive culture evidence. Diagnosis of a ventilator-associated pneumonia required a quantitative culture threshold of equal to or greater than $10^4$ colony-forming units (CFU) per milliliter from bronchoalveolar lavage specimens. Diagnosis of catheter-related blood stream infections requires positive peripheral cultures with an identical organism obtained from either a positive semiquantitative culture (>15 CFU per segment) or a positive quantitative culture (>$10^3$ CFU per segment) from a catheter segment specimen. Urinary tract infections required greater than $10^5$ organisms per milliliter of urine.

First, male and female patients underwent unadjusted comparison of demographics, injury characteristics, resuscitation and transfusion requirements, clinical outcomes, and sex hormones. Correlation analysis was then performed between sex hormone levels and cytokine/chemokine measurements following variable log transformation. Finally, multivariable logistic regression analysis was then used to determine the independent odds of our clinical outcomes associated with sex hormone levels (high vs. low) after adjusting for important confounders. Covariates adjusted for in the regression model included age (>50 years or ≤50 years), sex, Injury Severity Score (ISS), emergency department systolic blood pressure (SBP), emergency department Glasgow Coma Scale score (GCS score > 8 or GCS score ≤ 8), intubation status (yes/no), presenting coagulopathy (international normalized ratio > 1.3, yes/no), 6-hour or 24-hour crystalloid and blood component transfusion requirements (packed red blood cells, fresh frozen plasma, platelets), body mass index, and oral contraceptive use (yes/no).

Mortality was used as the primary outcome to determine our sample size because this is the most stringent outcome to occur relative to the development of MOF and NI. Based on trauma admissions to the ICU at the University of Pittsburgh and with the use of similar inclusion and exclusion criteria, for a similarly injured cohort as proposed, the mortality rate overall was 10%. Based on these projections, an allocation ratio of 0.10 (survivor vs. nonsurvivor) was used for sample size estimation. Based on the previous literature[23,24] where serum levels of EST in both males and females were found to be significantly associated with mortality; survivors-[EST] = 32.4 (50) pg/mL vs. nonsurvivors-[EST] = 66.9 (70) pg/mL, with an $\alpha = 0.05$ and a $\beta = 0.20$, our projected sample size using a two-sided Mann-Whitney U-test was 320 patients.

All data were summarized as mean (SD), median (interquartile range [IQR]), or percentage. Student's *t* or Mann-Whitney

statistical tests were used to compare continuous variables, while $X^2$ or Fisher's exact test was used for categorical variables. A $p \leq 0.05$ was considered statistically significant. The institutional review board at the University of Pittsburgh approved this study.

## RESULTS

During a 20-month period, more than 2,000 patients were screened, with 288 patients being prospectively enrolled and consented who met all inclusion and exclusion criteria and underwent early (<6HR) blood sampling from the time of injury (Fig. 1). This cohort of patients was 69% male, with a mean (SD) age of 50 (18) years, and constituted a moderately injured study cohort, with a median ISS of 16 (IQR, 10–21). More than 31% of the patients required blood transfusion in the first 24 hours, with the prevalence of MOF, NI, and in-hospital mortality being 13.6%, 29.9%, and 3.1%, respectively. Importantly, 24HR sample collection was attempted for all enrolled patients but were only able to be obtained in 237 patients, representing an 82% patient sample follow-up rate.

Males and females were statistically similar in age, injury severity, presenting injury characteristics, transfusion and resuscitation requirements, and important clinical outcomes (Table 1). Interestingly, there were no statistical differences in <6HR sex hormone measurements for either EST or TT as continuous variables across males or females. Males were, however, more likely to have pneumonia as a subtype of NI, despite NIs overall not being different across the groups.

When <6HR sex hormone levels were dichotomized into high and low groups based on the median of the measurement distribution, there was no statistical differences in early EST levels, early TT levels, or the EST/TT ratio across males and females (Table 2). To verify that EST and TT measurements were not concurrently elevated and colinear, we verified that more than 36% of the patients had either high TT with low EST measurements or vice versa irrespective of male or female sex ($p < 0.001$). We similarly found no significant differences in <6HR sex hormones (EST, TT) across age (≤50 years vs. >50 years, EST, $p = 0.444$; TT, $p = 0.958$) or when further stratified by male or female sex.

When high and low sex hormone and IL-6 cytokine levels were compared, both early (6 hours) and 24-hour high TT were significantly associated with elevated IL-6 levels ($p = 0.015$, $p = 0.004$), while no significant relationship was found between IL-6 levels and EST. When correlation analysis of TT, EST, and 24 cytokine/chemokine levels were performed following log transformation for normality considerations, no significant correlations were found for <6HR EST, rising EST, or 24HR EST with any of the measured cytokine/chemokine levels. Similar results were found when correlation analysis was performed between cytokine/chemokine levels and EST/TT ratio at any time point. Interestingly, when <6HR TT levels were correlated with cytokine/chemokine levels, 3 of the 24 measurements demonstrated a significant correlation (IP10, MIP-1α, and MIP-1β). When rising TT levels were analyzed, the majority (16 of 24) of the cytokine/chemokine panels were significantly correlated (positive correlation) with rising TT levels. When 24HR TT levels underwent correlation analysis, the majority (16 of 24) of cytokine/chemokine measurements again were significantly correlated (positive correlation) but with higher Pearson correlation coefficients in all cases, consistent with a greater

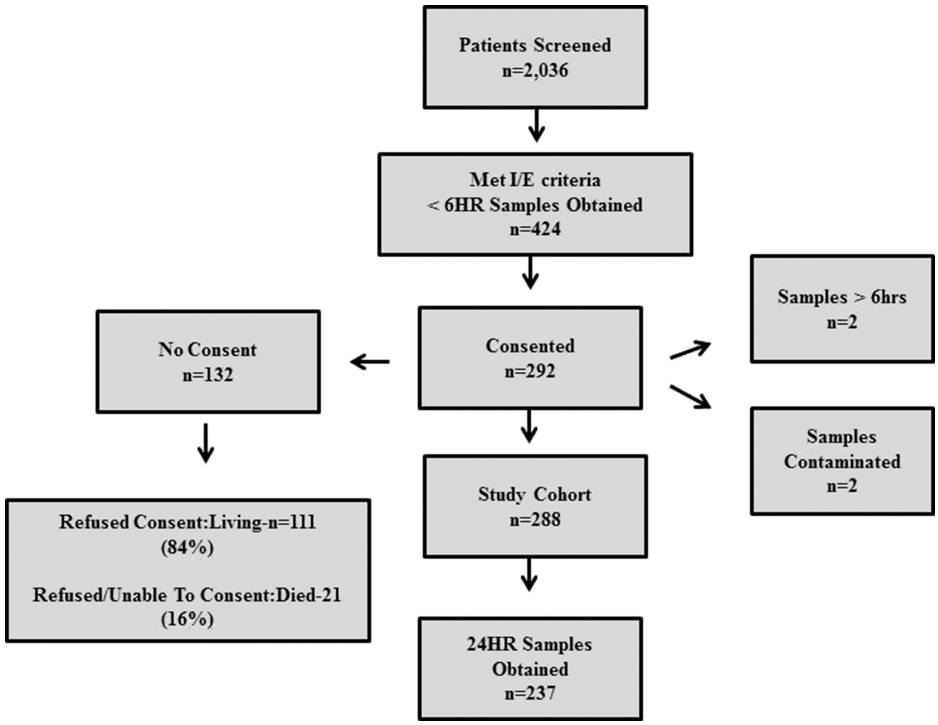


**Figure 1.** Study cohort enrollment diagram.

**TABLE 1.** Unadjusted Comparison of Male and Female Demographics, Injury Characteristics, Resuscitation Needs, and Clinical Outcomes

| | Males (n = 197) | Females (n = 91) | *P* |
|---|---|---|---|
| Age, mean (SD), y | 54 (18) | 50 (18) | 0.060 |
| ED SBP, mean (SD), mm Hg | 131 (27) | 126 (29) | 0.085 |
| ED hypotensive (SBP < 90 mm Hg), % | 8.1 | 10.0 | 0.601 |
| ED GCS score, median (IQR) | 15 (14–15) | 15 (15–15) | 0.446 |
| ED GCS score < 8, % | 16.8 | 15.6 | 0.800 |
| ISS, median (IQR) | 17 (10–22) | 14 (10–19) | 0.450 |
| ISS > 16, % | 51.3 | 45.6 | 0.386 |
| ED intubation status, yes, % | 13.7 | 11.2 | 0.573 |
| Presenting coagulopathy (international normalized ratio > 1.3), % | 17.9 | 24.6 | 0.221 |
| Body mass index, mean (SD) | 29.1 (7) | 28.3 (7) | 0.153 |
| ICU days, mean (SD) | 6.1 (6) | 5.0 (6) | 0.183 |
| Length of stay ICU | 11.7 (9) | 11.2 (9) | 0.685 |
| 24-h crystalloid, mean (SD), mL | 3,593 (2,527) | 3,354 (1,963) | 0.428 |
| 24-h blood transfusion, mean (SD), mL | 509 (1,244) | 445 (895) | 0.493 |
| 24-h plasma transfusion, mean (SD), mL | 264 (978) | 158 (520) | 0.335 |
| 24-h platelet transfusion, mean (SD), mL | 92 (284) | 41 (187) | 0.109 |
| Massive transfusion (≥10 U packed red blood cells in 24 h), % | 5.6 | 2.2 | 0.204 |
| NI, % | 30.5 | 27.8 | 0.645 |
| Pneumonia, % | 23.4 | 13.3 | 0.050* |
| MOF, % | 14.7 | 11.1 | 0.408 |
| Mortality, % | 4.1 | 1.1 | 0.183 |
| 6-h TT, mean (SD), pg/mL | 38.4 (44) | 33.6 (16) | 0.315 |
| 6-h EST, mean (SD), pg/mL | 44.2 (38) | 41.2 (22) | 0.849 |

magnitude of correlation (Supplemental Digital Content 1, http://links.lww.com/TA/A524).

Our regression models were excellent predictors of our primary outcomes based on the area under the curve from receiver operating characteristic curves and demonstrated adequate diagnostics (Table 3). After controlling for important confounders, logistic regression analysis demonstrated no significant independent relationship between <6HR TT levels or <6HR EST and the development of MOF, NI, or in-hospital mortality (Figs. 2 and 3). When the analysis focused on hormone levels, which increased between the early and 24-hour period, rising TT levels were significantly associated with more than a fivefold and a twofold higher independent odds of MOF and NI, respectively (odds ratio [OR], 5.2; $p = 0.02$; 95% confidence interval [CI], 1.2–22.3; and OR, 2.1; $p = 0.03$; 95% CI, 1.02–4.2). Rising EST levels were associated with a threefold higher odds of MOF, but this relationship failed to reach statistical significance (OR, 3.0; $p = 0.089$; 95% CI, 0.85–10). Interestingly, at the 24HR time point, TT levels were no longer significantly associated with the development of MOF or NI, while EST levels were significantly associated with almost a fourfold higher independent odds of MOF (OR, 3.9; $p = 0.04$; 95% CI, 1.05–13) at this time point.

**TABLE 2.** Dichotomized Sex Hormone Levels (High vs. Low) for Early (<6HR) Sex Hormone Level Compared Across Males and Females

| Early (<6HR) Sex Hormone Measurements (n = 288) | Male (n = 197) | Female (n = 90) | *p* |
|---|---|---|---|
| High EST | 52.2% | 49.2% | 0.639 |
| High TT | 48.9% | 50.3% | 0.830 |
| High EST/TT ratio | 48.7% | 53.3% | 0.469 |

## DISCUSSION

Significant advances in trauma care delivery and post-injury management practices have occurred during the last decade, yet patients who survive their initial injury continue to be plagued with the development of sepsis and MOF and their attributable morbidity and mortality.[27,31–35] Despite a significant increase in our basic understanding of these detrimental outcomes, a dearth of effective interventions exist. An important and persistent literature finding, with possible therapeutic potential, has been that males and females respond differently following traumatic injury and hemorrhagic shock.[1,17,18] A growing body of evidence from animal models suggests that this dimorphic

**TABLE 3.** Logistic Regression Model Diagnostics

| Logistic Regression Model Outcome | AUC via ROC Curve Analysis | Hosmer-Lemeshow |
|---|---|---|
| Mortality | 0.969 | 0.840 |
| MOF | 0.898 | 0.559 |
| NI | 0.760 | 0.463 |

AUC, area under the curve; ROC, receiver operating characteristic.

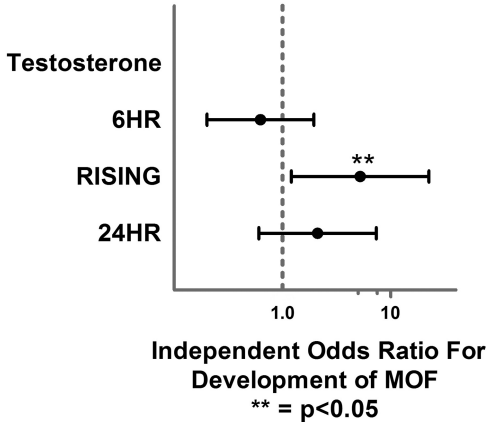


**Figure 2.** Forest plot depicting independent odds of MOF associated with early, increasing, and 24-hour TT levels.

response following trauma and hemorrhage is hormonally based (estrogen, testosterone, or their derivatives).[4,6,36] Despite these advancements in our understanding, clinical studies have been unable to consistently reproduce these laboratory findings and have provided clinical evidence that contradicts the majority of animal literature.[23–25] Lacking until this time has been a clear understanding of the early sex hormone environment, which potentially has effects on clinical outcomes, and the early immune response trajectory, which follows traumatic injury. The results of the current analysis demonstrate that despite a paucity of sex-specific differences in a moderate-sized blunt injury cohort of patients, the evolving sex hormone environment after injury is associated with both clinical outcome and innate immune response differences soon after injury. Despite sex hormones varying little across male and female sex early on (<6HR), these sex hormone–specific associations were strong and independent of important confounders. Early and rising testosterone levels were found to be significantly associated with an exaggerated cytokine/chemokine response and detrimental clinical outcomes, which diminished in strength over time up until 24 hours after injury. Concurrently, estrogen levels were found to be strongly associated with detrimental clinical outcome at the delayed 24-hour period alone.

These results correspond and add further understanding to the previous literature, which has demonstrated that estrogen is associated with mortality and poor outcome irrespective of male or female sex at 48 hours out from injury or sepsis.[23–25] These results provide insight into the possible mechanisms by which the sex-based outcome differences after injury come about.[2] Essential to understanding these associations is the fact that peripheral conversion of androgens to estrogens can occur via increased aromatase activity and may be stimulated by the early cytokine response, which complicates traumatic injury.[37–39] The current results suggest that early testosterone may be associated with an exaggerated innate immune response and an early evolving testosterone to estrogen hormonal environment is associated with a significantly higher independent risk of poor outcome following traumatic injury.

The potential implications of these results may bridge the current "bench to bedside divide"[2] in our understanding of experimental animal evidence, suggesting testosterone's detrimental effects following hemorrhagic shock and the clinical evidence in humans demonstrating the negative associations of estrogen. Although the current results cannot imply causation and although peripheral conversion of testosterone to estrogen was not measured, the strength of the independent findings in a relatively small, moderately injured cohort of patients does provide strength to the validity of these associations and provides the impetus to further study these relationships to determine if a therapeutic benefit can be derived from sex hormone therapy following injury.

The current analysis has several limitations that deserve discussion. First, the potential for selection and survivor bias exist, despite all attempts to minimize such difficulties, because of the nonrandomized enrollment. Although the data collected for the prospective cohort analysis were extensive, potential unknown or unmeasured confounding variables may be responsible for the associations described and the conclusions formulated. Prehospital medicines that may interfere with sex hormone measurements were prospectively collected and controlled for in the analysis, but unknown or undocumented medicines remain a potential confounder for the analysis. There was a lower-than-expected incidence of the selected pertinent outcomes of the study including MOF and mortality, which can have an exaggeratory effect on the ORs presented in certain circumstances. Despite showing a robust association with MOF and NI, no relationship was found between sex hormone levels and mortality. Importantly, it has been previously demonstrated that a large portion of the most critically injured patients experience mortality relatively early, commonly within the first 24 hours to 48 hours.[40] Because of the requirement of informed consent, the most critically ill patients had a lower consent rate significantly reducing the incidence of mortality for the study cohort. Although the <6HR early cytokine expression measurements that were performed represents a relatively early time point compared with most other studies, this may still represent a delayed measurement for cytokine/chemokine expression, which drives the development of MOF, NI, and mortality. The time of sample obtainment in the 6-hour inclusion criteria window was

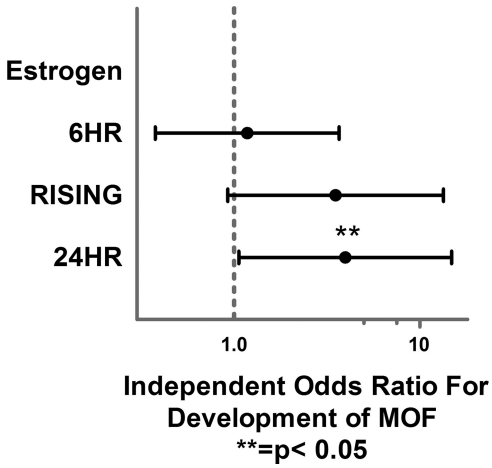


**Figure 3.** Forest plot depicting independent odds of MOF associated with early, increasing and 24-hour total EST levels.

not recorded and potentially may confound these early measurements and result in a time bias. There also existed a reduction or drop off in the number of samples collected from the enrolled 288 patients at the <6HR period to 237 samples at the 24HR period. The potential exists that the 18% of measurements could alter the reported results and conclusions of the study. Interestingly, there existed no differences in early sex hormone measurements across males and females. Similarly, there were no differences found across age (<50 years or ≥50 years) when compared. Despite this lack of hormone differences, there existed strong clinical associations for the sex hormone levels themselves. The study may be underpowered to see these sex- and age-based hormonal differences. The menstrual cycle status or the menopausal status was not obtained from females in the study cohort. Differences in these cycles and periods in females may result in spurious modeling and alter the significance of these findings and limit the applicability to other studies. Finally, this study was performed at a single Level I trauma center and may not be generalizable or pertinent to other centers with differing admission demographics, injury characteristics, or management practices.

In conclusion, early (<6 hours) elevations and increasing testosterone levels over the initial 24 hours are associated with an exaggerated inflammatory response and a significantly greater independent odds of MOF and NI. By 24 hours after injury, however, testosterone is no longer significantly associated with poor outcome. Early elevations and increasing estrogen levels were not associated with differences in the early inflammatory response or a significant greater odds of poor outcome, but estrogen levels at 24 hours after injury are independently associated with a greater odds of MOF. These results suggest that an early evolving testosterone to estrogen hormonal environment over the initial 24 hours after injury has the potential to predict clinical outcome trajectory. These sex hormone changes may in part be responsible for sex-based outcome differences following traumatic injury. Higher-level studies are required to determine if these sex hormone changes play a causal role in these outcome differences and whether therapeutic potential exist via their actions.

## AUTHORSHIP

S.J.Z. and J.L.S. designed the study and performed the literature search, data collection, and data analysis. S.J.Z., Y.V. J.B.B., M.R.R., R.M.F., and J.L.S. participated in the initial manuscript preparation. All authors contributed to the data interpretation and critical revision of the manuscript.

## DISCLOSURE

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## DISCUSSION

**Dr. Reuven Rabinovici** (Boston, Massachusetts): Before I discuss this paper I would like to congratulate the presenter, Samuel Zolin, who is a medical student, for being courageous enough to present his work at AAST. I hope he will continue to conduct trauma-related research and wish him success in these efforts.

Now, as a husband and father of three daughters I pretty quickly noticed that there are differences between males and females. As we all know, some of these differences are quite obvious. However, whether males and females respond differently to traumatic injury is not one of those.

In fact, in detailed review of the papers investigating this topic reveals nothing short of chaos and demonstrates conflicting reports on all aspects of potential trauma-related gender differences. Citing the many contradictory papers is beyond the scope of my discussion today. However, to spice it up I will quote some of the reported conclusions.

One study concluded that, "…these data suggest that gender has no relationship to mortality in blunt trauma patients…", while another study summarized that, "…females aged between 13 and 64 years exhibit significantly lower mortality than males after trauma-associated shock." Another study determined "…gender does not play a role in post-traumatic mortality or in the incidence of acute complications after any degree of traumatic brain injury." In contrast, other authors reported that female gender is independently associated with reduced mortality and decreased complications after TBI. And the list goes on and on.

So it is within this context that the authors aim to further investigate this complex topic by establishing the testosterone and estradiol profile during the first 24 post-injury hours in ICU blunt trauma patients. They also recorded multiple organ failure, nosocomial infection, and mortality rates as well as the serum levels of proinflammatory mediators. Lastly, they used multivariate logistic regression to identify which of the above influences is associated with the hormonal profile they described.The authors report that elevated testosterone within the initial six hours was associated with increased rate of multiple organ failure and nosocomial infection as well as an enhanced inflammatory response. They also stated that the 24-hour estradiol were associated with higher risk of multiple organ failure. I have four questions to the authors.

1. How do your data help put in order in the disorder I just described?
2. You did not find inter-gender and age-related hormonal differences. How do you explain that?
3. You did not find correlation between the hormonal profile and mortality, the ultimate outcome parameter. How do you explain that?

And, lastly, do you have any information to suggest whether the hormonal profile you described is responsible for or a marker of outcome?

In summary, this is a well-designed study. However, it seems to add more confusion to an already complex and much-debated topic. I congratulate the group from Pittsburgh for their continuous efforts to identify yet another difference between males and females and thank the association for the privilege of the floor.

**Dr. Carl J. Hauser** (Boston, Massachusetts): Thank you. Very nice paper. I'd like to ask whether the authors think that testosterone is an acute phase respondent here or whether one of the enzymes in the peripheral aromatase pathway may be, for instance, a negative acute phase respondent, perhaps under the influence of IL-6.

**Dr. David Livingston** (Newark, New Jersey): Yes, very nicely done. Very nicely presented as a student. Great job. We showed that being female and young you seem to be a lot more resistant to shock. That's really what a lot of the experimental studies did.

Did you look at differences in blood utilization, lactate, and base deficit? Were there any between some of your younger females and males eventually leading on to organ failure?

And, as you nicely showed, the milieu is kind of very complicated but at least early on, the females appear to be more resistant to shock.

**Mr. Samuel J. Zolin** (Pittsburgh, Pennsylvania): Thank you very much for these questions. With regard to what exactly this adds to our knowledge base and what it might clarify regarding the early sex hormone environment and outcomes, this study provided a much earlier measurement of serum sex hormones than previous work had done.

As I mentioned, previous work at 48 hours following injury had demonstrated poor outcome with differences in hormonal status.

We demonstrated that an evolving hormonal profile over the first 24 hours following injury may be associated with poor outcome.

Measurement of hormone level at earlier time points, as we did in this study, may reduce the confounding effect that peripheral aromatization may play, although we did not make any direct measurement of peripheral aromatization within subjects in this study.

To answer the line of questioning regarding testosterone's role as either being a marker of poor outcome versus a driver of poor outcome following injury, I believe further research is needed.

While we demonstrated significant associations between testosterone level at different time points and markers of the innate immune response and poor clinical outcome, this was a strictly observational study.

While we attempted to obtain blood samples from patients as soon as possible following injury in order to characterize their baseline hormonal status, which should give a more clear picture of the role of these hormones as markers or causative factors, it is possible that changes in hormone level begin very early after injury, perhaps even earlier than we accounted for.

It's worth recalling that animal studies do support a causative role for testosterone in poor outcome following trauma.

An interventional study of androgen modulation following trauma in humans would likely provide the most conclusive evidence regarding testosterone's role in outcome following injury.

With regard to the question of why there was no demonstrated difference between men and women with respect to sex hormone levels in this study, this is one of the first studies to analyze the early sex hormone environment following injuries in humans.

It may be that alternations of sex hormone levels following injury occur very soon after injury, even earlier than the six-hour window from injury to sampling that we used.

It may also be that lack of information regarding menstrual and menopause status of females in this study was a confounder.

Finally, regarding the question of mortality as an outcome, our analysis demonstrated no statistically significant difference with regard to the incidence of mortality based on hormone level.

This aspect of our study may have been influenced by the fact that there was a lower-than-expected consent rate for those with early mortality in our study population.

It is possible that with a higher incidence of in-hospital mortality, a hormone-based relationship would have become apparent.

Of course, it is also possible that a hormone-associated relationship with mortality following injury does not exist in humans.

Thank you again for your attention and for the opportunity to present today.

## Poster 18

# SEX BASED THROMBOELASTOGRAPHY DISPARITIES POST-INJURY: INDEPENDENTLY DIFFERENT EARLY ON BUT WHY?

Tiahuna Zhou, BS, Samuel Zolin, Timothy Billiar, MD,
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University of Pittsburgh Medical Center

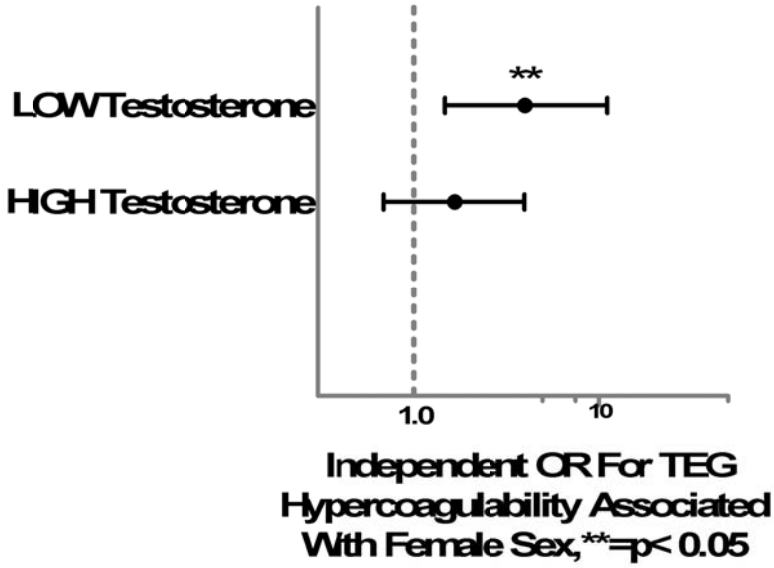
**Presenter:** Tiahuna Zhou, BS

**Objectives:** The beneficial use of thromboelastography (TEG) to adequately detect coagulopathy and direct blood component transfusion during resuscitation has been demonstrated. Despite this evidence, little is known regarding male and female differences in TEG measurements and the mechanisms responsible for disparities post-injury. We hypothesized there would be significant differences in TEG parameters with females being more hypercoaguable due to sex hormone differences.

**Methods:** Data were derived from a prospective cohort study designed to characterize mechanisms responsible for sex based outcome differences post injury. Blunt injured patients requiring ICU admission were included. Isolated TBI, cord injury or patients on anticoagulation were excluded. TEG parameters (r, k-time, alpha angle, MA, G, LY30) and sex hormone levels (estradiol, total testosterone) were obtained <6 hrs and at 24 hrs post injury.

**Results:** Males and females in the study cohort (n=208) were similar in injury severity, presenting vitals, GCS, 24 hour resuscitation/transfusion needs and presenting INR. Regression analysis demonstrated female sex was independently associated with hypercoaguable TEG parameters at 6 hours (R, k-time, MA, G) and at 24 hours (k-time, alpha angle) after controlling for important confounders. TEG based hypercoagulability in females was present irrespecitve of age (>/< 50yoa) and early estrogen levels (high/low). TEG based hypercoagulability in females was no longer apparent when early testosterone levels were elevated.

**Conclusions:** Independent disparities exist in TEG parameters across males and females post-injury. These differences were apparent early and remained persistent with females demonstrating a hypercoaguable phenotype. The data suggest that early testosterone rather than age or estrogen levels may be play a role in these independent TEG based disparities across males and females post injury.




Independent OR For TEG Hypercoagulability Associated With Female Sex,**=p< 0.05

# X Chromosome-Linked IRAK-1 Polymorphism Is a Strong Predictor of Multiple Organ Failure and Mortality Postinjury

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**Objective(s):** Clinical research characterizing the mechanisms responsible for sex-based outcome differences postinjury remain conflicting. We sought to characterize an X chromosome-linked IRAK-1 (IL-1 receptor-associated kinase) polymorphism as an alternative mechanism responsible for sex differences postinjury. IRAK-1 is key intermediate in the toll-like receptor (TLR) pathway thought to drive inflammation postinjury.

**Methods:** A prospective cohort study was performed over a 24-month period. Bluntly injured patients requiring intensive care unit admission were enrolled, whereas patients with isolated brain and spinal cord injuries were excluded. Outcomes of interest included multiple organ failure (MOF, Marshall MOD score > 5) and mortality. Logistic regression was utilized to determine the independent risk of poor outcome associated with the IRAK-1 variant after controlling for important differences.

**Results:** In an enrolled cohort of 321 patients, the IRAK-1 variant was common (12.5%). Patients with and without the variant were similar in age, injury severity, and 24hr blood transfusion. After controlling for important confounders, the IRAK1 variant was independently associated with more than eightfold (OR = 8.4, $P = 0.005$, 95% CI: 1.9–37.1) and 11-fold (OR = 11.8, $P = 0.037$, 95% CI: 1.1–121) greater risk of MOF and mortality, respectively. These differences were most prominent in men, whereas women heterozygous for the variant demonstrated worse outcome in a dose-dependent fashion.

**Conclusions:** The IRAK1 polymorphism is a strong independent predictor of MOF and mortality postinjury and represents a common variant with prognostic potential. These data demonstrate the importance of TLR signaling postinjury and supports that a genetic mechanism may drive sex outcome differences postinjury.

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Although significant advances in the care of the injured patient have occurred over the last decade, those who survive their initial injury continue to be plagued with the development of coagulopathy, multiple organ failure (MOF), nosocomial infection (NI), and their attributable morbid effects.[1–6] A persistent finding has been that men and women respond differently after traumatic injury with significant protection afforded to the female sex.[7,8] Controversy exists regarding the clinical explanation and underlying mechanisms responsible for this female protective effect.[7,9,10]

A large body of laboratory evidence suggests that a sex-hormone–based mechanism (estrogen being protective) is responsible for these postinjury differences.[8,11–14] In prior work, our group has shown that the protective effect afforded to women following severe injury is independent of age and the hormonal status of the female, suggesting other mechanisms may be involved clinically.[7,15] Men and women also are different genetically, primarily due to the method of inheritance of, and the genes which reside on, the X chromosome. Secondary to the known mosaic expression of the X chromosome, women would be less affected by unfavorable X chromosome-linked genetic variants.[16] Importantly, increasing evidence also has demonstrated that the Toll-like receptor (TLR) signaling cascade plays an essential role in the early activation of the innate immune response after traumatic injury.[17–24] The IL-1 receptor-associated kinase (IRAK-1) is a protein constituent member of the TLR signaling cascade, which resides on the X chromosome and has been demonstrated to have 2 haplotypes. The IRAK-1 variant haplotype has been demonstrated to be relatively common and associated with worse outcome in septic patients, thought to be secondary to an excessive innate immune response brought about by upregulated NF-$\kappa$B signaling.[25–27] No evidence currently exists regarding the significance of this TLR pathway variant, which resides on the X chromosome on pertinent outcomes after traumatic injury. We sought to characterize the IRAK-1 variant as an alternative mechanism responsible for sex-based outcome differences postinjury. We hypothesized that the IRAK-1 variant would be common and independently associated with poor clinical outcome after traumatic injury.

## METHODS

A prospective observational cohort study was performed over a 24-month time period (2011–2012) with the overarching goal to further characterize the mechanisms responsible for sex (male vs female) based outcome differences after traumatic injury. Inclusion criteria for the study included blunt injured patients older than 17 years requiring ICU (intensive care unit) admission. Patients older than 90 years, with isolated traumatic brain injury, preexisting immune-suppression, or those with an anticipated survival of less than 24 hours were excluded from enrollment. Blood samples were obtained within 6 hours of injury for serial cytokine measurements, coagulation assessment [international normalized ratio (INR), thromboelastography (TEG) analysis], and DNA isolation and haplotype discrimination. Clinical outcomes assessed included the development of MOF, NI, and mortality.

The IRAK-1 variant haplotype was determined by genotyping the single nucleotide polymorphism on the X chromosome where a T→ C substitution [rs1059703] at position 1595 in exon12 results in a nonsynonymous mutation (532, L→ S). Probe and primer combinations were designed for genotyping this polymorphism and polymerase chain reaction (PCR) was performed using an Applied

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Biosystems 7300 Real-Time PCR system using methods previously described.[25,27] Allelic discrimination was verified by direct DNA sequencing of a small subgroup of patients of each haplotype (men and women: wild-type, variant, and heterozygous, respectively) to assure the PCR-based assay was sufficiently accurate.

MOF was evaluated using the well-validated Marshall Multiple Organ Dysfunction Score.[5,28,29] A Marshall Multiple Organ Dysfunction Score of more than 5 beyond 48 hours of injury and ICU admission was classified as MOF. Primary infectious outcomes of interest include ventilator-associated pneumonia, blood stream infection (excluding those associated with an intra-abdominal abscess), and urinary tract infections.[30] These were selected in attempts to use those infectious outcomes that can be used as a marker for the degree of relative immune suppression. The development of these NIs was based on positive culture evidence.

Blood samples were serially obtained at 6 hours, 24 hours, and 72 hours of injury, and serum was separated and frozen at −80°C until assayed for cytokine analysis. Cytokine expression including IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-15, IFN-$\alpha$, and IFN-$\gamma$ were measured from patients' serum using a Luminex 100 IS System and commercially available human specific beadsets. Thromboelastography (TEG) was performed within the first 6 hours of injury and at 24 hours using on a TEG 5000 Thromboelastograph Hemostasis Analyzer and standard TEG parameters were recorded including *r* value, k time, $\alpha$ angle, maximal amplitude (MA), G value, and fibrinolysis at 30 minutes (LY30) as previously described.[31–35]

First, patients with and without the IRAK-1 polymorphism underwent unadjusted comparison of demographics, injury characteristics, resuscitation and transfusion requirements, and clinical outcomes. Multivariable logistic regression analysis was then utilized to determine the independent risks of our clinical outcomes associated with the IRAK-1 variant. Covariates adjusted for in the regression model included age, sex (male vs female), race, body mass index (BMI), injury severity score (ISS), presenting systolic blood pressure (SBP), presenting Glasgow Coma Score (GCS), intubation status, presenting coagulopathy (INR > 1.5), 24-hour crystalloid, and blood component transfusion requirements. Because of the X chromosome location of the polymorphism, we then characterized the risk of our clinical outcomes across whether the IRAK-1 variant existed in a homozygous manner (male-1 variant allele, female -2 variant alleles) or heterozygous manner (women—1 variant allele) to determine if a dose-response relationship existed. Finally, we characterized serial cytokine expression and TEG parameters for patients with and without the IRAK-1 polymorphism.

All data were summarized as mean ± SD, median (interquartile range), or percentage (%). Student *t* test or Mann-Whitney statistical test was used to compare continuous variables, whereas $\chi^2$ test or Fischer exact test was used for categorical variables. $P \leq 0.05$ was considered statistically significant. The institutional review board at the University of Pittsburgh approved this study.

## RESULTS

Over the study time period, 321 patients met inclusion and exclusion criteria and constituted the study cohort. The overall study cohort had a mean age of 50 ± 16 years, 70% male, and a median ISS of 16 [10, 21]. The cohort had an average ICU length of stay of 5.3 ± 6 days, and an overall incidence of MOF, NI, and mortality for the cohort was 8.1%, 27.0%, and 4.4%, respectively. The prevalence of the IRAK-1 polymorphism across men and women in the study cohort was 21.5% when heterozygous women (n = 29) were also included. For the purposes of the principal analyses, only homozygous patients (men—1 variant allele, women—2 variant alleles) were considered to have the IRAK-1 variant (12.5%). In the IRAK-1 variant group, 5 patients were female and were homozygous for the variant allele.

When IRAK-1 variant patients were compared with those with the normal haplotype, patients were similar in demographics, presenting vital and GCS, overall injury severity, and 24-hour resuscitation and transfusion requirements. (Table 1). IRAK-1 patients were more commonly male and had a significantly higher rate of MOF and mortality in unadjusted comparison.

**TABLE 1.** Unadjusted Comparison of IRAK-1 Variant and Normal Haplotype Demographics, Injury Characteristics, and Outcomes

| | IRAK-1 Variant (n = 40) | Normal Haplotype (n = 281) | *P* |
|---|---|---|---|
| Age (yrs) | 47 ± 22 | 50 ± 19 | 0.388 |
| Sex (%Male) | 87.5% | 67.3% | 0.009 |
| Race | | | |
| Caucasian | 72.5% | 81.5% | |
| African American | 7.5% | 2.5% | |
| Other/Unknown | 20% | 16.0% | 0.176 |
| ED SBP (mm Hg) | 130 ± 25 | 129 ± 28 | 0.817 |
| ED GCS | 15 [14, 15] | 15 [14, 15] | 0.645 |
| Injury Severity Score (ISS) | 17 [13, 20] | 16 [10, 21] | 0.442 |
| Intubation status (% yes) | 16.7% | 11.2% | 0.573 |
| Body mass index (BMI) | 26.9 ± 4 | 29.2 ± 7 | 0.078 |
| ICU days | 6.3 ± 7 | 5.2 ± 6 | 0.289 |
| Length of stay | 12 ± 10 | 11 ± 9 | 0.337 |
| 24-h crystalloid (cc) | 3770 ± 2900 | 3290 ± 2160 | 0.249 |
| 24-h blood transfusion (cc) | 447 ± 820 | 437 ± 1010 | 0.956 |
| 24-h plasma transfusion (cc) | 179 ± 653 | 218 ± 790 | 0.786 |
| 24-h platelet transfusion (cc) | 114 ± 326 | 70 ± 227 | 0.328 |
| NI | 33.3% | 26.1% | 0.381 |
| Pneumonia | 21.2% | 18.3% | 0.683 |
| MOF, % | 18.2% | 5.4% | 0.006 |
| Mortality, % | 12.5% | 3.2% | 0.007 |

ED indicates emergency department.

Our logistic regression model was an excellent predictor of mortality with an area under the curve of 0.94 via receiver operating characteristic curve analysis. The model was also a strong predictor of MOF and adequate predictor of NI with area under the curve of 0.90 and 0.70, respectively. After controlling for all important confounders, the IRAK-1 variant was not a significant independent risk factor for the development of NI (OR = 1.6, $P = 0.315$, 95% CI: 0.62–4.3). When both MOF and mortality were analyzed, the IRAK-1 variant was significantly associated with over an eightfold greater independent odds of MOF (OR = 8.4, $P = 0.005$, 95% CI: 1.9–37.1) and over an 11-fold greater independent odds of mortality (OR = 11.8, $P = 0.037$, 95% CI: 1.1–121) (Fig. 1).

To characterize significance of homozygous or heterozygous status of the IRAK-1 variant, we first looked at the incidence of MOF and mortality across the haplotype designation (Table 2). This unadjusted comparison revealed a dose-response relationship with heterozygous women having an intermediate incidence of MOF and mortality relative to the normal haplotype and homozygous IRAK-1 variant. When the haplotype (CT and CC relative to the normal haplotype TT) of the IRAK-1 variant was analyzed concurrently in the regression model, as compared to the odds of poor outcome associated with the normal haplotype, both the heterozygous haplotype and homozygous IRAK-1 variant were significant independent risk factors for MOF (*P*'s 0.012 and 0.003, respectively). Only the homozygous IRAK-1 variant (CC) remained a significant independent risk factor for mortality when both variant haplotypes were included in the model.

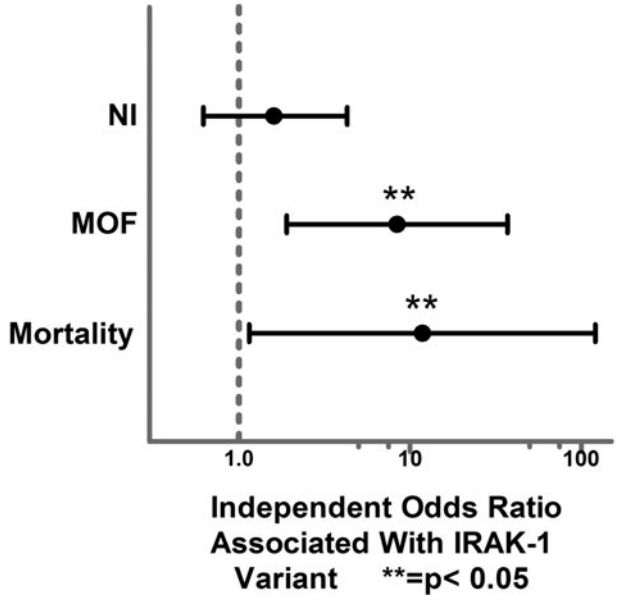


**FIGURE 1.** Forest plot depicting the independent Odds Ratio for the development of NI, MOF, and mortality associated with the IRAK-1 variant.

When serial cytokine measurements were characterized, early IL-6 and IL-10 levels were significantly correlated in a positive direction with the propensity to develop MOF and mortality; however, there was no significant relationship with serial cytokine expression and the IRAK-1 variant or IRAK-1 haplotype (TT, CT, CC).

When coagulopathy was further characterized, we first excluded those patients who presented on oral anticoagulation or antiplatelet medications (n = 91). We then looked the continuous TEG parameter variables and the extreme quartile (>75th percentile or < 25th percentile) associated with coagulopathy for each TEG parameter (*r* value, k time, $\alpha$-angle, MA, G value, and LY30). When these were compared across TEG measurements drawn in the first 6 hours from injury, there were no significant differences found across those with and without the IRAK-1 variant. When TEG measurements that were performed at 24 hours out from injury were analyzed, there were significantly higher k time, $\alpha$-angle, MA, and G values ($P = 0.029$, $P = 0.021$, $P = 0.45$, $P = 0.043$, respectively) in those patients with the IRAK-1 variant. As this represents a potential evolving coagulopathy over the initial 24 hours postinjury, we verified these significant differences in a regression model, which also controlled for differences in demographics, injury severity, and 24-hour resuscitation and transfusion requirements (age, sex, ISS, 24-hour blood, plasma, platelet, and crystalloid). After controlling for important differences across the groups, the IRAK-1 variant remained significantly associated in 3 out of the 4 TEG parameters with more than a threefold greater independent risk of coagulopathic tendency ($\alpha$-angle, $P = 0.018$; MA, $P = 0.047$; and G value, $P = 0.012$, Fig. 2).

## DISCUSSION

As few effective interventions exist, which alter the morbidity and mortality that inherently follows traumatic injury, investigation into novel mechanisms, which result in a protective effect may provide a route to reduce these sequelae postinjury. The ultimate elucidation of the mechanisms responsible for sex-based outcome differences will provide insight and understanding of novel therapeutic targets, which have significant potential to improve outcomes in both men and women postinjury.

TLRs are an evolutionarily conserved family of protein receptors, which are central to NF-$\kappa$B cellular signaling and the initiation of the innate immune response to infection.[36–38] Accumulating evidence suggests that TLRs also recognize endogenous ligands that arise from cellular damage that are unrelated to infection.[21–24] Compelling evidence has revealed that the TLR receptor, specifically TLR4, is required and plays a critical role in the early activation and upregulation of the innate immune response, the resultant systemic inflammatory response, and the secondary organ dysfunction, which is known to complicate and follow traumatic injury.[17–20] Concurrently, it is known that women would potentially be less affected by an unfavorable X chromosome-linked genetic polymorphism due to the mosaic expression pattern of the X chromosome, which has been shown in other disease processes to be protective for women.[16,39–41]

The results of the current prospective analysis suggest that an IRAK-1 polymorphism, which is a TLR signaling pathway constituent that also resides on the X chromosome that is known to result in increased NF-$\kappa$B cellular signalling, is strongly associated with the

**TABLE 2.** Unadjusted Rates of MOF and Mortality Across Haplotype of *IRAK-1* Gene

| | Normal Haplotype (TT, n = 281) | Variant Haplotype Heterozygous (CT, n = 29) | Variant Haplotype Homozygous (CC, n = 40) | *P* |
|---|---|---|---|---|
| MOF | 4.7% | 11.1% | 18.2% | 0.012 |
| Mortality | 2.4% | 10.3% | 12.5% | 0.004 |

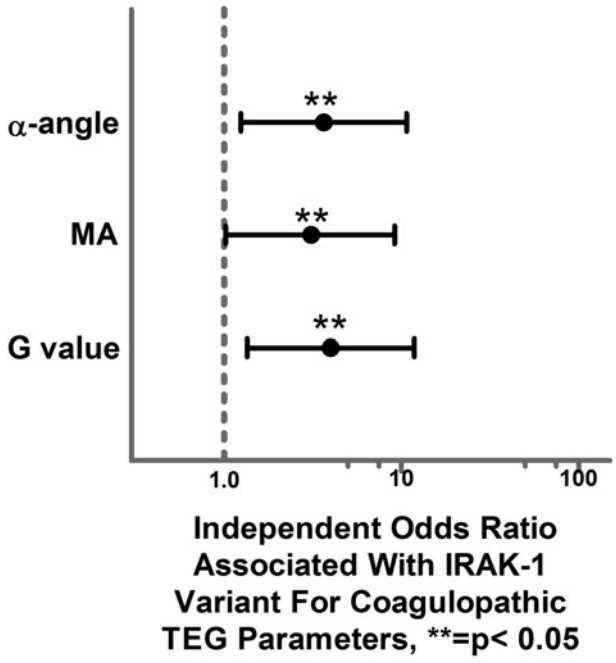


**FIGURE 2.** Forest plot depicting the independent odds ratio for the development of coagulopathic TEG parameters at 24 hours from injury associated with the IRAK-1 variant.

development of MOF and mortality in a prospectively enrolled cohort of injured patients that required ICU admission. Further confirmation of the significance of these findings is demonstrated by prevalence of the polymorphism in a single-center injured population and the dose-response relationship determined by the haplotype (heterozygous or homozygous expression) of the IRAK-1 variant. The current results verify that the IRAK-1 polymorphism represents a common variant with prognostic potential and demonstrates the importance of TLR signaling postinjury and further supports that a genetic mechanism may in part drive sex-based outcome differences postinjury.

These results compliment prior studies demonstrating a detrimental association of the IRAK-1 variant in patients with sepsis.[25,26] Arcaroli and colleagues studied the same polymorphism to identify the IRAK-1 variant haplotype and characterized its association with clinical outcomes in a septic population (n = 155). The IRAK-1 variant was relatively common in this septic population (prevalence = 21.3%) and was associated with increased nuclear translocation of NF-$\kappa$B (synonymous with NF-$\kappa$B activation), more severe organ dysfunction, and independently associated with a higher risk of mortality, in this cohort of patients. Similarly, evidence exists that racial disparities exist in the strength of sex-based outcome differences, which correlates with the known prevalence of the IRAK-1 variant across different racial groups.[42]

Importantly, the current results are not simply an extension of sex-based outcomes, which have been previously demonstrated after traumatic injury in multiple studies.[7,15,43–51] In the current 321 patient cohort, there were no significant differences in the clinical outcomes (NI, MOF, or mortality) across male and female sex nor was sex a significant covariate in any of the regression models. Prior studies demonstrating sex-based outcome differences postinjury have utilized larger retrospective and prospective injured populations and have demonstrated a significantly lower magnitude of risks of poor outcome across men and women with few able to characterize the risk of MOF and attributable complications.[7,43–51] The strength of the current findings, demonstrated in a relatively small cohort of patients, provides insight into the magnitude of effect the IRAK-1 variant may have on clinical outcomes postinjury. Despite the strength of these clinical outcome findings, the underlying mechanism responsible remains less clearly characterized.

It is somewhat surprising that no differences in serial cytokine expression between patients with and without the IRAK-1 variant were found. It is known that IL-6 levels are a strong predictor of the development of MOF[52,53] and despite the strong association between the IRAK-1 variant and MOF, no differences were found for IL-6 or other cytokine expression. Importantly, the full spectrum of circulating mediators that might contribute to the immune response driven by TLR and IRAK-1 were not able to be measured for the analysis. The most current paradigm holds that increased innate immune activity leads to proinflammatory mediators and subsequent organ dysfunction and attributable morbidity and mortality.[54] The lack of any significant measurable differences in the proteomic (cytokine) response may call into question this paradigm in this particular circumstance. It may be that either early proteomic or innate immune response differences exist but were not able to be appropriately measured by standard cytokine analysis which was undertaken, or that the clinical outcome differences found follow an alternative paradigm or model in this specific situation.

We attempted to characterize the early and evolving coagulopathy for the cohort as it has been shown to be a significant risk factor for poor outcome and we have previously demonstrated significant differences in the risk of coagulopathy across male and female sex postinjury.[55–60] Although no TEG parameter differences were demonstrated early (6 hours) postinjury, a strong relationship with evolving coagulopathy over the first 24 hours was demonstrated. It may be that patients at high risk for MOF have a tendency toward coagulopathy or these early differences in coagulation may be in part driving the risk of MOF. Mechanistic possibilities include that the TLR signaling cascade by way of the IRAK-1 polymorphism in some way drives this evolving coagulopathy. It has been previously demonstrated that hypoperfusion and activated protein C are principal drivers of trauma-induced coagulopathy.[61,62] Importantly, hemorrhagic shock and traumatic injury are principal drivers of TLR activation.[63,64] It may be that the principal drivers of these occurrences overlap. Importantly, there were no significant differences in the initial 24-hour transfusion or resuscitation requirements across patients with and without the IRAK-1 variant. The TEG parameters, which were found to be significantly abnormal after adjustment, were the $\alpha$-angle, MA, and G value. The $\alpha$-angle characterizes the rate of thrombin generation; conversion of fibrinogen to fibrin; and the interactions among fibrinogen, fibrin, and platelets. Both the MA and G value TEG parameters characterize the overall clot strength with contributors to clot strength including platelet and fibrinogen function. The current results verify there is an association with the IRAK-1 variant in this cohort with evolving coagulopathy based on serial TEG measurements. However, the current analysis is unable to provide causal information regarding these developments and the interaction of MOF, coagulopathy, and the early innate immune response postinjury.

The current analysis does have several limitations that deserve discussion. First, this study was performed at a single, level I trauma center and may not be generalizable or pertinent to other centers with differing admission demographics, injury characteristics, or management practices. Although the data collected for the prospective cohort analysis was extensive, potential unknown or unmeasured confounding variables may be responsible for the associations described and the conclusions formulated. The study group represents a smaller cohort than previous sex studies but is substantially larger than some of the prior sepsis studies for which the IRAK-1 variant has been characterized clinically.[15,25] There was a lower than expected incidence of the

selected pertinent outcomes of the study including MOF and mortality, which can have an exaggeratory effect on the odds ratios presented in certain circumstances. Importantly, it has been previously demonstrated that a large portion of the most critically injured patients suffer mortality relatively early, commonly within the first 48 hours.[65] Because of the requirement of informed consent, the most critically ill patients had a lower consent rate significantly reducing the incidence of mortality for the study cohort. Although the within 6-hour early cytokine expression measurements that were performed represent a relatively early time point compared with most other studies, this may still represent a delayed measurement for cytokine expression, which drives the development of MOF and mortality. Finally, our current understanding of the early coagulopathy, which complicates trauma, is just beginning to expand because of the complex nature of the process. The most appropriate analysis of TEG parameters remains controversial with variability in the methods of comparison across studies.[31–35] We utilized the extreme quartile, either more than 75% or less than 25% depending on the specific parameter for logistic regression modeling. This possibly may result in an underestimation or overestimation of coagulopathic tendency for specific patients.

## CONCLUSIONS

The IRAK-1 polymorphism is a strong independent predictor of MOF and mortality postinjury and represents a common variant with prognostic potential. These data demonstrate the importance of TLR signaling postinjury and supports that an X –chromosome-linked genetic mechanism may drive sex-based outcome differences postinjury.

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## DISCUSSANTS

### R. Maier (Seattle, WA):

It's not often that you discuss a paper that may change an entire paradigm of how we approach a disease. I believe this paper has that potential.

One of the holy grails of trauma care is elucidating why 2 similar people hit by the same truck with identical injuries have different outcomes. One of the major differences identified over the last decades is that women and men behave differently to identical injuries.

However, we have failed to fully explain why. As you heard, hormonal differences were the obvious cause invoked initially and confirmed in models. But, in the human setting, the mice results do not hold up. The obvious conclusion is that women are stronger than men and are better able to tolerate severe injury. Today, the authors further provide a unique insight of a potential genetic basis for this observed gender bias in outcome, and, in part, explain why previous studies focused on a proteomic gender difference, primarily hormonal, have not been reproducible.

The authors focus on the IRAK gene, and its polymorphisms as an X chromosome-linked gene. Men, as described, are much more likely to express any polymorphism, and express it homozygously, compared to the double-X chromosome female. In their study, they were then able to show their individuals having a homozygous dysfunctional polymorphism had a markedly increased risk of MOF and mortality using multiple different analyses.

The analysis is very clean and very exciting. The data focus on the genetic cause of the difference rather than chasing genomic products, or proteomes, which we have done for decades and have failed. Attempts at modifying protein levels have not succeeded in improving survival.

I have 3 questions for the authors.

The current paradigm is based on the variable response in hormonal levels between men and women. The authors do not mention whether they measured hormonal levels in their various cohorts of IRAK polymorphisms. Is there a linkage between select hormonal expressions and polymorphism particularly in the heterozygous female? Is hormonal protein production variable based on these various cohorts?

Second, the authors similarly demonstrate that, while IRAK is known to control inflammatory mediator production, they were unable to discern any differences in inflammatory mediator levels between the various polymorphism cohorts. Do they have an explanation? With the increased IRAK activation they demonstrate, there should have been a marked increase in proinflammatory mediators. Why were they unable to demonstrate any increase?

Is there another level of control that's more important than the gene? Is there evidence of increased inflammatory protein production that is not being released or is not being processed to a functional state?

The third question is an extension of this principle. The only functional assay examined was coagulation. Again, they demonstrate that coagulopathy was worse in patients with this genetic polymorphism variant. However, were they able to identify any of the recognized mediators of trauma-induced coagulopathy and whether the genetic polymorphism variant produced a difference in levels of those mediators? Was there any correlation between the genetic cohorts and the biology of coagulation?

### Response From B. Zuckerbraun:

Thank you. It has been a privilege to present this work and represent our lead author, Dr Jason Sperry. In regard to associating the IRAK1 variant with differences in hormonal production, at the level of simple analysis we did not see any measurable differences of statistical significance between patients with the IRAK1 variant and those without, again suggesting that the mechanisms of action related to IRAK1 and innate immune signaling may extend beyond and be independent of hormone production.

Dr Sperry is looking intensely at the temporal relationship of hormones, including estrogens and testosterones, which may suggest that there is a difference that occurs over time and that the relationship may be quite complex, without relationship to the IRAK1 variant.

With regard to looking at our association of IRAK1 variant and the cytokine response, we were a bit surprised when we did not see a difference, especially knowing that cytokines, such as IL-6, have been clearly shown to be associated with outcomes such as MOF. But as you mentioned, perhaps we shouldn't be so surprised for a number of reasons. The complexity of cytokines or chemokine measurements or other inflammatory mediators extends beyond that of simple measurements of absolute values and may have more to do with trends. In addition, values of these parameters may change drastically depending on when they are measured, specifically in relationship to the timing of injury, in relationship to the timing of resuscitation efforts, so on and so forth, and, again, may suggest that overinterpretation of the importance of these inflammatory parameters on a causal association with MOF or poor outcome measurements is not accurate.

In relationship to trauma-induced coagulopathy, again, I think there's a little bit of an oversimplification of looking at this as a single phenotypic entity, and perhaps the coagulopathy that's seen early is very different than a coagulopathy that you may see at 24 hours, which, again, may be a manifestation of a measurement of overall immune dysfunction that is occurring at this time point. However, we have not looked specifically at any of the known factors associated with coagulopathy other than looking at the coagulopathy as determined by thromboelastography itself.

## DISCUSSANTS

### D. Soybel (Hershey, PA):

I think this type of work is important and thought-provoking. Along those lines, I wondered if you could clarify for us just a little bit about the biology of the IRAK1 variant. First of all, you mentioned it's a nonsynonymous variant. My question in that regard is, is this a deletion or is it an alteration of the receptor so that it is more or less responsive to interleukin 1?

Second, this IRAK1 variant, I believe, has also been associated with autoimmune diseases like lupus that are more likely to occur in women. So, I sort of wonder if there is some broader issue involved, such as susceptibility to persistent inflammation or nonresolving inflammation. If so, what your thoughts are about why it persists in the population if it's so maladaptive.

### Response From B. Zuckerbraun:

The interesting thing about this IRAK1 variant is there are overall 8 polymorphisms seen in this variant. Invariably, almost all 8 are always seen in the presence of this variant. The one that we measured on this specific exon is just the one that's been described previously.

What that results in is definitely this hyper-exaggerated inflammatory response, which has been demonstrated in vitro. For example, increased NF-$\kappa$B signaling has been measured as part of that exaggerated response. What the genetic variant does to the protein levels or function has been less clear. Whether or not that alters the phosphorylating ability of the kinase or perhaps alters the ubiquitination sites of the protein. But functionally, it is clear that the variant does phenotypically result in exaggerated downstream signaling.

In addition, pertaining to your second question, it seems to be expressed in a recessive fashion in some circumstances, which may predispose to some of the ongoing inheritance of this variant. As far as the variant's role in other inflammatory diseases that is an ongoing question. We highlighted the response in sepsis and the results of this manuscript illustrate in patients that are surviving their initial traumatic insults are experiencing complications, including mortality and organ dysfunction related to that immune dysfunction of trauma. So, this is clearly a gene variant that has been associated with genetic predisposition to susceptibility to inflammatory responses in the setting of infection or other immune-mediated diseases makes is all I can comment on.

May this variant be protective for other disease processes where that hyperexaggerated immune response be beneficial? For example, in some cancers. It is known that the polymorphism exists quite commonly in certain populations. For example, 80% of Chinese populations have the polymorphism. So, it remains to be seen.

## DISCUSSANTS

### T. Buchman (Atlanta, GA):

I have a question as to the degree to which your analysis depends on the assumption that women who are heterozygous are expressing at 50%, if you will. Women are natural mosaics with regard to X chromosome inactivation. For example, as seen in the hair color of a calico cat or a tortoise shell cat, inactivation may not be 50% with respect to a given allele. There's a bell-shaped curve to it. Given the relatively small numbers in your study, I wonder about the extent to which your analysis might be affected by the heterozygotes whose X chromosomes are unevenly inactivated, that is they are at one end of the bell curve or the other.

### Response From B. Zuckerbraun:

That's a great point, and we don't know the answer to that question.

### T. Buchman (Atlanta, GA):

Did you consider doing a methylation analysis of a closely linked gene to see, in a given subject, whether the X chromosome inactivation pattern was even or distributed at one end of the curve or the other?

### Response From B. Zuckerbraun:

We could do that; we have not. We had done our analysis excluding heterozygotes from each group. Regardless of that, there were still differences between the normal haplotypes and the homozygous patients. But you bring up a good point that heterozygotes represent perhaps a very mixed population along that spectrum, based on differences in mosaic expression to varying extents throughout the body.

## DISCUSSANTS

### A. Harken (Oakland, CA):

I'm sure you, in chasing the mechanism, were disappointed that the inflammatory cytokines did not correlate with the IRAK polymorphism, but I guess my questions is, I think of a hormone as being a small amount of material working at a distance and a cytokine as a sometimes relatively large amount of material working locally.

You guys have a huge amount of experience in this. Can you help us or me interpret how we should think of circulating cytokines, just measuring them and relating them to anything that's happening locally?

### Response From B. Zuckerbraun:

Clearly, the background of others in our group, including Dr Vodovotz and Dr Billiar, really would suggest that the cytokine and chemokine relationships are much more complex than the absolute measurements. They are looking at these in the context of trends and as part of dynamic Bayesian networks and looking at it that way may reveal a more rigorous relationship or causal relationship, or associations at the very least, with outcomes.

So, I think the real question is, can you apply that to clinical care? Can you perform these analyses, the measurements, and then the interpretation of these measurements to affect care real time? I think that will continue to be a challenge.

The beauty of the genetic variant is that although, again, there's still some challenge in measuring that in real time, but the genetic variant is not changed in relationship to the timing postinjury, so on and so forth. If it could be measured early, you could perhaps target that higher at-risk population early in the course of their care or down the road as this genetic predisposition is going to be omnipresent throughout their hospital stay and life.

# The early evolving sex hormone environment is associated with significant outcome and inflammatory response differences after injury

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**BACKGROUND:** Clinical research characterizing the mechanisms responsible for sex-based outcome differences after injury remains conflicting. Currently lacking is an understanding of the early sex hormone milieu of the injured patient and the effects these early hormone differences have on clinical outcomes and the innate immune response following injury.

**METHODS:** A prospective cohort study was performed over a 20-month period. Blunt injury patients requiring intensive care unit admission were enrolled. Samples were collected within 6 hours and at 24 hours after injury and were analyzed for total testosterone (TT) and estradiol concentrations. Outcomes of interest included multiple-organ failure (MOF; Marshall Multiple Organ Dysfunction Score [MODScore] > 5), nosocomial infection (NI), mortality, and serial cytokine/chemokine measurements. Multivariate logistic regression was used to determine the independent risks associated with early sex hormone measurements.

**RESULTS:** In 288 prospectively enrolled patients, 69% were male, with a median Injury Severity Score (ISS) of 16 (interquartile range 10–21). Elevated TT levels at 6 hours were associated with elevated interleukin 6 levels and cytokine/chemokine measurements (18 of 24 measured). Rising TT levels were significantly associated with more than a fivefold and twofold higher independent risk of MOF and NI, respectively (odds ratio [OR], 5.2; $p = 0.02$; 95% confidence interval [CI], 1.2–22.3; and OR, 2.1; $p = 0.03$; 95% CI, 1.02–4.2). At 24 hours, TT levels were no longer associated with poor outcome, while estradiol levels were significantly associated with nearly a fourfold higher independent risk of MOF (OR, 3.9; $p = 0.04$, 95% CI, 1.05–13).

**CONCLUSION:** Early elevations and increasing testosterone levels over initial 24 hours after injury are associated with an exaggerated inflammatory response and a significantly greater risk of MOF and NI. High estrogen levels at 24 hours are independently associated with an increased risk of MOF. The current analysis suggests that an early evolving testosterone to estrogen hormonal environment is associated with a significantly higher independent risk of poor outcome following traumatic injury. (*J Trauma Acute Care Surg*. 2015;78: 451–458. 

**LEVEL OF EVIDENCE:** Prognostic/epidemiologic study, level II.

**KEY WORDS:** Testosterone; estrogen; multiple-organ failure; nosocomial infection; regression.

An important and persistent finding has been that males and females respond differently following traumatic injury and hemorrhagic shock, with a relative protection afforded to females.[1,2] An increasing body of evidence from animal models has revealed that sex hormones and or their derivatives play an intricate role in the pathologic response to trauma hemorrhage. Estrogen and testosterone in disparate ways have been shown to influence the hemodynamic, immunologic, organ system, and cellular responses to traumatic insult in animals.[1–10]

The hormonal milieu of the proestrus female rodent has been shown to be protective following trauma and hemorrhage, while male sex steroids are associated with deleterious effects.[11–13] The strength of these laboratory findings has even led some to consider estrogen-based therapy as a possible therapeutic intervention following traumatic injury in human patients.[12,14]

Despite this mounting evidence, clinical studies have been unable to consistently reproduce these laboratory findings.[15–22] Recent prospective evidence, where sex hormone levels were measured 48 hours following injury, provides compelling evidence for estrogen (17β-estradiol [EST]) levels being associated with a greater risk of mortality, a conclusion which contradicts the majority of the experimental animal literature.[23] Similar findings for noninjured but critically ill patients have also been reported.[24,25] It remains unknown whether elevated endogenous estrogens out from the time of injury (>48 hours) are simply a

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marker or play a causal role for poor outcome.[23–25] Currently lacking is an understanding of the early sex hormone milieu of the injured patient (<6 hours from injury through 24 hours after injury) and the effects early sex hormones have on clinical outcomes and the immune response trajectory soon after injury.

In the present study, we sought to characterize the early sex hormone environment and its independent association with important clinical outcomes and the early innate immune response after injury. We hypothesized that estrogen would be associated with beneficial effects, while testosterone moieties would be associated with poor outcome.

## METHODS

A prospective observational cohort study was performed over a 20-month period (February 2011 to October 12) with the overarching goal of characterizing the mechanisms responsible for sex (male vs. female)–based outcome differences following traumatic injury. Inclusion criteria for the overall cohort study included blunt injury patients 17 years or older requiring intensive care unit (ICU) admission who arrived within 6 hours of injury to obtain early blood samples. Patients older than 90 years, those with isolated traumatic brain injury (no other injury identified other than brain injury), those with preexisting immunosuppression, those with an anticipated survival of less than 24 hours, or those patients where consent was unable to be obtained were excluded from enrollment. Blood samples were collected within 6 hours and again at 24 hours after injury and were analyzed for sex hormones (total testosterone [TT] and estradiol) and serial cytokine concentrations by specifically trained staff.[26] Clinical outcomes assessed included the development of multiple-organ failure (MOF, Marshall Multiple Organ Dysfunction Score [MODScore] > 5), nosocomial infection (NI), and in-hospital mortality.

Under the auspices of a waiver of initial consent (up to 48 hours), blood was obtained from enrolled patients upon arrival or soon after within 6 hours from the time of injury and again at 24 hours after injury in most patients. A 48-hour window was approved to obtain consent for the use of samples from the time of admission. All samples and data were destroyed if consent was unable to be obtained within the 48-hour widow. Plasma was separated from whole blood and stored at −70°C for batched analysis. TT and EST levels were measured using high sensitivity ELISA kits following the manufacturer's directions (Testosterone ELISA kit, catalog #ADI-900-176; 17β-estradiol ELISA kit, catalog # ADI-900-174; ENZO Life Sciences, Inc., Farmingdale, NY). Human inflammatory MILLIPLEX MAP Human Cytokine/Chemokine Panel-Premixed kits (catalog # HCYTOMAG-60K and # HCYTOMAG-60K; Millipore Corporation, Billerica, MA) and Luminex 100 IS (Luminex, Austin, TX) were used to measure plasma levels of cytokines and chemokines (interleukin 1β [IL-1β], IL-1RA, IL-2, sIL-2Rα, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-13, IL-15, IL-17, interferon γ, IP-10, MIG, MIP-1α, MIP-1β, MCP-1, GM-CSF, Eotaxin, tumor necrosis factor α, NO2/NO3, and interferon α) per the manufacturer's directions.

Sex hormone variables for TT and EST were first dichotomized at their median values into high and low groups. Sex hormone levels were further categorized over time into groups of less than 6 hours (<6HR), 24 hours (24HR), and additionally a group where hormone measurements were increasing between 6HR and 24HR measurements (rising). Finally, EST/TT ratios were also characterized and used for the cytokine and outcome analyses.

MOF was evaluated using the well-validated Marshall MODScore.[27–29] A MODScore greater than 5 beyond 48 hours from injury was classified as MOF. Primary nosocomial infectious outcomes of interest included ventilator-associated pneumonia, blood stream infection (excluding those associated with an intra-abdominal abscess), and urinary tract infections.[30] These were selected in attempts to use those infectious outcomes, which can be used as a marker for the degree of relative immune dysregulation/suppression. The development of these NIs was based on positive culture evidence. Diagnosis of a ventilator-associated pneumonia required a quantitative culture threshold of equal to or greater than $10^4$ colony-forming units (CFU) per milliliter from bronchoalveolar lavage specimens. Diagnosis of catheter-related blood stream infections requires positive peripheral cultures with an identical organism obtained from either a positive semiquantitative culture (>15 CFU per segment) or a positive quantitative culture (>$10^3$ CFU per segment) from a catheter segment specimen. Urinary tract infections required greater than $10^5$ organisms per milliliter of urine.

First, male and female patients underwent unadjusted comparison of demographics, injury characteristics, resuscitation and transfusion requirements, clinical outcomes, and sex hormones. Correlation analysis was then performed between sex hormone levels and cytokine/chemokine measurements following variable log transformation. Finally, multivariable logistic regression analysis was then used to determine the independent odds of our clinical outcomes associated with sex hormone levels (high vs. low) after adjusting for important confounders. Covariates adjusted for in the regression model included age (>50 years or ≤50 years), sex, Injury Severity Score (ISS), emergency department systolic blood pressure (SBP), emergency department Glasgow Coma Scale score (GCS score > 8 or GCS score ≤ 8), intubation status (yes/no), presenting coagulopathy (international normalized ratio > 1.3, yes/no), 6-hour or 24-hour crystalloid and blood component transfusion requirements (packed red blood cells, fresh frozen plasma, platelets), body mass index, and oral contraceptive use (yes/no).

Mortality was used as the primary outcome to determine our sample size because this is the most stringent outcome to occur relative to the development of MOF and NI. Based on trauma admissions to the ICU at the University of Pittsburgh and with the use of similar inclusion and exclusion criteria, for a similarly injured cohort as proposed, the mortality rate overall was 10%. Based on these projections, an allocation ratio of 0.10 (survivor vs. nonsurvivor) was used for sample size estimation. Based on the previous literature[23,24] where serum levels of EST in both males and females were found to be significantly associated with mortality; survivors-[EST] = 32.4 (50) pg/mL vs. nonsurvivors-[EST] = 66.9 (70) pg/mL, with an $\alpha = 0.05$ and a $\beta = 0.20$, our projected sample size using a two-sided Mann-Whitney U-test was 320 patients.

All data were summarized as mean (SD), median (interquartile range [IQR]), or percentage. Student's *t* or Mann-Whitney

statistical tests were used to compare continuous variables, while $X^2$ or Fisher's exact test was used for categorical variables. A $p \leq 0.05$ was considered statistically significant. The institutional review board at the University of Pittsburgh approved this study.

## RESULTS

During a 20-month period, more than 2,000 patients were screened, with 288 patients being prospectively enrolled and consented who met all inclusion and exclusion criteria and underwent early (<6HR) blood sampling from the time of injury (Fig. 1). This cohort of patients was 69% male, with a mean (SD) age of 50 (18) years, and constituted a moderately injured study cohort, with a median ISS of 16 (IQR, 10–21). More than 31% of the patients required blood transfusion in the first 24 hours, with the prevalence of MOF, NI, and in-hospital mortality being 13.6%, 29.9%, and 3.1%, respectively. Importantly, 24HR sample collection was attempted for all enrolled patients but were only able to be obtained in 237 patients, representing an 82% patient sample follow-up rate.

Males and females were statistically similar in age, injury severity, presenting injury characteristics, transfusion and resuscitation requirements, and important clinical outcomes (Table 1). Interestingly, there were no statistical differences in <6HR sex hormone measurements for either EST or TT as continuous variables across males or females. Males were, however, more likely to have pneumonia as a subtype of NI, despite NIs overall not being different across the groups.

When <6HR sex hormone levels were dichotomized into high and low groups based on the median of the measurement distribution, there was no statistical differences in early EST levels, early TT levels, or the EST/TT ratio across males and females (Table 2). To verify that EST and TT measurements were not concurrently elevated and colinear, we verified that more than 36% of the patients had either high TT with low EST measurements or vice versa irrespective of male or female sex ($p < 0.001$). We similarly found no significant differences in <6HR sex hormones (EST, TT) across age (≤50 years vs. >50 years, EST, $p = 0.444$; TT, $p = 0.958$) or when further stratified by male or female sex.

When high and low sex hormone and IL-6 cytokine levels were compared, both early (6 hours) and 24-hour high TT were significantly associated with elevated IL-6 levels ($p = 0.015$, $p = 0.004$), while no significant relationship was found between IL-6 levels and EST. When correlation analysis of TT, EST, and 24 cytokine/chemokine levels were performed following log transformation for normality considerations, no significant correlations were found for <6HR EST, rising EST, or 24HR EST with any of the measured cytokine/chemokine levels. Similar results were found when correlation analysis was performed between cytokine/chemokine levels and EST/TT ratio at any time point. Interestingly, when <6HR TT levels were correlated with cytokine/chemokine levels, 3 of the 24 measurements demonstrated a significant correlation (IP10, MIP-1α, and MIP-1β). When rising TT levels were analyzed, the majority (16 of 24) of the cytokine/chemokine panels were significantly correlated (positive correlation) with rising TT levels. When 24HR TT levels underwent correlation analysis, the majority (16 of 24) of cytokine/chemokine measurements again were significantly correlated (positive correlation) but with higher Pearson correlation coefficients in all cases, consistent with a greater

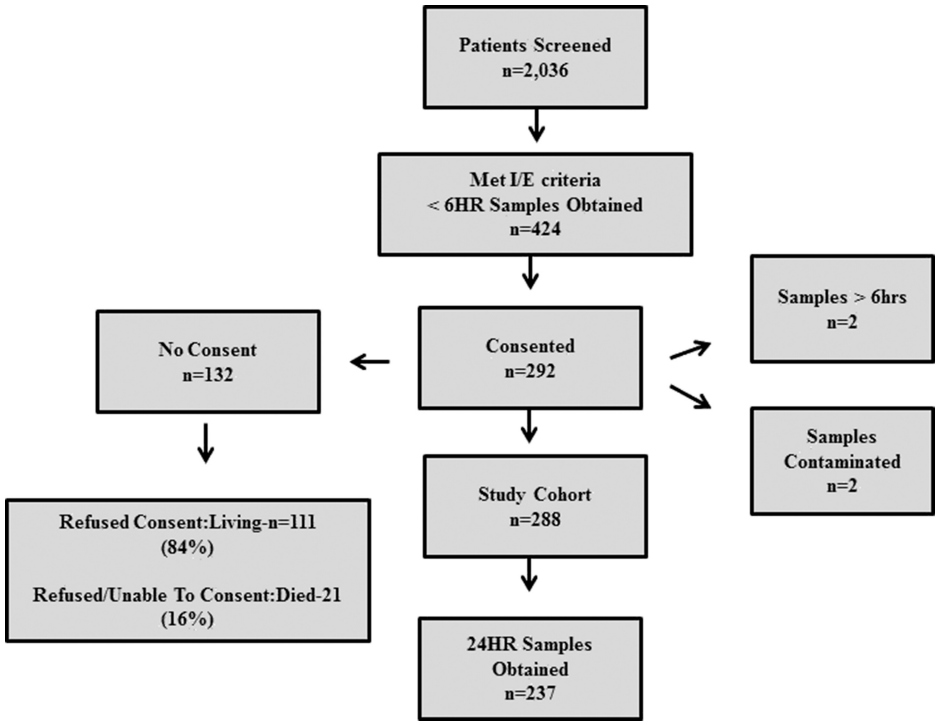


**Figure 1.** Study cohort enrollment diagram.

**TABLE 1.** Unadjusted Comparison of Male and Female Demographics, Injury Characteristics, Resuscitation Needs, and Clinical Outcomes

| | Males (n = 197) | Females (n = 91) | *P* |
|---|---|---|---|
| Age, mean (SD), y | 54 (18) | 50 (18) | 0.060 |
| ED SBP, mean (SD), mm Hg | 131 (27) | 126 (29) | 0.085 |
| ED hypotensive (SBP < 90 mm Hg), % | 8.1 | 10.0 | 0.601 |
| ED GCS score, median (IQR) | 15 (14–15) | 15 (15–15) | 0.446 |
| ED GCS score < 8, % | 16.8 | 15.6 | 0.800 |
| ISS, median (IQR) | 17 (10–22) | 14 (10–19) | 0.450 |
| ISS > 16, % | 51.3 | 45.6 | 0.386 |
| ED intubation status, yes, % | 13.7 | 11.2 | 0.573 |
| Presenting coagulopathy (international normalized ratio > 1.3), % | 17.9 | 24.6 | 0.221 |
| Body mass index, mean (SD) | 29.1 (7) | 28.3 (7) | 0.153 |
| ICU days, mean (SD) | 6.1 (6) | 5.0 (6) | 0.183 |
| Length of stay ICU | 11.7 (9) | 11.2 (9) | 0.685 |
| 24-h crystalloid, mean (SD), mL | 3,593 (2,527) | 3,354 (1,963) | 0.428 |
| 24-h blood transfusion, mean (SD), mL | 509 (1,244) | 445 (895) | 0.493 |
| 24-h plasma transfusion, mean (SD), mL | 264 (978) | 158 (520) | 0.335 |
| 24-h platelet transfusion, mean (SD), mL | 92 (284) | 41 (187) | 0.109 |
| Massive transfusion (≥10 U packed red blood cells in 24 h), % | 5.6 | 2.2 | 0.204 |
| NI, % | 30.5 | 27.8 | 0.645 |
| Pneumonia, % | 23.4 | 13.3 | 0.050* |
| MOF, % | 14.7 | 11.1 | 0.408 |
| Mortality, % | 4.1 | 1.1 | 0.183 |
| 6-h TT, mean (SD), pg/mL | 38.4 (44) | 33.6 (16) | 0.315 |
| 6-h EST, mean (SD), pg/mL | 44.2 (38) | 41.2 (22) | 0.849 |

magnitude of correlation (Supplemental Digital Content 1, http://links.lww.com/TA/A524).

Our regression models were excellent predictors of our primary outcomes based on the area under the curve from receiver operating characteristic curves and demonstrated adequate diagnostics (Table 3). After controlling for important confounders, logistic regression analysis demonstrated no significant independent relationship between <6HR TT levels or <6HR EST and the development of MOF, NI, or in-hospital mortality (Figs. 2 and 3). When the analysis focused on hormone levels, which increased between the early and 24-hour period, rising TT levels were significantly associated with more than a fivefold and a twofold higher independent odds of MOF and NI, respectively (odds ratio [OR], 5.2; $p = 0.02$; 95% confidence interval [CI], 1.2–22.3; and OR, 2.1; $p = 0.03$; 95% CI, 1.02–4.2). Rising EST levels were associated with a threefold higher odds of MOF, but this relationship failed to reach statistical significance (OR, 3.0; $p = 0.089$; 95% CI, 0.85–10). Interestingly, at the 24HR time point, TT levels were no longer significantly associated with the development of MOF or NI, while EST levels were significantly associated with almost a fourfold higher independent odds of MOF (OR, 3.9; $p = 0.04$; 95% CI, 1.05–13) at this time point.

**TABLE 2.** Dichotomized Sex Hormone Levels (High vs. Low) for Early (<6HR) Sex Hormone Level Compared Across Males and Females

| Early (<6HR) Sex Hormone Measurements (n = 288) | Male (n = 197) | Female (n = 90) | *p* |
|---|---|---|---|
| High EST | 52.2% | 49.2% | 0.639 |
| High TT | 48.9% | 50.3% | 0.830 |
| High EST/TT ratio | 48.7% | 53.3% | 0.469 |

## DISCUSSION

Significant advances in trauma care delivery and post-injury management practices have occurred during the last decade, yet patients who survive their initial injury continue to be plagued with the development of sepsis and MOF and their attributable morbidity and mortality.[27,31–35] Despite a significant increase in our basic understanding of these detrimental outcomes, a dearth of effective interventions exist. An important and persistent literature finding, with possible therapeutic potential, has been that males and females respond differently following traumatic injury and hemorrhagic shock.[1,17,18] A growing body of evidence from animal models suggests that this dimorphic

**TABLE 3.** Logistic Regression Model Diagnostics

| Logistic Regression Model Outcome | AUC via ROC Curve Analysis | Hosmer-Lemeshow |
|---|---|---|
| Mortality | 0.969 | 0.840 |
| MOF | 0.898 | 0.559 |
| NI | 0.760 | 0.463 |

AUC, area under the curve; ROC, receiver operating characteristic.

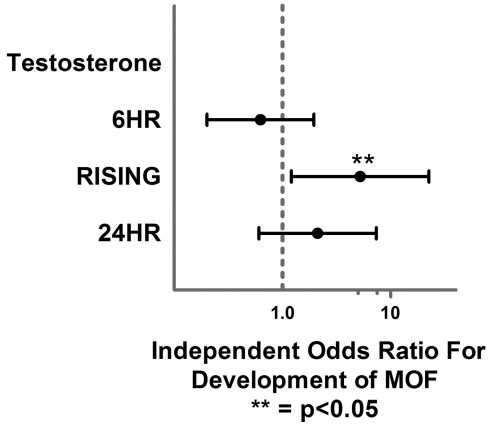


**Figure 2.** Forest plot depicting independent odds of MOF associated with early, increasing, and 24-hour TT levels.

response following trauma and hemorrhage is hormonally based (estrogen, testosterone, or their derivatives).[4,6,36] Despite these advancements in our understanding, clinical studies have been unable to consistently reproduce these laboratory findings and have provided clinical evidence that contradicts the majority of animal literature.[23–25] Lacking until this time has been a clear understanding of the early sex hormone environment, which potentially has effects on clinical outcomes, and the early immune response trajectory, which follows traumatic injury. The results of the current analysis demonstrate that despite a paucity of sex-specific differences in a moderate-sized blunt injury cohort of patients, the evolving sex hormone environment after injury is associated with both clinical outcome and innate immune response differences soon after injury. Despite sex hormones varying little across male and female sex early on (<6HR), these sex hormone–specific associations were strong and independent of important confounders. Early and rising testosterone levels were found to be significantly associated with an exaggerated cytokine/chemokine response and detrimental clinical outcomes, which diminished in strength over time up until 24 hours after injury. Concurrently, estrogen levels were found to be strongly associated with detrimental clinical outcome at the delayed 24-hour period alone.

These results correspond and add further understanding to the previous literature, which has demonstrated that estrogen is associated with mortality and poor outcome irrespective of male or female sex at 48 hours out from injury or sepsis.[23–25] These results provide insight into the possible mechanisms by which the sex-based outcome differences after injury come about.[2] Essential to understanding these associations is the fact that peripheral conversion of androgens to estrogens can occur via increased aromatase activity and may be stimulated by the early cytokine response, which complicates traumatic injury.[37–39] The current results suggest that early testosterone may be associated with an exaggerated innate immune response and an early evolving testosterone to estrogen hormonal environment is associated with a significantly higher independent risk of poor outcome following traumatic injury.

The potential implications of these results may bridge the current "bench to bedside divide"[2] in our understanding of experimental animal evidence, suggesting testosterone's detrimental effects following hemorrhagic shock and the clinical evidence in humans demonstrating the negative associations of estrogen. Although the current results cannot imply causation and although peripheral conversion of testosterone to estrogen was not measured, the strength of the independent findings in a relatively small, moderately injured cohort of patients does provide strength to the validity of these associations and provides the impetus to further study these relationships to determine if a therapeutic benefit can be derived from sex hormone therapy following injury.

The current analysis has several limitations that deserve discussion. First, the potential for selection and survivor bias exist, despite all attempts to minimize such difficulties, because of the nonrandomized enrollment. Although the data collected for the prospective cohort analysis were extensive, potential unknown or unmeasured confounding variables may be responsible for the associations described and the conclusions formulated. Prehospital medicines that may interfere with sex hormone measurements were prospectively collected and controlled for in the analysis, but unknown or undocumented medicines remain a potential confounder for the analysis. There was a lower-than-expected incidence of the selected pertinent outcomes of the study including MOF and mortality, which can have an exaggeratory effect on the ORs presented in certain circumstances. Despite showing a robust association with MOF and NI, no relationship was found between sex hormone levels and mortality. Importantly, it has been previously demonstrated that a large portion of the most critically injured patients experience mortality relatively early, commonly within the first 24 hours to 48 hours.[40] Because of the requirement of informed consent, the most critically ill patients had a lower consent rate significantly reducing the incidence of mortality for the study cohort. Although the <6HR early cytokine expression measurements that were performed represents a relatively early time point compared with most other studies, this may still represent a delayed measurement for cytokine/chemokine expression, which drives the development of MOF, NI, and mortality. The time of sample obtainment in the 6-hour inclusion criteria window was

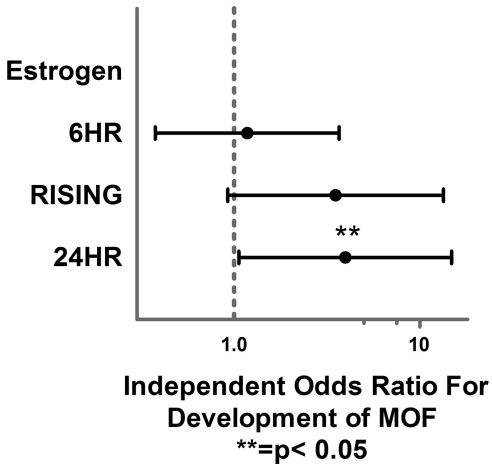


**Figure 3.** Forest plot depicting independent odds of MOF associated with early, increasing and 24-hour total EST levels.

not recorded and potentially may confound these early measurements and result in a time bias. There also existed a reduction or drop off in the number of samples collected from the enrolled 288 patients at the <6HR period to 237 samples at the 24HR period. The potential exists that the 18% of measurements could alter the reported results and conclusions of the study. Interestingly, there existed no differences in early sex hormone measurements across males and females. Similarly, there were no differences found across age (<50 years or ≥50 years) when compared. Despite this lack of hormone differences, there existed strong clinical associations for the sex hormone levels themselves. The study may be underpowered to see these sex- and age-based hormonal differences. The menstrual cycle status or the menopausal status was not obtained from females in the study cohort. Differences in these cycles and periods in females may result in spurious modeling and alter the significance of these findings and limit the applicability to other studies. Finally, this study was performed at a single Level I trauma center and may not be generalizable or pertinent to other centers with differing admission demographics, injury characteristics, or management practices.

In conclusion, early (<6 hours) elevations and increasing testosterone levels over the initial 24 hours are associated with an exaggerated inflammatory response and a significantly greater independent odds of MOF and NI. By 24 hours after injury, however, testosterone is no longer significantly associated with poor outcome. Early elevations and increasing estrogen levels were not associated with differences in the early inflammatory response or a significant greater odds of poor outcome, but estrogen levels at 24 hours after injury are independently associated with a greater odds of MOF. These results suggest that an early evolving testosterone to estrogen hormonal environment over the initial 24 hours after injury has the potential to predict clinical outcome trajectory. These sex hormone changes may in part be responsible for sex-based outcome differences following traumatic injury. Higher-level studies are required to determine if these sex hormone changes play a causal role in these outcome differences and whether therapeutic potential exist via their actions.

## AUTHORSHIP

S.J.Z. and J.L.S. designed the study and performed the literature search, data collection, and data analysis. S.J.Z., Y.V. J.B.B., M.R.R., R.M.F., and J.L.S. participated in the initial manuscript preparation. All authors contributed to the data interpretation and critical revision of the manuscript.

## DISCLOSURE

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## DISCUSSION

**Dr. Reuven Rabinovici** (Boston, Massachusetts): Before I discuss this paper I would like to congratulate the presenter, Samuel Zolin, who is a medical student, for being courageous enough to present his work at AAST. I hope he will continue to conduct trauma-related research and wish him success in these efforts.

Now, as a husband and father of three daughters I pretty quickly noticed that there are differences between males and females. As we all know, some of these differences are quite obvious. However, whether males and females respond differently to traumatic injury is not one of those.

In fact, in detailed review of the papers investigating this topic reveals nothing short of chaos and demonstrates conflicting reports on all aspects of potential trauma-related gender differences. Citing the many contradictory papers is beyond the scope of my discussion today. However, to spice it up I will quote some of the reported conclusions.

One study concluded that, "…these data suggest that gender has no relationship to mortality in blunt trauma patients…", while another study summarized that, "…females aged between 13 and 64 years exhibit significantly lower mortality than males after trauma-associated shock." Another study determined "…gender does not play a role in post-traumatic mortality or in the incidence of acute complications after any degree of traumatic brain injury." In contrast, other authors reported that female gender is independently associated with reduced mortality and decreased complications after TBI. And the list goes on and on.

So it is within this context that the authors aim to further investigate this complex topic by establishing the testosterone and estradiol profile during the first 24 post-injury hours in ICU blunt trauma patients. They also recorded multiple organ failure, nosocomial infection, and mortality rates as well as the serum levels of proinflammatory mediators. Lastly, they used multivariate logistic regression to identify which of the above influences is associated with the hormonal profile they described.The authors report that elevated testosterone within the initial six hours was associated with increased rate of multiple organ failure and nosocomial infection as well as an enhanced inflammatory response. They also stated that the 24-hour estradiol were associated with higher risk of multiple organ failure. I have four questions to the authors.

1. How do your data help put in order in the disorder I just described?
2. You did not find inter-gender and age-related hormonal differences. How do you explain that?
3. You did not find correlation between the hormonal profile and mortality, the ultimate outcome parameter. How do you explain that?

And, lastly, do you have any information to suggest whether the hormonal profile you described is responsible for or a marker of outcome?

In summary, this is a well-designed study. However, it seems to add more confusion to an already complex and much-debated topic. I congratulate the group from Pittsburgh for their continuous efforts to identify yet another difference between males and females and thank the association for the privilege of the floor.

**Dr. Carl J. Hauser** (Boston, Massachusetts): Thank you. Very nice paper. I'd like to ask whether the authors think that testosterone is an acute phase respondent here or whether one of the enzymes in the peripheral aromatase pathway may be, for instance, a negative acute phase respondent, perhaps under the influence of IL-6.

**Dr. David Livingston** (Newark, New Jersey): Yes, very nicely done. Very nicely presented as a student. Great job. We showed that being female and young you seem to be a lot more resistant to shock. That's really what a lot of the experimental studies did.

Did you look at differences in blood utilization, lactate, and base deficit? Were there any between some of your younger females and males eventually leading on to organ failure?

And, as you nicely showed, the milieu is kind of very complicated but at least early on, the females appear to be more resistant to shock.

**Mr. Samuel J. Zolin** (Pittsburgh, Pennsylvania): Thank you very much for these questions. With regard to what exactly this adds to our knowledge base and what it might clarify regarding the early sex hormone environment and outcomes, this study provided a much earlier measurement of serum sex hormones than previous work had done.

As I mentioned, previous work at 48 hours following injury had demonstrated poor outcome with differences in hormonal status.

We demonstrated that an evolving hormonal profile over the first 24 hours following injury may be associated with poor outcome.

Measurement of hormone level at earlier time points, as we did in this study, may reduce the confounding effect that peripheral aromatization may play, although we did not make any direct measurement of peripheral aromatization within subjects in this study.

To answer the line of questioning regarding testosterone's role as either being a marker of poor outcome versus a driver of poor outcome following injury, I believe further research is needed.

While we demonstrated significant associations between testosterone level at different time points and markers of the innate immune response and poor clinical outcome, this was a strictly observational study.

While we attempted to obtain blood samples from patients as soon as possible following injury in order to characterize their baseline hormonal status, which should give a more clear picture of the role of these hormones as markers or causative factors, it is possible that changes in hormone level begin very early after injury, perhaps even earlier than we accounted for.

It's worth recalling that animal studies do support a causative role for testosterone in poor outcome following trauma.

An interventional study of androgen modulation following trauma in humans would likely provide the most conclusive evidence regarding testosterone's role in outcome following injury.

With regard to the question of why there was no demonstrated difference between men and women with respect to sex hormone levels in this study, this is one of the first studies to analyze the early sex hormone environment following injuries in humans.

It may be that alternations of sex hormone levels following injury occur very soon after injury, even earlier than the six-hour window from injury to sampling that we used.

It may also be that lack of information regarding menstrual and menopause status of females in this study was a confounder.

Finally, regarding the question of mortality as an outcome, our analysis demonstrated no statistically significant difference with regard to the incidence of mortality based on hormone level.

This aspect of our study may have been influenced by the fact that there was a lower-than-expected consent rate for those with early mortality in our study population.

It is possible that with a higher incidence of in-hospital mortality, a hormone-based relationship would have become apparent.

Of course, it is also possible that a hormone-associated relationship with mortality following injury does not exist in humans.

Thank you again for your attention and for the opportunity to present today.

# The National Trauma Institute: Lessons learned in the funding and conduct of 16 trauma research studies

**National Trauma Institute Research Group, Michelle A. Price, PhD, Gregory J. Beilman, MD, Timothy C. Fabian, MD, David B. Hoyt, MD, Gregory J. Jurkovich, MD, M. Margaret Knudson, MD, Ellen J. MacKenzie, PhD, Vivienne S. Marshall, PhD, Kimberly E. Overton, RN, Andrew B. Peitzman, MD, Monica J. Phillips, MSN, MBA, Basil A. Pruitt, Jr., MD, Sharon L. Smith, MS, Ronald M. Stewart, MD,** *and* **Donald H. Jenkins, MD**, *San Antonio, Texas*

**BACKGROUND:** To increase trauma-related research and elevate trauma on the national research agenda, the National Trauma Institute (NTI) issued calls for proposals, selected funding recipients, and coordinated 16 federally funded (Department of Defense) trauma research awards over a 4-year period. We sought to collect and describe the lessons learned from this activity to inform future researchers of barriers and facilitators.

**METHODS:** Fifteen principal investigators participated in semistructured interviews focused on study management issues such as securing institutional approvals, screening and enrollment, multisite trials management, project funding, staffing, and institutional support. NTI Science Committee meeting minutes and study management data were included in the analysis. Simple descriptive statistics were generated and textual data were analyzed for common themes.

**RESULTS:** Principal investigators reported challenges in obtaining institutional approvals, delays in study initiation, screening and enrollment, multisite management, and study funding. Most were able to successfully resolve challenges and have been productive in terms of scholarly publications, securing additional research funding, and training future trauma investigators.

**CONCLUSION:** Lessons learned in the conduct of the first two funding rounds managed by NTI are instructive in four key areas: regulatory processes, multisite coordination, adequate funding, and the importance of an established research infrastructure to ensure study success. Recommendations for addressing institution-related and investigator-related challenges are discussed along with ongoing advocacy efforts to secure sustained federal funding of a national trauma research program commensurate with the burden of injury.


**KEY WORDS:** Trauma; research in emergency settings; multicenter study; NTI.

Trauma is the leading cause of death among individuals 46 years and younger and the single largest cause for years of life lost in the United States.[1] In the United States, 199,756 persons experienced fatal injury in 2014, and 30,888,063 were treated in emergency departments for nonfatal injuries in 2013.[2] Medical treatment and work loss costs for civilian fatal and nonfatal injuries in the United States totaled more than $586 billion in 2010.[2] In the conflicts in Iraq and Afghanistan, there have been 52,407 injured US military and Department of Defense (DoD) civilians and 6,881 deaths from trauma.[3] These statistics point to the dramatic burden of injuries on the health of this country in both civilian and military sectors.

Military medicine has been a rich source of information and experience that fosters investigation and advances trauma patient care.[4] The investment of the United States in combat casualty care research since 2001 has contributed to the lowest case-fatality rate ever recorded in war and subsequent translation of lifesaving interventions to civilian trauma care.[5] Similarly, advances in civilian trauma care transformed the military's joint trauma system.[6] Experiences with mass casualty events during conflicts have also been instructive during civilian disasters.[7] Therefore, properly conducted, well-funded trauma research directly benefits combat casualty care and has the potential to impact the primary public health problem in the United States.

Despite the impact of trauma deaths, years of potential life lost, and treatment costs, there is no federally funded national institute or dedicated funding mechanism for the systematic study of trauma care. Currently, trauma receives a small fraction of the funding awarded to cancer and heart disease research. National Institutes of Health funding of clinical trauma research is disproportionate to the burden of the disease and by that metric ranks last among 27 disease categories.[8] The DoD funds research that is relevant to the military but cannot address or fund all research needs. The National Trauma Institute (NTI) was founded in 2006 to secure and manage funding for trauma research and to be a national coordinating center

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for such research. Civilian and military collaboration has always been an integral part of the NTI's vision, as is cross-discipline research. Active and retired members of the Army, Air Force, and Navy are included on its Board of Directors, along with senior civilian leaders from the American Association for the Surgery of Trauma (AAST), American College of Surgeons Committee on Trauma (ACS COT), Eastern Association for the Surgery of Trauma (EAST), Western Trauma Association (WTA), the American College of Emergency Physicians (ACEP), the Shock Society, the Orthopedic Trauma Association (OTA), and the American Association of Neurological Surgeons (AANS).

NTI receives and distributes research funding to clinical investigators across the United States through a rigorous peer review process led by its Science Committee and Board of Directors. NTI received congressional funding in federal FY2008, FY2009, and FY2010 (executed by the DoD) to issue and coordinate awards for trauma research projects (Contract #W81XWH-08-1-0758, #W81XWH-10-1-0924 and #W81XWH-11-1-0841). NTI issued calls for proposals in 2009 and 2010. The 2009 announcement solicited preproposals for multicenter translational or clinical research with special interest in hemorrhage/shock/coagulopathy, hospital-acquired infection, technology development, airway and ventilation, disaster preparedness, and burns. In response, investigators submitted 85 preproposals, from which 15 full proposals were invited. Seven proposals were funded. The 2010 announcement solicited preproposals for translational or clinical trauma research with priority areas of hemorrhage, intensive care, trauma systems, and prehospital care. Seventy-two preproposals were submitted, and 22 full proposals were invited. Nine applications were funded.

NTI's Science Committee, composed of senior trauma researchers, reviewed the preproposals, invited full proposals, and selected awards on the basis of the following: military and NTI relevance of research objectives, scientific merit, clinical relevance and potential impact, multicenter collaboration, innovation, potential for follow-on studies, and feasibility. The goals of the Science Committee were to fund as many feasible studies as possible with geographic dispersion as well as to fund both established and developing investigators. The committee met to review the applications, assigning primary and secondary reviewers to each application. Each proposal was discussed, scored, and ranked. The Science Committee made recommendations on study design modifications and budget adjustments. The budget and scope of activity for 10 proposals were reduced. The top proposals were recommended for funding to the full NTI Board of Directors, which subsequently approved the selected studies.

NTI funded 16 applications totaling $3,889,938. The funding awards ranged from $125,000 to $675,761 and averaged $243,341. Because of the novel nature of this funding mechanism, the studies had to be selected and submitted as part of the full NTI's prime application to the DoD before the award to NTI and the subawards to the selected sites were issued. This requirement delayed the first contracts by 5 months and the second group by nearly 10 months.

During the past 5 years, 16 studies in 35 cities and 22 states involving 59 investigators were initiated. Ten of the studies were multi-institutional. The funded studies were composed of seven randomized clinical trials (RCTs), seven prospective observational or cohort studies, one study using healthy volunteers, and one retrospective review study (Table 1) Twelve studies have been completed, three were closed without completion because of slow enrollment or failure to initiate, and one continues to enroll (80% success rate). Nine clinical trials were registered on www.clinicaltrials.gov (Table 2).

**TABLE 1.** Summary of Studies Funded Through the NTI

| Study | Study Type | Award | No. Sites |
|---|---|---|---|
| 1 | RCT | $125,000 | 1 |
| 2 | Prospective observational | $190,000 | 6 |
| 3 | Prospective observational | $230,000 | 4 |
| 4 | Healthy volunteer | $200,000 | 1 |
| 5 | RCT | $180,000 | 2 |
| 6 | Prospective observational | $225,000 | 6 |
| 7 | Prospective cohort | $224,950 | 3 |
| 8 | Prospective observational | $299,422 | 11 |
| 9 | RCT | $295,172 | 6 |
| 10 | Prospective observational | $235,000 | 1 |
| 11 | RCT | $188,541 | 4 |
| 12 | Prospective cohort | $154,109 | 1 |
| 13 | Retrospective review | $225,000 | 4 |
| 14 | RCT | $130,500 | 1 |
| 15 | RCT | $675,761 | 3 |
| 16 | RCT | $300,000 | 1 |

In January 2014, the principal investigators (PIs) presented study updates at the annual NTI Board of Directors meeting. At that meeting, the Science Committee decided to seek investigators' input regarding their experiences conducting the studies to identify barriers and facilitators to the research process. This article presents the investigators' responses along with study management data and provides "lessons learned" for trauma investigators planning single-site or multisite research protocols. It also offers guidance for grant reviewers and funders on the selection of proposals and investigators that are likely to succeed.

## METHODS

Members of the NTI Science Committee and executive board identified key topics pertaining to study management. A semistructured interview was developed, which consisted of 30 open-ended questions addressing the following: study management, regulatory review, financial management, investigator development, and scientific productivity. Telephone interviews were conducted between March and September 2014. Of the 16 PIs, 15 participated, and 1 declined (93% participation). Interview responses were deidentified and analyzed in aggregate. NTI Science Committee meeting minutes were reviewed regarding study selection criteria and study oversight. NTI study management data were also analyzed. Data were entered into a Microsoft Excel workbook (Microsoft Excel 2013, Microsoft Corp, Redmond, WA). Descriptive statistics were calculated. Qualitative analysis focused on identifying common themes.

## RESULTS

### Study Management

All PIs submitted quarterly progress reports that were reviewed by NTI staff and the Science Committee. The Science

**TABLE 2.** Clinical Trials Registered on Clinicaltrials.gov

| Identifier | Protocol Title |
|---|---|
| NCT00990236 | Thrombelastography based dosing of enoxaparin for thromboprophylaxis: A prospective randomized trial |
| NCT01180894 | A multi-center, randomized, double-blind comparison of intravenous iron supplementation to placebo for anemia of traumatic critical illness |
| NCT01580267 | Hepcidin and anemia in trauma |
| NCT01611935 | Arginine vasopressin during the early resuscitation of traumatic shock |
| NCT01810276 | The safety and efficacy of platelet transfusion in patients receiving antiplatelet therapy that sustain intracranial hemorrhage |
| NCT01820455 | Methicillin-resistant *Staphylococcus aureus* in a trauma population: Does decolonization prevent infection? |
| NCT01897792 | Effects of antioxidant vitamins on coagulopathy and nosocomial pneumonia after severe trauma |
| NCT01901354 | Acute lung injury ventilation (ALIVE) trial |
| NCT01989273 | Detection and management of non-compressible hemorrhage by vena cava ultrasonography |

Committee met regularly to discuss study progress. When there were concerns regarding protection of human subjects, accrual, or other issues, a member of the Science Committee met with the PI via telephone and reported back to the committee. The Science Committee decided if the correction plan was appropriate or if the study should be closed. Three studies were closed because of low enrollment or startup delays.

## Institutional Approval and Delays of Study Initiation

The DoD Human Subjects Protection Regulatory Requirements stipulate specific language in contracts that involve human subjects.[9] The DoD Human Research Protection Office (HRPO) must approve any research involving human subjects before the implementation of the DoD-funded research. Therefore, contracts were not issued to the recipient institutions until institutional review board (IRB) and DoD HRPO approval of the protocols was secured. There was wide variability among the sites in the time required to obtain approval (Table 3). Six studies had secured IRB approval by the date they received notification of NTI funding selection. Among the remaining 10 studies, the mean number of days from funding selection to IRB approval was 210 days (minimum, 51; maximum, 537; SD, 142). The RCTs had the highest mean days from funding selection to IRB approval (mean [SD], 262 [140] days) and the highest mean days from IRB to DoD HRPO approval (mean [SD], 239 [93] days) compared with prospective observational or cohort studies, with a mean (SD) of 131 (103) days from selection to IRB approval and a mean (SD) of 126 (64) days from IRB to DoD HRPO approval, respectively. The mean (SD) total number of days from notice of selection to HRPO approval for all studies was 401 (245) days. One RCT study and three prospective cohort studies secured approval for a waiver or delay of informed consent provision. Three of the RCTs also required an Investigational New Drug approval from the Food and Drug Administration.

Forty percent of the investigators reported challenges in obtaining regulatory approval at one or more institutional levels. Several investigators reported challenges in navigating the

**TABLE 3.** Study Progression—Measured in Calendar Days

| Study | Study Type | Selection to IRB Approval | IRB Approval to DoD HRPO Approval | DoD HRPO Approval to Enrollment | NTI Prime Contract to Site Enrollment | Enrollment and Data Collection |
|---|---|---|---|---|---|---|
| 1 | RCT | 537 | 424 | 133 | 950 | Ongoing |
| 2 | PO | * | ** | 0 | 125 | 693 |
| 3 | PO | * | ** | 194 | 242 | 751 |
| 4 | HV | * | ** | 280 | 437 | 105 |
| 5 | RCT | 128 | 220 | 115 | 226 | 673 |
| 6 | PO | 76 | 92 | 8 | 29 | 686 |
| 7 | PC | 51 | 234 | 0 | 138 | 943 |
| 8 | PO | * | ** | 88 | 40 | 382 |
| 9 | RCT | 155 | 779 | 7 | 704 | 140 |
| 10 | PO | 88 | 67 | 116 | 128 | 794 |
| 11 | RCT | 248 | 115 | 30 | 246 | 829 |
| 12 | PO | 307 | 111 | 30 | 211 | 688 |
| 13 | RR | * | ** | NA | NA | NA |
| 14 | RCT | 173 | 249 | 68 | 253 | 381 |
| 15 | RCT | * | ** | 141 | 482 | 828 |
| 16 | RCT | 332 | 222 | 276 | 593 | 104 |
| | Mean days | 210 | 251 | 99 | 320 | 571 |
| | Minimum | 51 | 67 | 0 | 29 | 104 |
| | Maximum | 537 | 779 | 280 | 950 | 943 |
| | SD | 142 | 221 | 91 | 254 | 280 |

*Studies that had IRB approval at the time of selection notification.
**Unknown.
HV, healthy volunteer; PC, prospective cohort; PO, prospective observational; RR, retrospective review; NA, not applicable.

requirements for the DoD HRPO approval processes. Multisite studies had additional delays because of multiple IRB reviews with conflicting revisions and subcontracting processes. One PI relocated to another institution during the review process and had to start over at the new institution. During the 1-year approval process for one of the studies, another research group published a study that obviated the study design. As a result of the published study, the proposed experimental treatment became standard of care in most hospitals, so the NTI study design had to be revised. The time required to obtain approvals delayed the funding awards considerably and resulted in the loss of study sites, turnover in research trainees, and the need to use alternate sources of funds for research staff salaries, protocol review, and community consultation costs. PIs reported that turnover in research trainees and other research staff while securing approvals further delayed the onset of some of the studies because of replacement and retraining. The mean time from HRPO approval to initiation of enrollment was 99 days (minimum, 0; maximum, 280; SD, 91) (Table 3).

## Screening and Enrollment

Active enrollment periods for the completed studies ranged from 104 to 943 calendar days (mean [SD], 551 [280] calendar days). The enrollment periods were substantially longer than originally estimated on the applications. As of January 2016, 28,725 patients were screened, and 5,579 participants were enrolled. Among the RCTs and prospective studies (n = 12), screening and enrollment varied widely. Four investigators (33%) reported that screening and enrollment were at or above initial targets, and eight (67%) reported that rates had been below initial estimates. Factors associated with lower screening and/or enrollment were lower incidence of disease, sicker patients, early mortality, shorter stays in the intensive care unit, inconsistent or lower screening/enrollment at multiple sites, patient or family refusal, lack of off-hour staffing for screening/enrollment, insufficient funding for staffing, and shortened enrollment period caused by delays in institutional approval. The definition of a screen varied as well. Half of the RCTs or prospective protocols defined a screen as any high-level trauma activation attended by study personnel or admission of a trauma patient to the intensive care unit, whereas the other half used more specific screen criteria (e.g., specific medical condition or intervention). Therefore, screening to enrollment rates varied greatly, from 3% to 100% of screened patients being enrolled into the prospective observational or cohort studies and from 1% to 29% in the RCTs.

## Obtaining Participant or Legally Authorized Representative Consent

Previous trauma research has shown severely injured trauma patients can seldom provide consent, and legally authorized representatives are often unavailable, suggesting the Exception from Informed Consent (EFIC) is necessary to recruit a representative sample.[10] Under the Federal Drug Administration's policy for EFIC, emergency research EFIC may only be conducted when (1) the human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and collection of valid scientific evidence is necessary to determine the safety and effectiveness of particular interventions; (2) obtaining informed consent is not feasible; (3) research participation may provide direct benefit to the subject; (4) clinical investigation could not practicably be conducted without the waiver; (5) the investigational plan specifies the potential therapeutic window, and the investigator attempts to contact a legally authorized representative within that period; (6) the IRB has approved the informed consent procedure that will be used when feasible; and (7) additional protections of the rights of the subjects will be provided including community consultation.[11] A waiver of consent in the PRospective Observational Multi-center Major Trauma Transfusion (PROMMTT) study was invaluable in enrolling sufficient numbers of participants and avoiding consent bias.[12] Three of the NTI prospective (cohort or observational) studies and one of the RCTs received approval for EFIC. Of the 13 protocols using informed consent, 10 (77%) had consent documents and interpreters for languages other than English (e.g., Spanish, Chinese, or other language) and 8 (61.5%) reported encountering potential participants with a primary language other than English.

## Multisite Study Coordination

Ten of the studies were multisite (ranging from 2 to 11 participating sites). Of these, four had one or more sites withdraw from the study before enrolling participants (three RCTs and one retrospective review study). Some sites withdrew because they were unable to obtain IRB approval or because of delays in IRB and/or HRPO approvals. Others withdrew because of changes in the protocol that were required by the IRB or HRPO. One military site was unable to participate because of the site PI's deployment. One site withdrew because the funding was insufficient. Several PIs discussed challenges in coordinating across multiple sites. Strategies used to manage multiple sites were funding additional research nurse/coordinator effort and holding regular teleconferences to monitor progress at all sites.

## Study Financial Management

Nine of the PIs (60%) reported that the study budget was inadequate, particularly for research staffing and coverage. Six of these study budgets were reduced by the Science Committee during the review process. Budgeted full-time equivalents (FTEs) for the studies ranged from 0.6 or 60% of one research staff member to 2.4 FTEs (mean, 0.85 FTE). Nine PIs reported augmenting the study funding with other sources of funds (either departmental/institutional startup or bridge funds). Seven investigators reported that they were able to achieve 24 hours 7 days per week research staffing through leveraged funds from other sources. Budgeted effort for PIs ranged from 0.0 to 0.25 FTE, with a mean of 0.09 or 9% effort. Other areas of insufficient funding cited were diagnostic or laboratory testing, IRB approval and community consultation costs, statistical analysis, travel to satellite sites for study coordination, and indirect costs (which was set at 10% of direct costs).

## Initial Scientific Contributions

As of January 2016, 10 NTI-funded studies completed initial data analysis, 2 were analyzing data, 1 was enrolling participants, and 3 had closed because of low enrollment or startup issues. In total, the studies have generated 16 publications,[13–29] 2 manuscripts under review, and 15 presentations at national

meetings, 2 presentations at regional meetings, and 6 presentations at state or local trauma meetings. Of the 13 studies, 10 (76%) produced one or more peer-reviewed publication(s) or manuscripts under review. This level of productivity compares favorably to a recent study that found only 29% of completed clinical trials conducted at academic medical centers were published within 2 years of study completion.[30] Four investigators have submitted or are in the process of submitting funding applications for additional investigation of their NTI-funded research questions. Two PIs have received $500,000 each for further investigation through the Congressionally Directed Medical Research Program's Joint Warfighter Medical Research Program. Twelve of the PIs (80%) reported training junior researchers, residents, fellows, or students in the conduct of their study. Moreover, the completed and ongoing studies have been productive with respect to scholarly contribution, obtaining additional research funding and training investigators.

## DISCUSSION

This article describes the first two funding cycles of DoD-funded trauma studies coordinated by the NTI. Study management data and NTI Science Committee minutes were combined with PI interviews regarding regulatory review, accrual, multisite and financial management, and productivity to date. Lessons learned in the conduct of these 16 studies are instructive to trauma researchers in four key areas as follows: regulatory processes, multisite coordination, adequate funding, and the importance of an established research infrastructure to ensure study success.

First, investigators should anticipate an extended lead-time for institutional approval, particularly for studies with multiple local IRBs and/or external review by entities such as HRPO or with EFIC. The IRB submission and review process took an average of 210 days or roughly 7 months (for the studies that did not have approval at the time of selection). This is similar to the time to IRB approval reported by the Resuscitation Outcomes Consortium (ROC) (median, 10.5 months), which had similar regulatory challenges with informed consent and EFIC in the emergency setting.[31] Other multisite studies have reported timelines of up to a year to obtain approval.[32–34]

Because of the novel funding mechanisms of these studies, there were significant delays between the date the proposals were selected for funding and the issuance of the prime funding contract to NTI (232 days and 321 days). This contracting process resulted in some studies going back to their local IRBs with revisions required by HRPO, which added to the overall lead time. To minimize further amendments at the local IRB level, consent language and protocol stipulations required by the funding source should be incorporated into the initial IRB submission. Funding sites, program officers, or coordinating centers may provide toolkits or other guides (e.g., https://mrmc.amedd.army.mil/index.cfm?pageid=Research_Protections.orpToolkit.getTools).

For multisite emergency research studies with more than minimal risk, development of a centralized IRB may be more efficient than managing approval from multiple IRBs. Although not a panacea for all regulatory challenges, they may improve review processes for emergency care research by providing expertise, reducing variability inherent in multisite review, and reducing redundancy.[35] Additional new approaches with collaborative efforts from investigators, IRBs, and funding sources are needed to overcome the regulatory challenges.[35] The newly formed Coalition for National Trauma Research (CNTR) could encourage the use of centralized IRB models or other novel approaches within clinical trial networks (at http://coalitionntr.org).

Second, managing multisite protocols requires a high level of PI diligence during site selection, institutional approval, and contracting processes as well as participant accrual. Lead PIs of the multicenter studies stressed the need to assess whether the supporting sites have adequate eligible patient populations, research infrastructure, and an understanding of what resources will be required to meet study enrollment goals at the outset. The observed site attrition supports the need for thorough discussion with investigators at each site regarding requirements and commitment at the time of application; review of study budget, funding, and infrastructure at each site; and ongoing site visits or teleconferences to monitor study progress. Lead PIs can use a Web-based questionnaire in the pretrial phase to assess prospective sites' patient populations, research team expertise, and barriers and facilitators of accrual.[36] Another strategy is to establish a study coordinating center that oversees and assists with administrative and research processes across all sites.

Third, successful study management is highly dependent on adequate study budgeting for staff efforts. Alternatively, sites may leverage institutional funding (e.g., departmental startup or hospital funding) to achieve required staffing levels. This is an important consideration for the staff costs involved in securing IRB approval, particularly when community consultation is required for a waiver of informed consent, if these costs will be incurred as a precondition for funding. Given the amount of PI attention required, it is also imperative that PIs'/co-investigators' effort is included in the budget. Otherwise, clinical productivity or other revenue-generating expectations may not be adjusted to allow for research time. Most studies will require at least 10% of an FTE or 4 h/wk of a PI's time. Clearly, adequate budgeting must be supported by sustained federal funding for a national trauma clinical research program.

Finally, studies were most successful in institutions with an established research infrastructure. Research resources should be assessed as part of the review process for funding selection. Components of a well-developed infrastructure include experienced research coordinators or nurses, ability to staff 24 hours per day or at least during key recruitment times, an electronic data collection system, biostatistical collaboration, and a research administrator.[37] Support of research residents or fellows to assist with subject enrollment, study management, and manuscript preparation is also important. At the academic department level, there should be alignment between the investigators research objectives and department management regarding signature research areas and expectations for protected time. At the institutional level, IRBs, hospital research management, and offices of sponsored programs that are supportive of research and provide timely responses to investigators are also critical. Research resources and infrastructure will be a selection criterion for future NTI-funded projects.

In summary, the challenges encountered on the NTI studies can be categorized as either institution/process related or

**TABLE 4.** Summary of Institution- and Investigator-Related Challenges and Recommendations

| Institution- or Process-Related Challenges | Recommendations |
|---|---|
| 1. Multiple human subject review processes at two or more levels (IRB and HRPO) | Incorporate required IRB and HRPO language in protocol and consent documents in first submission to IRB; academic departments should facilitate IRB application submissions. IRB approval should be obtained before submission of the funding application. |
| 2. Completing community consultation process before the grant award | Identify funding from alternate source (e.g., departmental startup or bridge funds) if funding is not provided by granting institution. Community consultation should be completed before submission of funding application. |
| 3. Data sharing restrictions between trauma centers | Determine the potential for data sharing before including investigative sites in proposal |
| 4. Adequacy of translation services for non–English-speaking patients | Explore using translation services available through hospital when research staff are not able to translate |
| **Investigator-Related Challenges** | **Recommendations** |
| 1. Inadequate assessment of eligible patient density | Require that the PI document study patient accessibility and report recruitment success in clinical studies completed at the hospital over the past three years. |
| 2. Underestimation of PI effort, personnel and other study costs | Application budgets should accurately include PI effort, staff and other costs at all sites. PIs should also document adequate research infrastructure and institutional support. |
| 3. Site attrition among multisite studies | Thorough assessment of site capacity and study requirements (by each site PI) should be completed at the time of site enrollment during the application process. PIs and funding organizations should establish quarterly progress goals and require explanation of failure to meet goals in quarterly progress reports. |

investigator related. Institution-related challenges include human subjects review; funding for preaward activities such as community consultation, data sharing restrictions, availability of translation services for non–English-speaking participants and family members; and adequate funding at a national level to conduct several high-impact, well-powered clinical trials at multiple trauma centers. Investigator-related challenges include inaccurate estimates of numbers of eligible patients, underestimation of staffing requirements in the study budget, and site attrition among multisite studies. Table 4 presents challenges along with recommendations for proactively managing these challenges.

## Limitations

The experiences drawn from this group of 16 studies and the NTI Science Committee may not be representative of study management in all settings. Therefore, the generalizability of these observations is somewhat limited. In addition, the PIs were interviewed during a 7-month period when they were at varying stages in the research process. Their perspectives on the barriers and facilitators may have been affected by where they were in the research process. Moreover, the study management data were reviewed retrospectively, and some data points were equivocal or missing. Finally, there may be other variables that impact the research process that were not considered or were overlooked.

## Next Steps

Advances in trauma care have markedly reduced trauma-related deaths and complications.[38] The initial NTI experience demonstrates the existence of a large number of potential investigators and that investment in these investigators' projects leads to productive scholarly output. Investigators should plan for institutional hurdles, judiciously select and actively manage multisite studies, and ensure that studies are adequately funded to achieve recruitment targets. DoD may wish to evaluate current practices and timeliness as well. In the amount of time it takes for a research idea to produce a study finding, many individuals will suffer morbidity and mortality; thus, any processes that can be streamlined stand to benefit those citizens and soldiers most in need of this research information. As available research funding shrinks and federal budget pressure increases, it is essential that the return from dollars invested in research be maximized by the timely initiation of well-planned and productive research protocols.

Nationally, a unified, stronger voice to advocate for additional trauma research funding and supporting infrastructure is required. The CNTR was formed in 2015 with member organizations of the AAST, EAST, WTA, the ACS COT, and NTI to advocate for a national trauma research agenda, a robust infrastructure to support a Trauma Clinical Trials Network, and additional, sustained federal funding for clinical trials.[39] In 2015, CNTR held its first Trauma Research Advocacy Day in Washington, District of Columbia, with 40 trauma surgeons visiting key Congressional offices. This resulted in the addition of $10 million to the FY2016 DoD budget, specifically for a National Trauma Clinical Trials Network. CNTR returned to Washington, District of Columbia in 2016 to request additional funding for the research network in the 2017 federal budget. Reducing the burden of injury through clinical trials will require sustained federal funding at a level commensurate with the problem.

### AUTHORSHIP

T.C.F., D.H.J., G.J.J, M.M.K., M.A.P., B.A.P., S.L.S., and R.M.S. designed this study. M.A.P. conducted the literature search. K.E.O. and M.A.P. contributed to data collection and performed statistical analyses. M.A.P., K.E.O., and S.L.S. analyzed and interpreted the data. M.A.P. and S.L.S. wrote the manuscript. All authors participated in critical revision.

### DISCLOSURE

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# The Coalition for National Trauma Research (CNTR) Supports the Call for a National Trauma Research Action Plan

--Manuscript Draft--

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Re: The Coalition for National Trauma Research (CNTR) Supports the Call for a National Trauma Research Action Plan

Dear Dr. Moore,

Enclosed please find our original article, titled "The Coalition for National Trauma Research (CNTR) Supports the Call for a National Trauma Research Action Plan" submitted for your consideration.

The work described in this Current Opinions manuscript has not been presented elsewhere. The manuscript is not under consideration elsewhere, and no part of it has been published previously.

This paper summarizes the Coalition for National Trauma Research (CNTR) activities in support of the development of a National Trauma Research Action Plan.

Please feel free to contact me should you have any questions.

Sincerely,

Raul Coimbra, MD

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# The Coalition for National Trauma Research (CNTR) Supports the Call for a National Trauma Research Action Plan

Short title: CNTR Supports National Trauma Research Action Plan

Manuscript Type: Current Opinions

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## Background

Several forums have been convened in the last two decades regarding civilian research priorities in trauma, including but not limited to National Institutes of Health (NIH) roundtables, Centers for Disease Control meetings, and others (1-3). In 2015, the NIH and American College of Surgeons (ACS) convened a group of 60 leading researchers and clinicians to develop a national surgical disparities research agenda (4). Most recently, the National Academies of Sciences, Engineering and Medicine (NASEM) released a report calling for a national, integrated, military-civilian plan to achieve zero preventable deaths after injury (5). This aim (zero preventable deaths) is similar to other national goals to spur progress in treatment research for challenging health conditions such as infectious disease (i.e., "the countdown to the cure" for HIV) and cancer (i.e., the "moonshot" to end cancer) (6, 7). Among the recommendations in that report was the formation of a National Trauma Research Action Plan requiring a resourced, coordinated, joint approach to trauma care research (5). With the emergence of new scientific and clinical paradigms, the need for an updated research agenda is evident. As new knowledge is incorporated into clinical practice and new challenges in clinical care are identified in both civilian and military environments, research remains the driving force behind advances in the care of injured patients. Overlapping priorities among the military casualty care and civilian trauma care communities mandate the formulation of a new combined research agenda.

The current ongoing military conflicts in Iraq and Afghanistan and the global war on terror have brought to light the need for strong collaboration between civilian and military sectors in clinical care, training, education, and particularly in research. The

NASEM report examined how the U.S. military's use of focused empiricism to reduce morbidity and mortality after injury might have implications for improving care in civilian settings (8). Research manpower and capacity are clearly abundant in the civilian sector, and the US Department of Defense (DoD) is of utmost importance in research funding and priorities (Figure 1). Currently, DoD funding represents more than 80% of the United States federal government's annual investment in trauma care research (8).

In 2014 the American Association for the Surgery of Trauma (AAST) and National Trauma Institute (NTI) began discussing the need for a unified, stronger voice to advocate for additional trauma research funding, as well as a mechanism to conduct large multi-institutional clinical trials. This discussion, initially held at the headquarters of the ACS, escalated rapidly. Several months later, the Coalition for National Trauma Research (CNTR) was formed to include not only the AAST and NTI, but also the ACS Committee on Trauma (ACS COT), Eastern Association for Surgery of Trauma (EAST), and Western Trauma Association (WTA) (9). CNTR is focused on developing a centralized national trauma research agenda that establishes priorities and eliminates redundancies in both civilian and military injury treatment, building a robust trauma research infrastructure that includes a Trauma Clinical Trials Network, and securing consistent and significant federal funding for research that increases the understanding of injury and informs clinical practice (10, 11).

CNTR's Executive Committee established three working committees: the Clinical Trials Network Committee (CTN), the National Trauma Research Repository (NTRR) Committee, and the Research Agenda (RA) Committee. The CTN Committee is charged with developing a national clinical trials network, comprising trauma research centers of

various sizes and capabilities, using a fair and publicly available process with representative geographic distribution. This committee collaborates and coordinates activities with the AAST Multi-Institutional Trials Committee (MITC) as well as the CNTR RA Committee. The NTRR Committee is charged with establishing a multidisciplinary steering committee that will guide the planning, development, and implementation of an electronic database that combines civilian trauma registries, such as the National Trauma Data Bank of the ACS, and – as permissible - military trauma data repositories to create the "big data" necessary to define and explore critical issues. Additionally, the trauma research repository is envisioned to contain the data elements of all studies funded and implemented through CNTR activities. The RA Committee is charged with developing a national trauma research agenda that reflects scientific questions and research gaps, both civilian and military, based on a review of relevant and recent work groups or publications by other trauma organizations or entities. The committee's charge also includes prioritizing the agenda so that resources will be directed toward the questions needing answers first, and clinical trials related to these questions will evolve over the next five to 10 years.

**Methods**

The CNTR RA Committee is comprised of 10 expert scientist-practitioners in the care of injured patients. AAST, WTA, EAST, and NTI each nominated surgeons and/or injury researchers to serve on the committee (Table 1). A member of the CNTR Executive committee served as an ex officio member of the committee. Using conference call technology, the RA Committee met three times during January and February 2015. Each

member was asked to review DoD documents and literature provided (1, 2, 12, 13), and to list research topics/priorities and gaps in three domains: Clinical, Translational, and Mechanistic trauma research. A modified Delphi process was used for the collection of research priorities (1). Topics were compiled after three rounds of analysis and comments by the committee members. There was a high level of concurrence among committee members in identifying the research topics and gaps (80%). The committee members determined that the "Clinical" and "Translational" domains should be combined, and hence, the final product is organized into two domains: Clinical/Translational and Mechanistic. The lists were reviewed by the RA Committee members and approved for discussion with the CNTR Executive Committee.

In addition to a list of priorities, the RA Committee was asked to provide a condensed prioritized document, which would be aligned with the gap analysis already performed by the DoD for military casualty care research. The priority areas are, therefore, those that are intended to be relevant for both the civilian and military sectors. Specifically, the RA Committee was asked to provide three major focus areas with described goals and specific projects suggested. The final work condensed the lists of research topics. The research priorities were presented to the CNTR leadership. The Executive Committee of CNTR reviewed the RA Committee's work and considered it a comprehensive template to guide future funding and research programs.

**Results**

There are three major focus areas in which there is considerable overlap between military casualty care research and civilian trauma care research needs. These are acute

resuscitation topics, central nervous system trauma, and transfer to definitive care (Table 2). Under the clinical/translational domain, the research priorities focus on three areas. The first large area focuses globally on resuscitation, including optimal timing for and type of resuscitation fluids, endpoints for resuscitation, methods of hemorrhage control, and the identification and management of coagulopathies and their contribution to posttraumatic thromboembolic disorders. Sequelae of massive resuscitation, including the development of multisystem organ dysfunction and wound healing dyscrasias, were included in this topic area. The second large area under the clinical/translational domain is specific patient populations, with a focus on patients with traumatic brain injury and those who are elderly. Optimal management strategies in these two disparate populations and outcomes are included. The final large category under the clinical/translational domain focuses on the prehospital environment and the development of trauma systems of care. Specific to this area is the development of registries to facilitate data capture. Details of the clinical/translational domain are illustrated in Figure 2.

The second major domain for trauma research priorities is mechanistic. Topics for study in this domain include mechanisms of immune modulation, the impact of genomics on the response to trauma and outcome trajectories, and the identification of novel targets for therapy (Figure 3). Although mechanistic research is not the focus of CNTR, it is important for the advancement of trauma research as a whole.

**Discussion**

In examining the multitude of priorities and needs for trauma research, the RA Committee was particularly interested in examining scientific questions that would

address both civilian and military trauma surgeon needs. To that end, the three major topics (Table 2) of acute resuscitation, traumatic brain injury, and the interface between field (prehospital) care and definitive (hospital) care rose to the top.

In the area of acute resuscitation, it was determined that focused research efforts yielding the greatest benefit to injured patients (and soldiers) would be clinical trials on novel fluid resuscitation strategies that could potentially minimize ischemia and reperfusion injury, and prevent or treat the development of coagulopathy. It was theorized that a combination of new or developing pharmacologic agents, blood substitutes, or more durable forms of blood and plasma storage (lyophilized or dried formulations) could address these needs. It was determined that prospective, randomized trials comparing different treatment strategies including, but not limited to, forms of inflow occlusion (Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA)), aortic cross-clamping, direct hemorrhage control and novel packing agents, etc., in severe traumatic shock are also needed to refine the indications and results of each method. Studies are also needed to determine the safety, efficacy, and effectiveness of modulators of inflammation and coagulation, specifically blood component therapy, pro-coagulation complexes (PCCs), fibrinogen, and other procoagulant agents. This would include the specific role of modulators on perception and treatment of pain. Additionally, the effect of resuscitation strategies on the development of heterotopic ossification and functional limb outcomes should be prioritized.

Traumatic brain injury (TBI), a second major area of interest that crosses multiple disciplines, encompasses both direct impact and blast injury. The committee selected three specific goals of research: better methods of diagnosing and characterizing brain

injury; better methods of preventing brain injury and its sequelae, and better methods of predicting outcome of brain injuries to provide the resources needed for recovery. Multimodal imaging and biomarkers can be used for diagnosis, follow-up, and determination of outcomes following TBI. Multi-well plates to measure biomarkers known to be related to TBI-could be used to create a risk index to predict intracranial hemorrhage in mild to moderate injury patients, and to predict progression of injury in moderate to severely injured patients. The correlation of clinical data, biomarkers, and imaging could lead to the development of more timely and specific treatment strategies. In addition, the biomarker levels could be used to improve selectivity of patients who require cerebral computed tomography following mild to moderate injury to reduce overall radiation exposure and to improve prediction/detection of progression of brain injury, as well as identification of patients who require earlier or more frequent re-imaging or surgical intervention. TBI studies should have long-term follow-up to estimate and measure quality of life; to validate CDE, Patient Reported Outcomes Measurement Information System (PROMIS), Quality of Life in Neurological Disorders (Neuro-QOL), and NIH Toolbox initiatives; and to utilize neurocognitive testing. This would include impact on recovery from concomitant extremity injury, especially when blast is the mechanism.

The third overlapping area of civilian and military trauma care is the interface between field care and hospital care. This area includes the most time-sensitive injuries, and the research agenda suggests that focus areas that might lead to improved outcomes by the most rapid interventions include physiologic derangements, improved communication strategies and tools between these areas of care, and finally, novel

management strategies for the prehospital/field arena. The study of the interface between the prehospital system and the definitive care facility is important to allow for the development of better care at the scene and during transport in civilian as well as in military austere settings.

In most urban systems, transport time is short, and there is very little time for interpretation of data prior to implementing life-saving interventions. In the battlefield, this time from injury to definitive care may be longer, as it would be in many rural or austere environments. The development and testing of miniaturized biomonitoring systems that allow advanced assessment and interpretation of the physiologic response to injury, linked to automated decision support systems that inform medics about interventions needed in a timely fashion, may improve prehospital trauma care. These data points, as well as real-time video streaming at the scene and during transport, could be transmitted wirelessly to definitive care facilities (trauma centers, forward surgical hospitals) for resource mobilization and team preparation. Studies could be designed to measure the impact of data and image transmission from the prehospital to the hospital setting in terms of resource utilization, timing of interventions (e.g., intubation, chest tube placement, diagnostic peritoneal aspiration (DPA), etc.), improved resuscitation (e.g., early use of blood or novel agents), and cost. Ultimately, the data transmitted from the prehospital phase of care should be incorporated into trauma registries.

In selected groups of bleeding patients, the development and application in the prehospital phase of novel techniques and/or drugs to achieve bleeding control should be performed. Studies on the effectiveness of prehospital administration of blood, blood components, and procoagulant factors should be performed. Techniques (devices or

substances) used to temporarily control junctional or cavitary hemorrhage should be tested. Time to definitive care and monitoring of physiologic response to resuscitation may impact type and degree of options for extremity injury reconstruction and will be subject to thorough investigation, especially in the polytrauma patient.

In conclusion, research in the areas of acute resuscitation, traumatic brain injury, and the interface between field (pre-hospital) care and definitive (hospital) care addresses gaps in knowledge that impact the care of both civilian and military critically injured patients. The DoD's Combat Casualty Care Research Program and the military's learning health system have already resulted in knowledge or materiel solutions in these areas (8). Successful execution of the research agenda proposed herein would go a long way to address the NASEM report goal of achieving zero preventable deaths after injury (5). CNTR views the NASEM report to be in complete alignment with its mission and will continue to advocate for the development of a National Trauma Research Action Plan (14).

**Table 1: CNTR Research Agenda Committee**

| Member | Representation/Affiliation |
|---|---|
| Raul Coimbra, M.D. (Chair) | AAST |
| Ronald V. Maier, M.D. (Co-Chair) | AAST |
| Alex Valadka, M.D. | AAST |
| Jason W. Smith, M.D., Ph.D. | EAST |
| Ben L. Zarzaur, M.D. | EAST |
| Jeff A. Bailey, M.D. | NTI |
| Frederick A. Moore, M.D. | NTI |
| Carl J. Hauser, M.D. | WTA |
| Rosemary A. Kozar, M.D. Ph.D. | WTA |
| Gregory J. Jurkovich, M.D. | CNTR Executive Committee – Ex officio member |

**Table 2: Overlapping Trauma Research Priorities in Military and Civilian Settings**

| **Major Areas** | **Goals** | **Specific Projects** |
|---|---|---|
| Acute Resuscitation | Hemorrhage control & resuscitation | Novel fluids, components or transfusion, modulation of coagulation and inflammation |
| Central Nervous System Injury | Diagnosis, brain protection, outcomes | Multimodal imaging, biomarkers of injury, prevention/limitation of secondary brain injury, outcome predictions by multi-modal monitoring, maxillofacial trauma related to TBI |
| Scene to Definitive Care Interface | Improve physiology, communication, and management interface | Advanced monitoring, automated decision support technology, wireless data & image transmission, interface hospital based physicians with pre-hospital non-physicians, prehospital hemorrhage control strategies |

**Author Contribution Statement:**

RC, RVM, GJJ and MAP conducted the literature search. RC, RVM, AV, JWS, BLZ, JAB, FAM, CJH, RAK, GJJ served on the CNTR Research Agenda Committee. RC, RVM, and GJJ conducted data analysis. RC, RVM, GJJ, DHJ, KAD, and MAP wrote the manuscript. RC, RAK, AV, JAB, GJJ, DHJ, KAD, MAP, RVM assisted with critical revisions.

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**Figure 1: Defense Health Board Research, Development, Training and Evaluation High Priorities (13)**

1. Unit-based prehospital trauma registries
2. Food and Drug Administration (FDA)-approved freeze-dried blood products (such as plasma and platelets)
3. Clinicopathological review of every U.S. Combat fatality, including preventable death analyses from combat units
4. Development and testing of non-compressible torso and junctional hemorrhage control devices
5. Optimized airway devices and training
6. Optimized fluid resuscitation for casualties with TBI and shock
7. Training and evaluation methods for Traumatic Combat Casualty Care (TCCC) skills
8. Impact of TCCC interventions in preventing Post Traumatic Stress Disorder (PTSD) and TBI, including the role of analgesia in preventing PTSD
9. Combat casualty care monitoring devices
10. Impact of Tactical Evacuation (TACEVAC) provider level and skill sets on survival

**Figure 2: Clinical/Translational Trauma Research Priorities**

**Clinical/Translational**
**RESUSCITATION**

- Optimal resuscitation strategies
- Shock resuscitation
    - Fluids
        - Freeze-dried plasma
        - Blood products
            - Whole blood
            - 1:1:1 component therapy
            - 1:1 component therapy
            - Plasma alone
            - Cold-stored platelets
    - Genomics/Proteomics – defining trends in inflammatory response to blunt trauma and identifying possible biomarkers to guide resuscitation and predict outcome trajectories
    - Novel adjuncts to resuscitation: Modulation of coagulation/inflammation
        - Drugs
        - Fibrinogen
    - End points
        - Cardiovascular Reserve Monitor-Driven Resuscitation from Hemorrhagic Shock
        - Tissue oxygenation monitoring
        - Use of transesophageal echocardiography and/or transthoracic ultrasonography in optimizing shock resuscitation
        - Develop novel technology to assist clinicians in shock resuscitation (computer software guided resuscitation, new technologies to monitor patients, etc.)
    - Attenuation of metabolic demand and extension of viability (suspended animation)
    - Extremity injury management effects of resuscitation, including the development of heterotopic ossification

**HEMORRHAGE CONTROL**

- Novel means of hemorrhage control
- Endovascular hemorrhage control
- Development of innovative technologies to be used in pre-hospital management of hemorrhaging patient
- REBOA- identify optimal patients, device, technique +/- imaging
- Prospective trial on the utilization of REBOA in trauma patients with hemorrhagic shock. Comparison of REBOA to resuscitative thoracotomy.

- Determine effect of REBOA on mortality, identify ideal time and patient population to utilize REBOA.
- Determine institutional characteristics hospital type, trauma level, location of resuscitation bay, presence/absence of in house trauma attending, vascular attending, interventional radiology attending, hybrid operating room, etc. for evaluation of extremity salvage and functional outcome in those with extremity injury.

**COAGULATION/COAGULOPATHY**

- Development of strategies to utilize thromboelastography (TEG) to control traumatic coagulopathy
- Effect of new class of anticoagulants (e.g., rivaroxaban) on bleeding risk in elderly
- Acute coagulopathy of trauma
    - Identification
    - Prevention
    - Correction
        - Procoagulant concentrates
        - Tranexamic Acid (TXA)
- The role of TEG in the management of coagulopathy after trauma, focused on the impact of patient co-morbidities and medication use.
- Optimal platelet storage and preservation
- Understanding the interplay between coagulation and inflammation after trauma
- Approaches to correct acute coagulopathy during massive transfusion.

**BIOMARKERS/GENETIC PROFILING/POCT/RISK MODELING**

1. Biomarkers to predict:
    - Injury severity
    - Injury severity response – time
    - Shock and shock response
    - Inflammation following severe injury and shock
    - TBI (GFA, NSE, S100 and ceruloplasmin)
    - Polytrauma
    - Early biomarkers of severe injury (predict transfusion, need for surgery)
    - Early biomarker of increased venous thromboembolism (VTE) risk
    - Early biomarker of increased heterotopic ossification risk
    - Early biomarker of increased pain and long term pain syndromes

2. Therapeutic targets
    - Human specific genes or gene pathways
    - Signaling

3. Development of applications for risk prediction

- Creation of an application that incorporates complex risk models including Trauma and Injury Severity Score (TRISS), Revised Injury Severity Classification (RISC/RISCII) as well as injury specific risk adjustors (like out unplanned intubation risk calculator) that can be used to rapidly predict risk at time of patient admission. +/- incorporation of technology into an electronic medical record (EMR). May include continuous updates with information that is gathered over time such as Acute Physiology and Chronic Health Evaluation (APACHE), Sequential Organ Failure Assessment (SOFA) etc., that can be used to give a daily "overall risk" for mortality like a "5th" vital sign that will be displayed to physicians whenever vital signs are checked and may prompt an upgrade or downgrade in level of care based on risk. This may also be used to predict functional extremity outcome and development of pain syndromes.

**VENOUS THROMBOEMBOLISM (VTE)/DEEP VEIN THROMBOSIS (DVT)**

- Optimal strategy for VTE prophylaxis (dosing interval, algorithm, dose adjustments)
- Oral anti-Xa inhibitor for inpatient VTE prophylaxis
- Duration of VTE prophylaxis post-discharge
- Long term morbidity for patients with VTE after trauma
- DVT Prophylaxis
    - Continuation and duration of Lovenox after discharge, and the immobility factor?
    - Prolonged VTE prophylaxis after spine injury: quadrapalegic vs paraplegic?
    - When is it safe to start prophylaxis after spine surgery?
- Trial to determine the safety and efficacy of early pharmacologic VTE prophylaxis in trauma patients with spinal fractures with and without spinal cord injury. Variables of interest include type of fracture, patient demographics, surgical intervention. Outcomes include bleeding, progression of neurological injury, need for surgery, epidural hematoma, VTE, mortality.

**TRAUMATIC BRAIN INJURY (TBI)**

- Optimal resuscitation strategies after TBI
- Intracranial pressure (ICP) monitors and outcome
- Interstitial oxygenation monitoring and optimization
- Hypernatremia in TBI: bolus vs. infusion, dose, sodium target, and duration
- Comparative efficacy of reversal strategies for patients on anticoagulants and anti-platelet agents. Examine effects, if any, of prothrombin complex concentrate (PCC), plasma, platelet transfusion, desmopressin (DDAVP), dialysis, or other reversal agents on progression of brain injury, need for surgical intervention in TBI, mortality, complications, and neurological outcome.
- Impact of New Technologies and Assays:
    - TEG
    - Thrombogram
    - "Plavix" assay

**ORGAN FAILURE/SEPSIS/Multiple Organ Failure (MOF)/Intensive Care Unit (ICU) Care**

- Organ insufficiency and failure
    - Risk stratification and early identification
    - Organ replacement therapy
        - Cardiopulmonary
        - Hepatic
        - Renal based on AKIN classification
        - Pulmonary – extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS)
- Modern classification and assessment of post traumatic sepsis and MOF
- Impact of nutrition and mobility on outcomes after ICU admission
- ECLS after trauma
- Study feasibility of developing regional centers of excellence in resource intense therapies – i.e., – ECMO / ECLS
- Computer based algorithm to detect risk of clinical deterioration/transfer to ICU for patients on floor/Intensive Medicine Unit (IMU)
- The timing of an optimal method of tracheostomy: examining the possible benefits of early tracheostomy in specific patient populations and outcomes relative to the technique used.
- Sedation and analgesia regimen to limit delirium after traumatic and septic shock
- Closed loop clinical decision support to provide basic ICU care (e.g. ICP management, ventilator management, resuscitation)
- Early exercise and physical therapy in the ICU
- Optimize perioperative care to limit acute kidney injury
- Optimal antibiotics in treating nosocomial infections
- Strategies to limit nosocomial infections
- Polymerase chain reaction (PCR) based early detection of bacterial pneumonia
- Effect of prolonged shock on organ injury and recovery
- Effect of aortic occlusion on organ injury and MOF
- Effect of aortic occlusion on functional extremity salvage

**ELDERLY**

- Long term outcomes after trauma in the elderly – functional recovery and mortality
- Quality improvement for geriatric trauma
- Elderly TBI - Effectiveness of pathways and bundles
    - Cohort elderly patients in a unit
    - Establishing sleep/wake immediately
        - Dim the lights at 9pm on at 7am
        - Soothing music
    - Swallow evaluation and timing
    - The role of early enteral tube feeding in patients with altered levels of consciousness in the prevention of aspiration
    - Mobility

- Elderly rib fractures
    - Mobility
    - Respiratory therapy
    - Pain control algorithm
- Performance improvement and outcomes assessment of the geriatric trauma patient, with a focus on the identification of appropriate metrics
- Ethical decision making in Elderly trauma patients

**TRAUMA SYSTEM/TRAUMA CENTERS/REGISTRIES**

- Development of formula/paradigm for optimal placement of trauma centers (Can we develop an echelon system within the US?)
- Study feasibility of developing surgical strike teams for rapid deployment to rural hospitals or disaster areas for management of (multiple?) bleeding patients
- Develop technology to automate population of registries with data
- EHR and Registry Interaction
    - Data acquisition
        - Epidemiology
        - Mechanism
        - Physiology
        - Injury Severity
        - Biomarkers
        - Interventions
        - Co-morbidity
        - Morbidity
        - Autopsy
        - Pre-hospital data management
            - Registries
            - Automated data collection
            - Remote virtual management augmentation
    - Analytics
        - Performance metrics and outcomes
        - Risk identification and adjusted benchmarks
    - Enhanced interoperability and data sharing
- Preventable causes of mortality
- Evaluation of impact of hybrid OR's. Outcomes of interest mortality/morbidity following orthopedic injuries, vascular injuries, time to definitive control of hemorrhage, need for repeat surgical/interventional procedures, transfusion requirements, cost/charges. Variables to study, presence/absence of hybrid OR, location of hybrid OR, service primarily involved (vascular, IR, trauma surgery), teaching facility, trauma level, hospital size, trauma volume, percent penetrating injuries.

**PREHOSPITAL**

- Novel pre-hospital diagnostics and therapeutics
- Optimal use of blood products in the pre-hospital setting

- Optimal use of military CCCT techniques in the civilian pre-hospital environment (Tourniquets, Combat Gauze, Celox, etc.)
- Pre-hospital (pre-surgical) hemorrhage control
    - Truncal (thoracic, abdominal, pelvic)
    - Junctional
    - Extremity (including analysis of salvage and function)
- Advanced pre-hospital resuscitation during prolonged transportation times
- Video streaming to trauma centers from pre-hospital (scene and ambulance)
- Real time data streaming of physiologic data from pre-hospital to trauma centers
- Pre-injury environment/transportation and relationship to post-injury recovery and outcome following major trauma

**WOUND HEALING AND PAIN CONTROL**

- Novel methods of optimizing wound healing, especially in craniomaxillofacial injury as well as prevention of heterotopic ossification in extremity injury
    - New Drugs
    - Gene Therapy
    - Others
- Novel use of current pain agents, continuous versus bolus and utilization of novel pain control agents to optimize recovery and long term functional outcomes

**Figure 3: Mechanistic Trauma Research Priorities**

- Mechanisms contributing to age-related outcomes after trauma
- Genomics of trauma to predict outcomes
- Mechanisms of coagulopathy of trauma and TBI
- Identify novel methods/compounds for restoring hemostasis following hemorrhagic shock induced coagulopathy
- Influence of microbiota of outcomes after trauma
- Mechanism of immune suppression/alteration following severe TBI
- Molecules as therapeutic targets after hemorrhage
- Identify alternative resuscitation strategies/methods for correcting shock and its underlying physiologic derangements.
- Acute Coagulopathy of Trauma (ACOT)
- Ischemia reperfusion identification and prevention/treatment
- Attenuation of metabolic demand and extension of viability (suspended animation)
- Biomarkers and genetic profiling
    - Injury Severity
    - Injury severity response – time
    - Shock
    - TBI
    - Polytrauma including extremity salvage and function
- Therapeutic targets
    - Human specific genes
    - Signaling
- Improved animal models of injury (polytrauma models, humanized mice)
- Human specific genes
- Mechanism of trauma induced coagulopathy
- Gut and lung microbiome (effect on SIRS, effect on nosocomial infection)
- Exosomes as mediator of SIRS
- Regenerate or reverse extremity dysfunction with stem cell therapy
- Extend survival and limit organ failure after hypotensive resuscitation
- Regenerate or reverse TBI and SCI with stem cell therapy
- Optimal fluid resuscitation for shock resuscitation
- Regenerate or reverse craniomaxillofacial injury with stem cell therapy
- Early genomic and proteomics responses to trauma and septic shock
- Tracking and treatment of late inflammation and immunosuppression after trauma and septic shock
- Mechanisms of diminished resistance to infection after injury
- Mechanisms of the perpetuation of inflammation (and thus organ failure) after injury
- Non-antibiotic means of diminishing infection and the emergence of resistant organisms.

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# Impact of Department of Defense Funded Research at the

NATIONAL TRAUMA INSTITUTE

Funding Research ■ Changing Practice ■ Creating Awareness

# Disclosure

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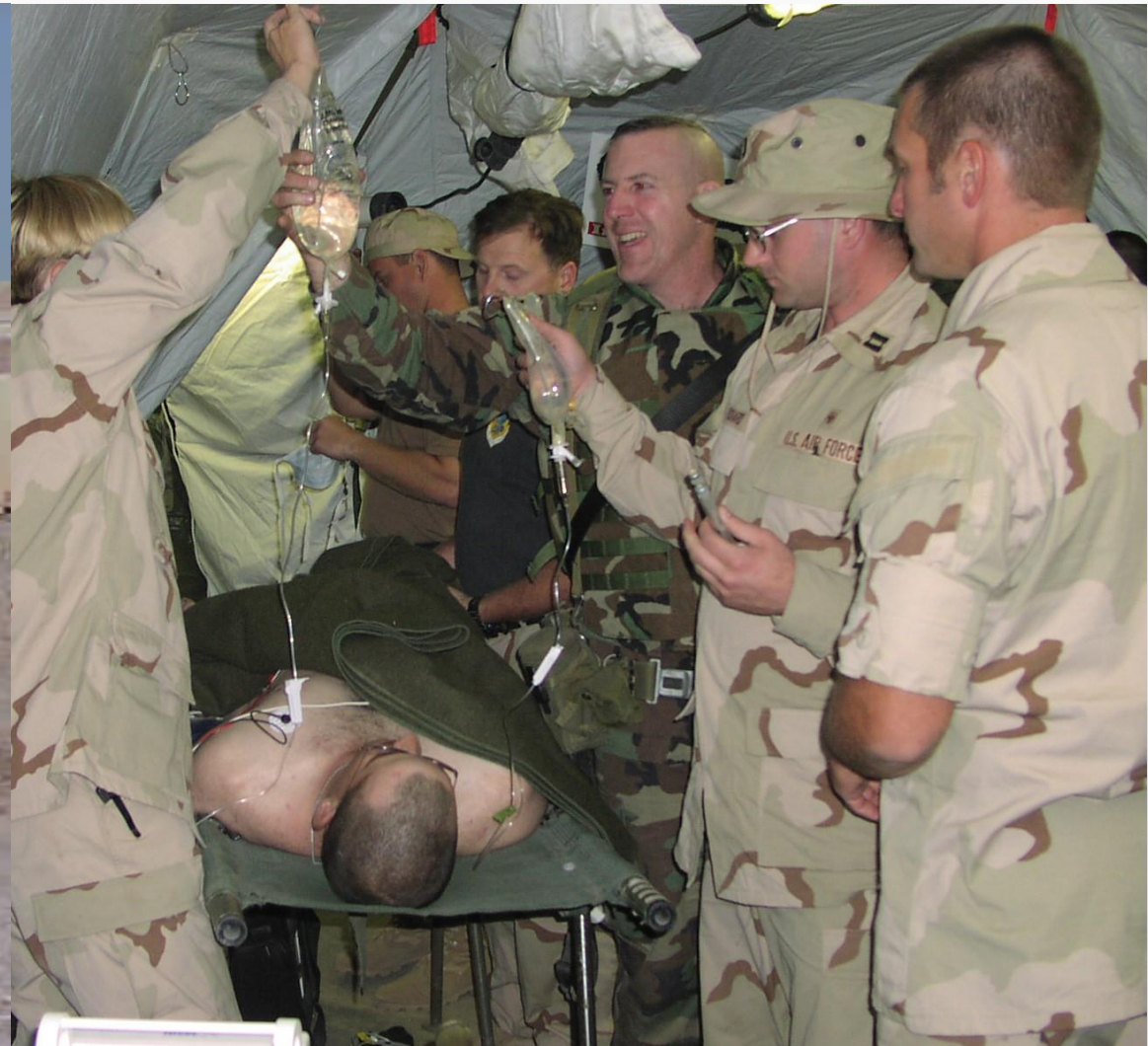
The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the view of the Department of the Army or the Department of Defense.

# Management of Blunt Abdominal Trauma (BAT) and Splenic Injury



# *Splenic Injury Prospective Outcomes Trial: An American Association for the Surgery of Trauma Multi-Institutional Study*

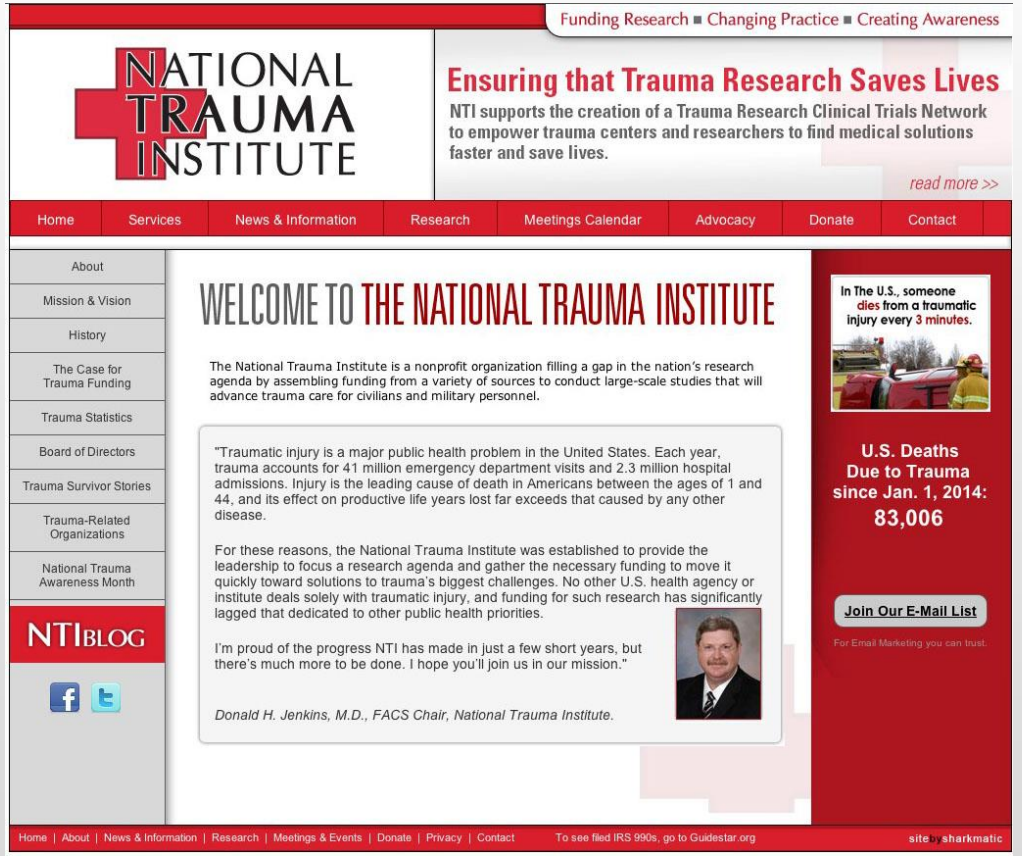
- Principal Investigator: Ben Zarzaur, MD, MPH at University of Tennessee Health Science Center
- First multi-institutional, long-term prospective study of patients with blunt splenic injury
- Funded by the DoD through the National Trauma Institute for $299,422 (NTI-NCH-10-020 & W81XW-11-1-0841)

# Findings and Clinical Impact of *Splenic Injury Prospective Outcomes Trial: An AAST Multi-Institutional Study*

- After the first 24 hour of nonoperative management, risk of splenectomy is rare:
  - 3.1% during inpatient phase of care
  - 0.27% during 180 days after discharge
- The benefits of splenic preservation techniques (angiography and embolization) are unclear.
- This study highlighted the need for further large scale multicenter trials that randomize to either management with angiography and embolization or nonoperative management. (*J Trauma Acute Care Surg*. 2015.79;3, 335-342 and AAST Plenary Paper in 2014)

# National Trauma Institute Mission

- To generate funds for clinical trauma research
- To discover new funding opportunities
- To advocate for trauma research across federal entities as well as other agencies
- To distribute those funds to clinical investigators, but to do no research ourselves



# National Trauma Institute Origins

NATIONAL TRAUMA INSTITUTE

- 2003: Began as local organization of 3 Level 1 Trauma Centers (TRISAT); based within University of Texas Health Science Center at San Antonio (UTHSCSA)
- Product of both civilian and military trauma centers
- 2003-2006: Worked within UTHSCSA to achieve federal appropriations
  - $4.2M total awarded for local trauma research/education & training; recruitment of first civilian burn center director at BAMC, funding salary for 5 years
- 2006: Reorganized as national non-profit entity
  - New Mission: to address lack of federal trauma research funding
  - New Leadership: National Board of Directors

# NTI Board of Directors includes members of…

- American Association for the Surgery of Trauma
- Eastern Association for the Surgery of Trauma
- Western Trauma Association
- Shock Society
- American College of Emergency Physicians
- Orthopedic Trauma Association
- American Association of Neurological Surgeons
- US Army Institute of Surgical Research
- US Navy
- US Army
- US Air Force

# NTI Research Priorities

- Hemorrhage
  - Non-compressible (truncal/torso)
  - Blood Products
  - Resuscitation
  - Shock and bleeding
  - Coagulopathy
  - Systemic and local hemostatic therapy
- Airway and Ventilation
- Infection
  - Eliminating hospital acquired infections in the ICU
  - Antibiotic utilization
- Disaster Preparedness
  - Mass casualty
  - Transportation of the critically ill
- Burn
  - New skin
  - Off the shelf skin
- Technology development

# NTI Trauma Studies Funding Rounds

## FIRST

- Issued first Request for Proposals (RFP) October 1, 2009 with $1.4M available funds
- 85 pre-proposals
- 15 full proposals reviewed on February 5, 2010
- 7 selected for funding March, 2010

## SECOND

- Issued second RFP June 10, 2010 with $2.46M available funds
- 92 pre-proposals
- 21 full proposals reviewed on August 30, 2010
- 9 selected for funding January, 2011

# NTI Funded Studies


16 Lead Sites


43 Participating Sites

**NTI Research in 35 cities in 22 states**

# Funded Awards

| PI Name | Institution | Study | $ Awarded | Participating Sites |
|---|---|---|---|---|
| Martin Croce | UTenn HSC | Multicenter Prospective Evaluation of the Ventilator Bundle in Injured Patients | $225,000 | 5 |
| Joel Baseman | UTHSC - San Antonio | *Mycoplasma Pneumoniae* in the ICU | $190,000 | 5 |
| Fred Pieracci | U Co. Denver | A Multicenter, Randomized, Double-blind Comparison of Intravenous Iron Supplementation to Placebo for the Anemia of Traumatic Critical Illness | $188,541 | 3 |
| Shahid Shafi | Baylor Hosp, Dallas | Comparative Effectiveness of Clinical Care Processes in Resuscitation and Management of Moderate to Severe Traumatic Injuries | $225,000 | 3 |
| Jason Sperry | U. Pittsburgh | Characterization of the Effects of the Early Sex-Hormone Environment Following Injury | $225,000 | Single Center |
| Mitchell Cohen | UC-SF | Timing and Mechanism of Traumatic Coagulopathy | $225,000 | 2 |
| Carrie Sims | U. Penn. | Vasopressin Supplementation during the Resuscitation of Hemorrhagic Shock | $125,000 | Single Center |
| Ben Zarzaur | AAST/PI: UTenn HSC | Splenic Injury Prospective Outcomes Trial | $299,422 | 11 |

# Funded Awards (continued)

| PI Name | Institution | Study | $ Awarded | Participating Sites |
|---|---|---|---|---|
| Jay J Doucet | UC San Diego | Detection and Management of Non-Compressible Hemorrhage by Vena Cava Ultrasonography | $230,000 | 3 |
| Jean-Francois Pittet | U AL Birmingham | Effect of Antioxidant Vitamins on Coagulopathy and Nosocomial Pneumonia after Severe Trauma | $300,000 | Single Center |
| Mark Cipolle | Christiana HCS, DE | The Safety and Efficacy of Platelet Transfusion in Patients Receiving Antiplatelet Therapy that Sustain Intracranial Hemorrhage | $130,500 | Single Center |
| Henry Cryer | UCLA | Transfusion of Stored Fresh Whole Blood in a Civilian Trauma Center: A Prospective Evaluation of Feasibility and Outcomes | $200,000 | Single Center |
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| Lena M. Napolitano | U Mich Health System, Ann Arbor | Hepcidin and Anemia in Trauma | $154,109 | Single Center |

# Initial Scientific Contributions

- Sixteen peer-reviewed publications
- Two publications in press
- One manuscript submitted/under review
- Sixteen national, 2 regional and 6 local presentations
- Ten of the 13 completed studies have published or submitted a manuscript (76%)
- Two PIs received additional funding through NTI applications to the Joint Warfighter Medical Research Program ($500K each)
- Twelve PIs trained junior researchers, fellows, residents or students on their study

# *Timing and Mechanism of Traumatic Coagulopathy*

- Principal Investigator: Mitchell Cohen, MD, at University of California San Francisco
- Funded by the DoD through the National Trauma Institute for $224,950 (W81XWH-10-1-0924 & NTI-TRA-09-034)
- Prospective, multi-institutional observational study to characterize coagulation parameters in the severely injured, to use systems biology to identify the central mediators involved in coagulopathic phenotypes and to develop a predictive model to support diagnosis and treatment

# Findings and Clinical Impact of *Timing and Mechanism of Traumatic Coagulopathy*

- Identified clinical significant platelet dysfunction after trauma in the presence of a reassuring platelet count and clotting, with profound implications for mortality. Arachidonic acid and collagen responsiveness are independent predictors of mortality (*J Trauma Acute Care Surg*. 2012; 73: 13-19)
- Consideration of empiric antifibrinolytic therapy is warranted in trauma patients presenting with acidosis, hypothermia, coagulopathy, or relative thrombocytopenia. These criteria facilitate empiric treatment of hypofibrinolysis for clinicians without access to thromboelastography (*J Trauma Acute Care Surg*. 2012; 73: 87-93)

# Findings and Clinical Impact of *Timing and Mechanism of Traumatic Coagulopathy* (continued)

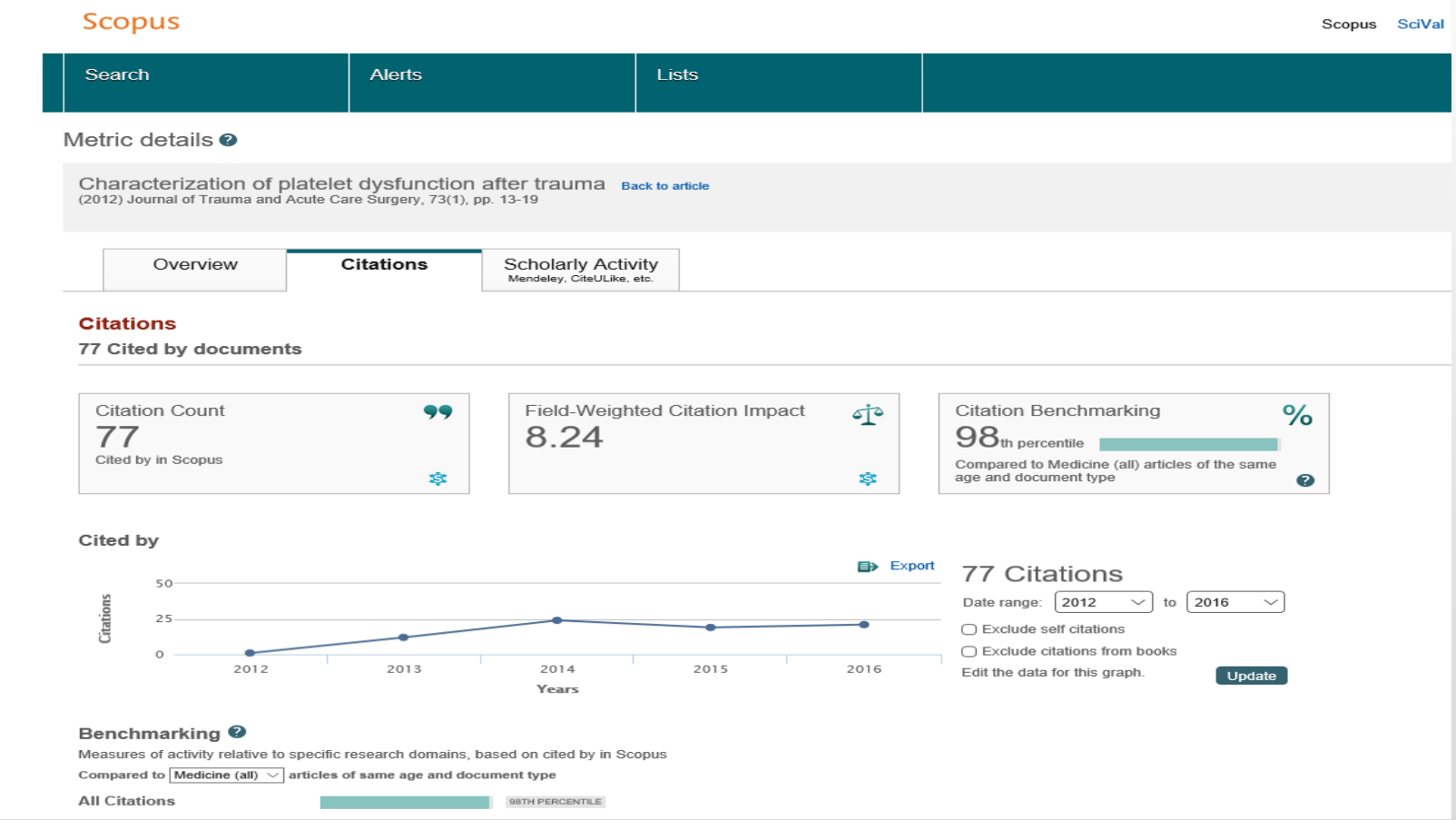
- Extracellular histone levels are elevated in response to traumatic injury, correlate with fibrinolysis and activation of anticoagulants and are predictive of mortality from admission to 6 hours.
- Concomitant elevation of activated protein C (aPC) abrogates this effect, suggesting a possible role for aPC in mitigating sterile inflammatory response through the proteolysis of circulating histones (*J Trauma Acute Care Surg*. 2012; 73: 1389-1394 & WTA 2012 Plenary Paper)
- Characterization of the cause death in severely injured patients requiring massive transfusion suggest targeted surgical and resuscitative strategies to increase the physiologic reserve time and potential survivability (*J Trauma Acute Care Surg*. 2013;75: S255-262)

# Findings and Clinical Impact of *Timing and Mechanism of Traumatic Coagulopathy* (continued)

- Although 1:1:1 reconstituted whole blood (RWB) had a superior clotting profile relative to 2:1:1 RWB, platelet modified whole blood (MWB) exhibited even better global hemostasis than 1:1:1 RWB.
- Characterization of factor-level and functional clotting differences between WB variants is imperative for understanding the clinical benefits of hemostatic resuscitation. (*J Trauma Acute Care Surg*. 2014;77: 818-827 and WTA 2014 Plenary Paper)

# Scientific Impact of *Timing and Mechanism of Traumatic Coagulopathy* (PI: Mitchell J. Cohen, MD)

The most cited publication from this study is the 2013 *JOT* manuscript *Characterization of platelet dysfunction after trauma*. It has been cited 77 times.



# The Science of Conducting Trauma Research


- National Trauma Institute Research Group et al. The National Trauma Institute: Lessons learned in the funding and conduct of sixteen trauma research studies. *J Trauma Acute Care Surg*. 2016 (epub ahead).
- Smith SL, Price MA, Fabian TC, Jurkovich G, Pruitt BA, Jr., Stewart RM, Jenkins DH. The National Trauma Research Repository: Ushering in a new era of trauma research. *SHOCK: 2016 Military Supplement*. Accepted for publication.

- A robust, searchable and scalable repository for data resulting from current and future clinical and basic trauma research
- All federally funded clinical trauma investigators will be eligible to contribute their data.
- Coordination between agencies and civilian academic and professional trauma organizations through data sharing will further data utilization, cooperation and collaboration.

# National Trauma Research Repository

# 10 Years of Advocating for Trauma Research

- Works with Congressional offices to seek sponsors and supporters to augment the Defense Health Agency budget for trauma research
- NTI works with principle investigators (PIs) and institutions to obtain funding through a competitive proposal process
- NTI has generated and/or managed $55M in trauma research funding since 2003

# Coalition for National Trauma Research (CNTR)

- In 2014, CNTR formed to advocate for adequate, sustained federal funding for trauma clinical research studies, a national research agenda and infrastructure
- CNTR successfully advocated for additional $10M in DoD budget for FY2016 for a clinical trauma research network
- Advocating for additional $10M in the DoD budget for FY2017 (supported by 15 senators and 69 representatives from 25 states)
- Received notification of first DoD award to CNTR for *Multi-institutional Multidisciplinary Injury Mortality Investigation in the Civilian Pre-Hospital Environment (MIMIC*) to investigate potentially preventable deaths in the prehospital setting in 6 states in partnership with the National Association of Medical Examiners and Johns Hopkins Bloomberg School of Public Health

NATIONAL TRAUMA INSTITUTE

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PROFESSOR/CLINICAL, DIVISION OF TRAUMA AND EMERGENCY SURGERY
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NATIONAL TRAUMA INSTITUTE

Funding Research ■ Changing Practice ■ Creating Awareness

# Lessons learned in funding 16 trauma studies

# Disclosure

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the view of the Department of the Army or the Department of Defense.

# This work is under review at the Journal of Trauma

| | |
|---|---|
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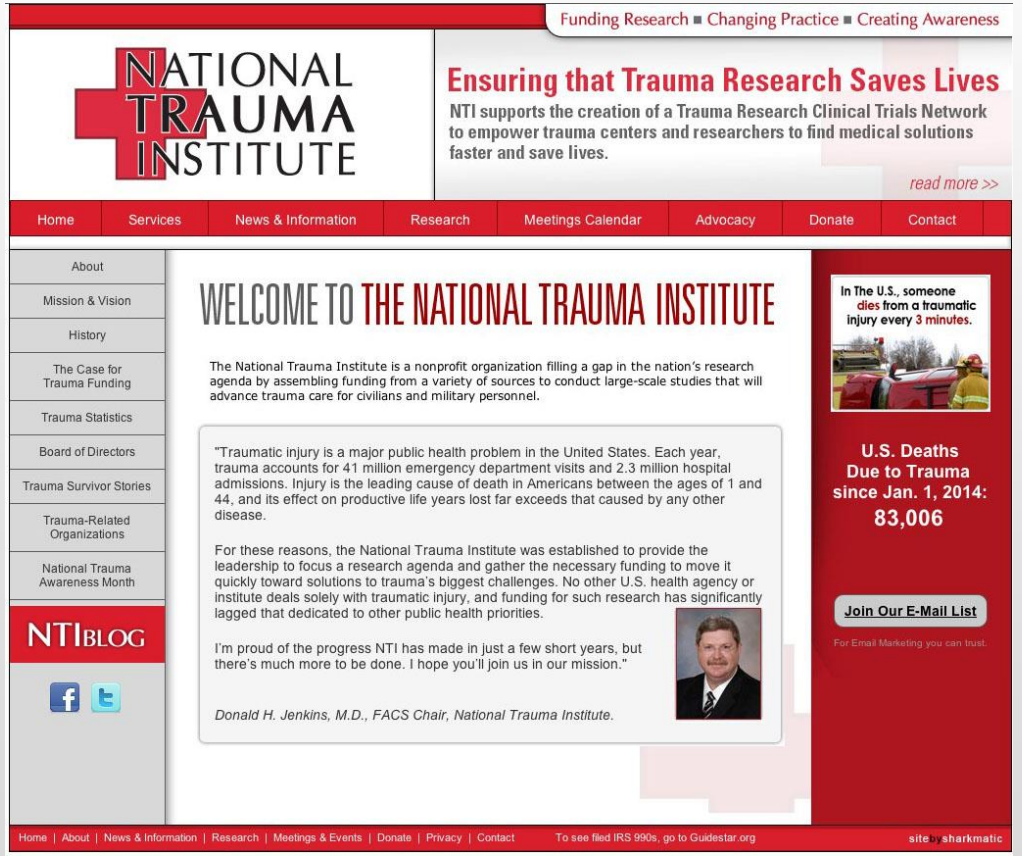
| Michelle Price, PhD | Kimberly Overton, RN |
| Gregory Beilman, MD | Andrew Peitzman, MD |
| Timothy Fabian, MD | Monica Phillips, MSN, MBA |
| David Hoyt, MD | Basil Pruitt, Jr., MD |
| Gregory Jurkovich, MD | Sharon Smith, MS |
| M. Margaret Knudson, MD | Ronald Stewart, MD |
| Ellen MacKenzie, PhD | Donald Jenkins, MD |

# National Trauma Institute Mission

- To generate funds for clinical trauma research
- To discover new funding opportunities
- To advocate for trauma research across federal entities as well as other agencies
- To distribute those funds to clinical investigators, but to do no research ourselves



# National Trauma Institute Origins

NATIONAL TRAUMA INSTITUTE

- 2003: Began as local organization of 3 Level 1 Trauma Centers (TRISAT); based within University of Texas Health Science Center at San Antonio
- Product of both civilian and military trauma centers
- 2003-2006: Worked within UTHSCSA to achieve earmarks/federal appropriations
  - $4.2M total awarded for local trauma research/education & training; recruitment of first civilian burn center director at BAMC, funding salary for 5 years
- 2006: Reorganized as national non-profit entity
  - New Mission: to address lack of federal trauma research funding
  - New Leadership: National Board of Directors

# NTI Board includes members of…

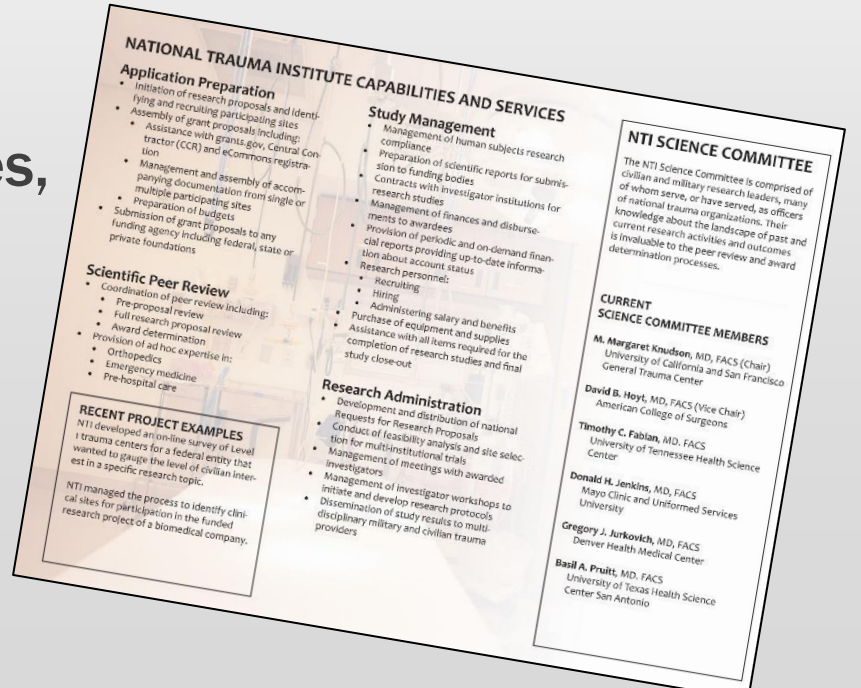
- American Association for the Surgery of Trauma
- Eastern Association for the Surgery of Trauma
- Western Trauma Association
- Shock Society
- US Army Institute of Surgical Research
- American College of Emergency Physicians
- Orthopedic Trauma Association
- American Association of Neurological Surgeons
- US Navy
- US Army
- US Air Force

# NTI Research Priorities

- Hemorrhage
  - Non-compressible (truncal/torso)
  - Blood Products
    - Freeze-dried blood
    - Blood substitute
  - Resuscitation
    - Optimal resuscitation, whether to resuscitate, what to resuscitate with
    - Prediction models of resuscitation requirements
    - Fluid treatments
    - Immunomodulatory effects of resuscitation
  - Shock and bleeding
  - Coagulopathy
  - Systemic and local hemostatic therapy
- Infection
  - Eliminating hospital acquired infections in the ICU
  - Antibiotic utilization
- Disaster Preparedness
  - Mass casualty
  - Transportation of the critically ill
- Burn
  - New skin
  - Off the shelf skin
- Airway and Ventilation
  - Ventilation-induced injury
- Technology development

# NTI Award and Contract Management

- Work with principle investigators (PIs) and institutions to obtain IRB and DoD (HRPO) approvals following funding rounds
- Execute sub-contracts with each lead organization and, in some cases, all participating institutions
- Manage funds and payments to sub-awardees
- Manage federal monitoring and compliance activities, gather periodic reports from sub-awardees and integrate into required federal reports



NATIONAL TRAUMA INSTITUTE CAPABILITIES AND SERVICES

**Application Preparation**
- Initiation of research proposals and identifying and recruiting participating sites
- Assembly of grant proposals including:
  - Assistance with grants.gov, Central Contractor (CCR) and eCommons registration
  - Management and assembly of accompanying documentation from single or multiple participating sites
  - Preparation of budgets
- Submission of grant proposals to any funding agency including federal, state or private foundations

**Scientific Peer Review**
- Coordination of peer review including:
  - Pre-proposal review
  - Full research proposal review
  - Award determination
- Provision of ad hoc expertise in:
  - Orthopedics
  - Emergency medicine
  - Pre-hospital care

**RECENT PROJECT EXAMPLES**

NTI developed an on-line survey of Level I trauma centers for a federal entity that wanted to gauge the level of civilian interest in a specific research topic.

NTI managed the process to identify clinical sites for participation in the funded research project of a biomedical company.

**Study Management**
- Management of human subjects research compliance
- Preparation of scientific reports for submission to funding bodies
- Contracts with investigator institutions for research studies
- Management of finances and disbursements to awardees
- Provision of periodic and on-demand financial reports providing up-to-date information about account status
- Research personnel:
  - Recruiting
  - Hiring
  - Administering salary and benefits
- Purchase of equipment and supplies
- Assistance with all items required for the completion of research studies and final study close-out

**Research Administration**
- Development and distribution of national Requests for Research Proposals
- Conduct of feasibility analysis and site selection for multiinstitutional trials
- Management of meetings with awarded investigators
- Management of investigator workshops to initiate and develop research protocols
- Dissemination of study results to multidisciplinary military and civilian trauma providers

**NTI SCIENCE COMMITTEE**

The NTI Science Committee is comprised of civilian and military research leaders, many of whom serve, or have served, as officers of national trauma organizations. Their knowledge about the landscape of past and current research activities and outcomes is invaluable to the peer review and award determination processes.

**CURRENT SCIENCE COMMITTEE MEMBERS**

**M. Margaret Knudson**, MD, FACS (Chair)
University of California and San Francisco General Trauma Center

**David B. Hoyt**, MD, FACS (Vice Chair)
American College of Surgeons

**Timothy C. Fabian**, MD, FACS
University of Tennessee Health Science Center

**Donald H. Jenkins**, MD, FACS
Mayo Clinic and Uniformed Services University

**Gregory J. Jurkovich**, MD, FACS
Denver Health Medical Center

**Basil A. Pruitt**, MD, FACS
University of Texas Health Science Center San Antonio

# NTI Trauma Studies Funding Rounds

## FIRST

- Issued first Request for Proposals (RFP) October 1, 2009 with $1.4M available funds
- 85 pre-proposals
- 15 full proposals reviewed on February 5, 2010
- 7 selected for funding March, 2010

## SECOND

- Issued second RFP June 10, 2010 with $2.46M available funds
- 92 pre-proposals
- 21 full proposals reviewed on August 30, 2010
- 9 selected for funding January, 2011

# NTI Funded Studies


16 Lead Sites


43 Participating Sites

**NTI Research in 35 cities in 22 states**

# Funded Award Details

| PI Name | Institution | Study | $ Awarded | Participating Sites |
|---|---|---|---|---|
| Martin Croce | UTenn HSC | Multicenter Prospective Evaluation of the Ventilator Bundle in Injured Patients | $225,000 | 5 |
| Joel Baseman | UTHSC - San Antonio | *Mycoplasma Pneumoniae* in the ICU | $190,000 | 5 |
| Fred Pieracci | U Co. Denver | A Multicenter, Randomized, Double-blind Comparison of Intravenous Iron Supplementation to Placebo for the Anemia of Traumatic Critical Illness | $188,541 | 3 |
| Shahid Shafi | Baylor Hosp, Dallas | Comparative Effectiveness of Clinical Care Processes in Resuscitation and Management of Moderate to Severe Traumatic Injuries | $225,000 | 3 |
| Jason Sperry | U. Pittsburgh | Characterization of the Effects of the Early Sex-Hormone Environment Following Injury | $225,000 | Single Center |
| Mitchell Cohen | UC-SF | Timing and Mechanism of Traumatic Coagulopathy | $225,000 | 2 |
| Carrie Sims | U. Penn. | Vasopressin Supplementation during the Resuscitation of Hemorrhagic Shock | $125,000 | Single Center |
| Ben Zarzaur | AAST/PI: UTenn HSC | Splenic Injury Prospective Outcomes Trial | $299,422 | 11 |

# Funded Award Details (continued)

| PI Name | Institution | Study | $ Awarded | Participating Sites |
|---|---|---|---|---|
| Jay J Doucet | UC San Diego | Detection and Management of Non-Compressible Hemorrhage by Vena Cava Ultrasonography | $230,000 | 3 |
| Jean-Francois Pittet | U AL Birmingham | Effect of Antioxidant Vitamins on Coagulopathy and Nosocomial Pneumonia after Severe Trauma | $300,000 | Single Center |
| Mark Cipolle | Christiana HCS, DE | The Safety and Efficacy of Platelet Transfusion in Patients Receiving Antiplatelet Therapy that Sustain Intracranial Hemorrhage | $130,500 | Single Center |
| Henry Cryer | UCLA | Transfusion of Stored Fresh Whole Blood in a Civilian Trauma Center: A Prospective Evaluation of Feasibility and Outcomes | $200,000 | Single Center |
| Suresh Agarwal | Boston Med Center | Acute Lung Injury Ventilation Evaluation (ALIVE) Trial | $295,172 | 5 |
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# Methods

- The NTI Executive and Science Committees identified key study management topics
- A semi-structured interview with 30 open-ended questions was developed addressing:
  - Project management
  - Regulatory review
  - Financial management
  - Investigator development
  - Scientific productivity
- 15 of 16 principal investigators (PIs) participated in the interviews

# Methods (Continued)

- PI responses were de-identified and analyzed in aggregate
- NTI Science Committee meeting minutes and policies were reviewed
- NTI project management data and reports were reviewed
- Descriptive statistics and qualitative analysis performed

# Results

- Study Oversight by NTI
  - PIs submitted quarterly progress reports to the NTI Science Committee
  - Science committee met regularly to review progress
  - Science committee members met with PIs regarding any concerns such as slow progress on IRB & HRPO and participant accruals to develop a corrective plan
  - Three studies were closed due to low enrollment or other start-up delays
  - NTI submitted quarterly progress reports to federal funding source

# Institutional Approval Challenges

- Studies were reviewed and approved by local Institutional Review Boards (IRBs) and then by the DoD Human Research Protection Office (HRPO)
- Funding contracts could not be issued until HRPO approval was obtained
- Time to IRB & HRPO approval varied widely
  - 6 studies had IRB approval by the time they were selected for funding
  - Among the remaining 10 studies, the mean number of days from funding selection to IRB approval was 210 days
  - Randomized clinical trials had the highest mean days (262 days)
  - Mean number days from selection to HRPO approval was 401 days
- 40% of PIs reported challenges in obtaining approval.

# Study Progression – Measured in Calendar Days

| Study | Study Type | Selection to IRB Approval | IRB Approval to DoD HRPO Approval | DoD HRPO Approval to Enrollment | NTI Prime Contract to Site Enrollment | Enrollment & Data Collection |
|---|---|---|---|---|---|---|
| 1 | RCT | 537 | 424 | 133 | 950 | Ongoing |
| 2 | PO | * | ** | 0 | 125 | 693 |
| 3 | PO | * | ** | 194 | 242 | 751 |
| 4 | HV | * | ** | 280 | 437 | 105 |
| 5 | RCT | 128 | 220 | 115 | 226 | 673 |
| 6 | PO | 76 | 92 | 8 | 29 | 686 |
| 7 | PC | 51 | 234 | 0 | 138 | 943 |
| 8 | PO | * | ** | 88 | 40 | 382 |
| 9 | RCT | 155 | 779 | 7 | 704 | 140 |
| 10 | PO | 88 | 67 | 116 | 128 | 794 |
| 11 | RCT | 248 | 115 | 30 | 246 | 829 |
| 12 | PO | 307 | 111 | 30 | 211 | 688 |
| 13 | RR | * | ** | NA | NA | NA |
| 14 | RCT | 173 | 249 | 68 | 253 | 381 |
| 15 | RCT | * | ** | 141 | 482 | 828 |
| 16 | RCT | 332 | 222 | 276 | 593 | 104 |
| | Mean Days | 210 | 251 | 99 | 320 | 571 |
| | Minimum | 51 | 67 | 0 | 29 | 104 |
| | Maximum | 537 | 779 | 280 | 950 | 943 |
| | Standard Deviation | 142 | 221 | 91 | 254 | 280 |

IRB: Institutional Review Board; DoD HRPO: Department of Defense Human Research Protection Office; HV: Healthy Volunteer; PC: Prospective Cohort; PO: Prospective Observational; RCT: Randomized Clinical Trial; RR: Retrospective Review; NA: Not Applicable; *Denotes studies that had IRB approval at the time of selection notification; **Unknown

# Screening & Enrollment

- Enrollment periods ranged from 104 – 943 days (Mean=551; SD=280 days)
- 28,725 patients were screened and 5,579 were participants were enrolled (as of January 2016)
- 33% of PIs reported screening & enrollment were at or above targets
- 67% of PIs reported screening & enrollment were below targets
  - Lower incidence of disease
  - Sicker patients or shorter lengths of stay
  - Patient or family refusal to consent
  - Insufficient staffing during evenings, nights & weekends

# Multi-site Study Coordination

- 10 studies were multi-site (ranging from 2-11 sites)
- 4 studies had site attrition
  - IRB/HRPO delays or required protocol changes
  - PI was deployed
  - Insufficient funding
- PIs emphasized importance of monitoring screening & enrollment at multiple sites with regular meetings and reporting

# Study Financial Management

- Nine PIs reported study funding was insufficient (6 of these budgets had been reduced by the NTI Science Committee)
- Budgeted staffing ranged from 0.6 to 2.4 full time equivalents (FTEs)
- Budgeted PI time ranged from 0.0 to 0.25 FTEs
- Nine PIs augmented study funding from other sources
- Seven PIs achieved 24/7 coverage with funding from other sources

# Current Status of Studies

- Ten studies completed initial data analysis
- Two studies are analyzing initial data
- One study is still enrolling
- Three studies were closed due to low enrollment or start-up issues

# Initial Scientific Contributions

- Sixteen peer-reviewed publications
- Two manuscripts submitted/under review
- Fifteen national, 2 regional and 6 local presentations
- Ten of the 13 completed studies have published or submitted a manuscript (76%)
- Two PIs received additional funding through NTI applications to the Joint Warfighter Medical Research Program ($500K each)
- Twelve PIs trained junior researchers, fellows, residents or students on their study

# Discussion – Lessons Learned

- Regulatory process management
- Multi-site coordination
- Funding adequacy
- Importance of an existing research infrastructure

# Institution- or Process-Related Challenges

| Challenges | Recommendations |
| --- | --- |
| Multiple human subject review processes at two or more levels (IRB & HRPO) | Incorporate required IRB and HRPO language in protocol and consent documents in first submission to IRB; Academic departments should facilitate IRB application submissions. IRB approval should be obtained prior to submission of the funding application. |
| Completing community consultation process prior to the grant award | Identify funding from alternate source (e.g., departmental start-up or bridge funds) if funding is not provided by granting institution. Community consultation should be completed prior to submission of funding application. |
| Data sharing restrictions between trauma centers | Determine the potential for data sharing prior to including investigative sites in proposal |

# Investigator-Related Challenges

| Challenges | Recommendations |
| --- | --- |
| Inadequate assessment of eligible patient density | Require that the PI document study patient accessibility and report recruitment success in clinical studies completed at the hospital over the past three years. |
| Underestimation of PI effort, personnel and other study costs | Application budgets should accurately include PI effort, staff and other costs at all sites. PIs should also document adequate research infrastructure and institutional support. |
| Site attrition among multi-site studies | Thorough assessment of site capacity and study requirements (by each site PI) should be completed at the time of site enrollment during the application process. PIs and funding organizations should establish quarterly progress goals and require explanation of failure to meet goals in quarterly progress reports. |

# Limitations

- Experiences drawn from this group of studies may not be representative of study management in all settings
- PIs were interviewed at various stages of the research process so their perspectives on barriers and facilitators may have been impacted
- Study management data were reviewed retrospectively with some equivocal or missing data

# Next Steps

- Center for National Trauma Research (CNTR) formed to advocate for adequate, sustained federal funding for trauma clinical research studies and infrastructure
- CNTR successfully advocated for additional $10M in DoD budget for FY2016 for a clinical trauma research network
- Advocating for additional $20M in the DoD budget for FY2017 (currently supported by 15 senators and 69 representatives from a total of 25 states)
- NTI secured DoD funding to develop a National Trauma Research Repository

NATIONAL TRAUMA INSTITUTE

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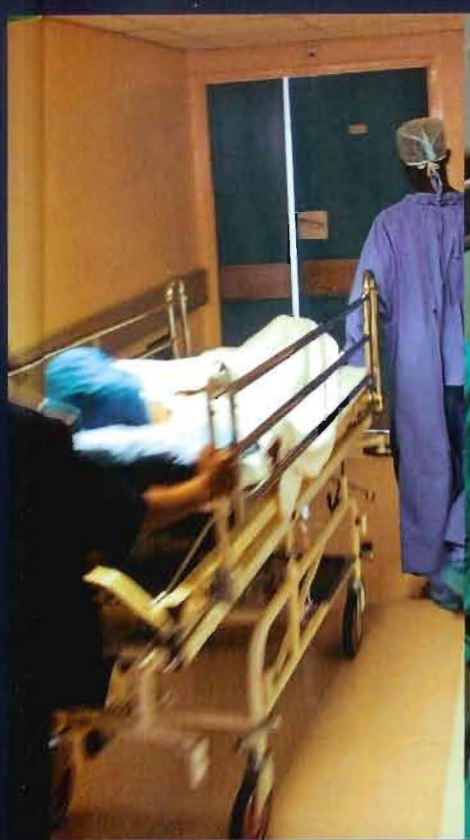
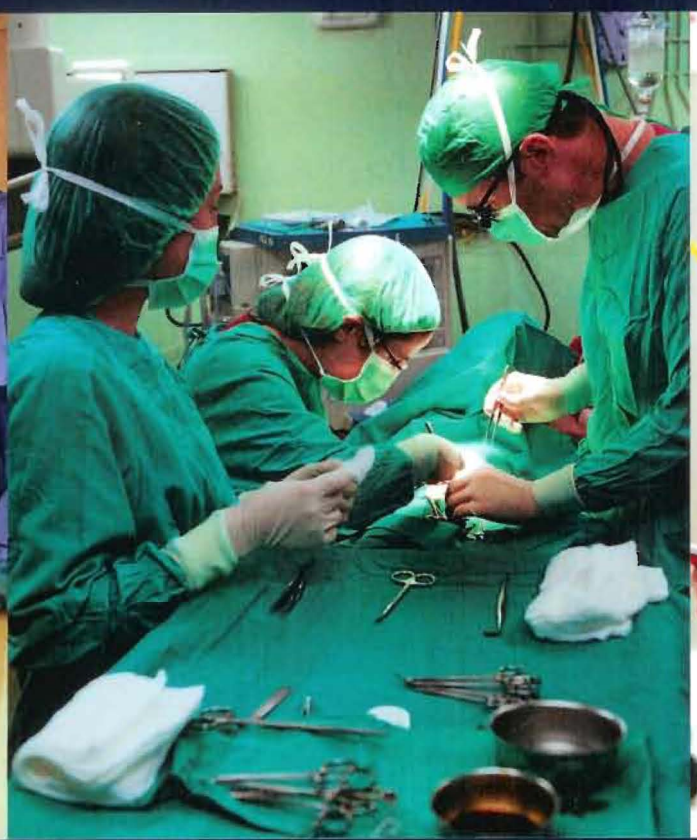
SECOND EDITION

# ACUTE CARE SURGERY AND TRAUMA

## EVIDENCE-BASED PRACTICE



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CRC Press
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# 2

# *Evidence-Based Injury Prevention Strategies*

Michelle A. Price and Cynthia L. Villarreal

CONTENTS



## 2.1 Introduction

Traumatic injury is a preventable disease. In the United States, unintentional and intentional injuries are the leading cause of death among persons aged <35 years and the fourth leading cause of death among persons of all ages [1]. In 2010, 180,811 persons in the United States suffered fatal injury, 2,529,169 were hospitalized and 28,550,424 were treated in emergency departments for nonfatal injuries. Medical treatment and work loss costs for civilian fatal and nonfatal injuries in the United States totaled more than $586 billion in 2005 [2]. These estimates, however, do not represent the true economic burden on society because they do not include the lives lost due to premature mortality, loss of patient and caregiver time, insurance costs, property damage, litigation, and diminished quality of life.

The development of trauma systems from the prehospital arena to rehabilitation services has been effective in reducing morbidity and mortality from injury. Nevertheless, 50% of deaths still occur at the scene or within minutes of the event. Thus, the mission of trauma care must also include injury prevention in addition to advances in resuscitation, definitive care, and rehabilitation. The American College of Surgeons (ACS) has recognized the importance of injury prevention initiatives in reducing the injury death and disability rate [3]. For this reason, an organized injury prevention program is required for trauma center verification. Similarly, the ACS Committee on Trauma has added a requirement for trauma centers to provide alcohol screening followed by a brief intervention for those testing positive for alcohol or those identified with an alcohol problem.

Injury prevention strategies in the health-care system are provided on a continuum ranging from hospital-funded community-based educational programs to anticipatory guidance in a primary care setting (prior to injury) and targeted interventions with injured patients with the goal of reducing the likelihood of future reinjury. Community education programs are usually conducted by trauma center outreach staff and include unintentional injury prevention (e.g., infant car seat installation training and home safety) and violence prevention programs (e.g., domestic violence and suicide prevention). The most effective programs are empirically based, conducted for a sufficient duration, and delivered in a culturally appropriate format to a cohesive target community [4].

In this chapter, we systematically review the available literature concerning the prevention of unintentional and violent injury and the effectiveness of physician-provided prevention counseling. We focus on the most prevalent mechanism of unintentional injury (motor vehicle collisions and falls) and violent injuries (e.g., domestic violence and handguns). Finally, we review the effectiveness of physician or health-care provider injury prevention counseling in primary care settings.

## 2.2 What Is the Estimated Number of Lives Saved by the Implementation of Primary Safety Belt Laws in the United States?

Motor vehicle traffic collisions are the leading cause of death among people aged 5–24 years in the United States [2]. Studies indicate that motor vehicle collisions are the leading cause of traumatic brain injuries, where the brain is injured in 70% of all collisions and the spinal cord in 5% of all collisions [5,6]. Unrestrained motor vehicle occupants account for 52% of the vehicle occupants killed on roadways in the United States [7]. Research has shown that safety belts are the single most effective means of reducing collision-related injury and mortality. Due to the fact that safety belts are very effective, laws have been established to encourage safety belt use. Safety belt laws are divided into two categories: primary and secondary. A primary safety belt law allows a law enforcement officer to stop a vehicle and issue a citation when the officer observes an unbelted driver or passenger in a motor vehicle, whereas secondary laws allow law enforcement officers to issue a ticket for not wearing a seat belt only when there is another citable traffic violation [8]. In the United States, only 34 states have primary safety belt use laws [9]. Over time, with the expansion of safety belt use laws to additional states, seat belt use rates have steadily increased, especially in the past decade in response to a national push to increase safety belt use.

Studies suggest that passing a primary law can increase safety belt use rates among nonusers by 40% [10]. In 1994, the overall observed shoulder belt use rate was 58%, a decade later, that number had risen to 80%, and in 2005, the national average was 82% [10]. Among states with primary versus secondary safety belt use laws, the average safety belt use rate was about 8% points higher in those states who had primary enforcement laws; 83 versus 75% [8]. In a study done by the Insurance Institute for Highway Safety [11], it was found that states that strengthened their laws from secondary enforcement to primary saw an estimated 7% decline in driver death rate. If the 28 states that still have secondary safety belt laws would have changed their safety belt law, more than 5000 lives could have been saved since 1996 [11]. The National Highway Traffic Safety Administration [10] suggests that lap/shoulder belts, when used properly, reduce the risk of fatal injury to front seat passenger car occupants by 45% and the risk of moderate to critical injury by 50%. Furthermore, for light truck occupants, safety belts reduce the risk of total injury by 60% and moderate to critical injury by 65%.

*Recommendation*: Educating patients and supporting community-based initiatives to increase safety belt use has great potential in the continuum of saving lives, preventing injuries, and reducing the economic costs associated with motor vehicle collisions. Physicians and other health-care providers should encourage patients to use safety belts, as well as participate in the policy-making process in those states without primary safety belt laws. Trauma surgeons can play a particularly poignant role in advocating for the passage of these laws, as they can speak to state legislators and the media regarding their experiences with motor vehicle collision patients who were unrestrained.

*Grade of recommendation*: A

## 2.3 What Evidence Exists on the Effectiveness of Screening and Brief Intervention for Alcohol Problems for Reducing Subsequent Injury among Emergency Room Patients?

In trauma systems today, estimates show that between 50% and 70% of patients have positive blood alcohol concentrations at the time of admission [12]. According to the Center for Disease Control and Prevention, alcohol is the leading contributor to both intentional and unintentional injuries [13]. Research has also shown that alcohol use contributes to patients having multiple traumatic injuries over time, supporting the need to provide screening and brief intervention (SBI) to reduce the likelihood of subsequent trauma among patients [14]. Yet, until recently, relatively few trauma patients who were under the influence of alcohol were screened for alcohol abuse, referred for treatment, or even acknowledged as having alcohol in their system. One of the greatest challenges to addressing alcohol problems is identifying patients who are in need of treatment. A promising technique is SBI. Hospital emergency rooms in many states are using this strategy to identify patients with problem drinking and addiction. In 2007, the ACS instituted the requirement that all ACS-verified Level I trauma centers screen all trauma patients for high-risk alcohol use and provide intervention to patients with elevated blood alcohol levels [14].

The purpose of SBI in trauma settings is to prevent substance abuse-related disabilities in persons at risk or to prevent further harm among those in the early stage of substance abuse [15]. SBI can be accomplished using a variety of tools that assist clinicians in asking about alcohol use, assessing the problem severity, advising the patient to decrease alcohol use, and monitoring progress. Two widely used brief instruments are Alcohol Use Disorders Identification Test (AUDIT) and CAGE. The AUDIT helps identify excessive drinking as the cause of the presenting illness and provides a framework for intervention to help risky drinkers reduce alcohol use (thus avoiding dangerous consequences) [16]. The CAGE instrument has been shown to be both sensitive and specific to identifying persons who meet criteria for alcohol abuse and dependence [17]. The CAGE is a very short and simple screening instrument that asks about attempting to Cut down on alcohol, being Annoyed by other criticizing you about your drinking, feeling Guilty about drinking, and having an Eye-opener (an alcoholic beverage) in the morning.

SBI is not only effective in reducing subsequent injuries, but reduces alcohol-related costs to health-care facilities. Brief alcohol counseling sessions have reduced recidivism by 50% and have significantly reduced both binge drinking episodes and drinks consumed per week [18,19]. Studies have shown that SBI among trauma patients significantly reduces self-reported drinking, injuries, and other alcohol dependence symptoms [20–23]. Monti et al. [21] found that a single intervention session in the emergency department, versus standard treatment, reduced alcohol-related injuries 50 versus 21%. Gentilello found that a single 40 min session reduced weekly drinking by 22 drinks compared to 7 drinks among the control group, with a 47% reduction in hospital readmission among study participants [20].

Further, cost–benefit analysis research conducted by Gentilello et al. showed that SBI conducted in trauma centers could save hospitals $1.82 billion a year, and that for every dollar spent on screening and intervention, $3.81 in health-care costs was saved [19]. The Substance Abuse and Mental Health Services Administration indicates that trauma centers are in an ideal position to take advantage of the teachable moment generated from an injury by implementing SBI for at-risk and dependent drinkers [24]. Although data show that screening injured patients for the presence of an alcohol problem has been shown to reduce subsequent alcohol use, hospital readmissions, and related consequences, many trauma centers do not provide the service [19].

A review conducted by Field et al. (2010) suggests that the general efficacy of brief alcohol interventions is recognized as having mixed reviews [25]. The implementation of SBI varies from provider to provider, therefore; Eisenberg and Woodruff, recommend using provider training and development protocols that lead to high skill mastery [26]. With successful implementation of injury prevention strategies such as SBI, the overall public health approach available in trauma hospital settings will make great strides in improving prevention services among this vulnerable population (Table 2.1).

*Recommendation*: Trauma surgeons, emergency department physicians, and other health-care providers can detect alcohol problems using screening tools that are easy to administer, reliable, and effective in reducing repeat traumas. Screening tools and physician guides are available on the ACS website (https://www.facs.org/~/media/files/quality%20programs/trauma/publications/sbirtguide.ashx) and the National Institute of Alcohol Abuse and Alcoholism website (http://pubs.niaaa.nih.gov/publications/aa65/AA65.htm).

*Grade of recommendation*: A

## 2.4 What Are the Applications of Preventive Medicine to the Control of Domestic Violence?

Violence prevention encompasses a wide spectrum of interpersonal violence (i.e., child maltreatment, intimate partner violence [IPV], sexual violence, and elder abuse) and self-directed violence (i.e., self-harm and suicide). Much of the research on evidence-based prevention practices in health-care settings has focused on domestic or IPV. Annually, in the United States, women experience approximately 4.8 million IPV assaults or rapes and men experience about 2.9 million IPV assaults [27]. In a study of the prevalence of domestic violence victimization among women attending general practice, Richardson et al. found that 41% of female patients had experienced IPV and 17% had experienced it within the past year [28].

Health-care services play a central role in the care of IPV victims; however, the effectiveness of health-care professionals' responses has been a focus of concern since the 1970s [29]. Nelson et al. [30] systematically reviewed the evidence for screening women and the elderly for IPV and found that despite the extensive literature on IPV, few studies provide data on detection and management to guide clinicians. Ramsay et al. [31] conducted a systematic review of the effectiveness of health professional screening and intervention for IPV among women presenting in emergency departments, primary care

TABLE 2.1
Summary of Evidence-Based Injury Prevention Studies

| Author | References | Year | Evidence Level | Groups | Design | Median Follow-up | End Point |
|---|---|---|---|---|---|---|---|
| Dunn et al. | [18] | 2003 | II | Trauma patients (no control group) | CS | 6 and 12 months | Hazardous drinking patterns |
| Gentilello et al. | [19] | 2005 | II | Injured patients, 18 years or older, positive BAC | PCS | None | None |
| Monti et al. | [21] | 1999 | I | Motivation interview versus standard care | RCT | 3 and 6 months | Alcohol interventions, harm reduction |
| Longabaugh et al. | [22] | 2001 | I | Brief intervention versus brief intervention with booster session versus standard care | RCT | 12-months follow-up | Ongoing intervention, decrease alcohol recidivism |
| Hungerford et al. | [23] | 2003 | II | Convenience sample of alcohol positive patients | PCS | 4 months | Increased feasibility of alcohol screening and counseling |
| Nelson et al. | [30] | 2004 | II | Varied | SR | Varied | Varied |
| Ramsay et al. | [31] | 2002 | II | Varied | SR | Varied | Varied |
| Carbone et al. | [42] | 2005 | II | Gun safety counseling session, STOP 2 brochure plus a gun lock versus anticipatory guidance | PCS | 1 month | Gun ownership, gun storage practices |
| Albright and Burge | [48] | 2003 | I | Verbal counseling alone versus counseling plus a gun safety brochure versus no counseling | RCT | 60–90 days | Gun ownership, gun storage practices |
| Oatis et al. | [44] | 1999 | IV | STOP gun safety counseling plus brochure (no control group) | CS | ≥1 year | Gun ownership, gun storage practices |
| Grossman et al. | [45] | 2000 | I | Gun safety counseling with STOP brochure plus gun lock coupon versus standard care | RCT | 3 months | Gun ownership, gun storage practices |
| DiGuiseppi and Roberts | [51] | 2000 | I | Varied | SR | Varied | Varied |
| DiGuiseppi and Higgins | [52] | 2001 | I | Varied | SR | Varied | Varied |
| Bass et al. | [53] | 1993 | II | Varied | SR | Varied | Varied |

*Note:* CS, case study; RCT, randomized controlled trial; PCS, prospective cohort study; BAC, blood alcohol content; SR, systematic review.

facilities, or antenatal clinics. Eight of the nine screening studies found higher rates of IPV identification at the sites utilizing various screening tools. However, the one randomized controlled trial did not find evidence of increased identification rates related to the introduction of screening procedures [32]. The authors also reviewed six studies evaluating the effectiveness of IPV interventions in health-care settings and found no relation between type of intervention or health-care setting and the effect of the intervention [31]. In 2012, Klevens et al. conducted a randomized clinical trial at 10 primary health-care centers and found that providing a partner violence resource list with or without screening did not result in improved health [33]. In 2013, Taft et al. reviewed 11 trials that recruited 13,027 women and found that while screening was not harmful, there is insufficient evidence to justify universal screening in health-care settings [34].

*Recommendation*: IPV screening programs moderately increase rates of victim identification in health-care settings; however, there is limited evidence of effectiveness of associated interventions. Therefore, it would be premature to recommend implementation of a universal screening program. Further research utilizing randomized clinical trials is required to better quantify the effectiveness of IPV prevention strategies in health-care settings. Health-care professionals should, however, receive training on selectively screening for IPV for patients who meet specific criteria with well-validated, brief screening tools such as the Hurt, Insulted, Threatened, or Screamed at instrument [35] or the Partner Violence Screen instrument [36].

*Grade of recommendation*: B

## 2.5 What Is the Evidence for the Effectiveness of Clinician Counseling Regarding Firearm Safety?

In 2012, there were 33,563 firearm deaths in the United States (or 10.5 deaths per 100,000 population) [37]. Since the mid-1980s, organized medicine has crafted policies and programs to reduce firearm morbidity and mortality [38]. Longjohn and Christoffel found 5 consensus areas among 14 national medical societies: access prevention, gun commerce, research, public education, and clinical counseling [39]. The American Academy of Pediatrics recommends violence prevention anticipatory guidance at every health maintenance visit, including urging gun removal from homes [40]. However, the evidence on the effectiveness of patient counseling regarding gun removal or safer storage behaviors has been equivocal [41]. In an investigation of gun safety counseling coupled with a gun lock giveaway in a pediatric outpatient setting, Carbone et al. [42] found significant improvements in safe gun storage behaviors among families in the intervention group (62%) versus the control group (27%). In a similar study conducted in a family practice clinic, Albright and Burge [43] found improved gun storage behaviors among gun-owning patients who received either verbal counseling alone (64%) or verbal counseling plus a gun safety brochure (58%) compared to controls (33%). Conversely, two earlier studies that used Steps to Prevent Firearm Injury (STOP) did not find significant effects. Oatis et al. [44] did not find statistically significant declines in gun ownership or improvement in gun storage practices among participants who received gun safety counseling and written materials during a well-child visit at a pediatric practice. Similarly, Grossman et al. found that the gun safety counseling intervention did not lead to changes in gun ownership or significant changes in storage practices [45].

In the aftermath of the school shooting that killed 20 children and 6 educators in Newtown, Connecticut, President Obama issued 23 executive orders directing federal agencies to improve knowledge of the causes of firearm violence, prevention efforts, and strategies to reduce the public health burden of firearm violence. The Centers for Disease Control and Prevention (CDC) commissioned the Institute of Medicine to develop a research agenda based on gaps in the evidence [46]. The Institute of Medicine (IOM) research agenda focuses on the characteristics of firearm violence, risk and protective factors, interventions and strategies, gun safety technology and the influence of video games and other media [47]. Among the priorities for research on prevention and other intervention, the IOM report called for research to determine the degree to which various childhood education or prevention programs (including routine primary care counseling) reduce firearm violence.

*Recommendation*: Research on the effectiveness of physician counseling regarding gun removal and safe storage has been limited with mixed results. Further study is warranted cost–benefit ratio of these brief interventions is warranted [48].

*Grade of recommendation*: B

## 2.6 What Is the Effectiveness of Injury Prevention Counseling Delivered by a Health-Care Provider in Improving Safety Practices among Pediatric Patients?

Unintentional injuries are a leading cause of death for all Americans, regardless of age, race, gender, or economic status [13]. In particular, injury is the leading cause of death and a substantial cause of disability for children and adolescents [49]. Given the pervasive and preventable nature of these injuries, injury prevention counseling or anticipatory guidance should be integrated into physician visits and other health-care settings to educate parents, caretakers, and children about age-appropriate behavioral risks and safety strategies. However, the proportion of children receiving injury prevention counseling was relatively unchanged from 40% in 1994 to 42.4% in 2003 [50].

Injury prevention topics for office-based counseling include motor vehicle restraints, smoke detectors, pool fencing, hazards of infant walkers, and the safe storage of poisons and medications. There is sufficient evidence that clinical counseling can influence child safety seat use and use of a functioning smoke alarm in the home [51–53]. Due to the fact that children and adolescents are at greatest risk for concussions, it is important that injury prevention counseling encompass topics such as helmet use, seat belt or restraint system use, and the use of protective equipment while participating in athletic activities [54]. A review of the literature on childhood injury prevention counseling in primary care settings illustrated that the majority of studies, 18 of 20, demonstrated positive outcomes in increasing overall knowledge and safety practices along with decreasing childhood injury rates [53]. Furthermore, a systematic review of over 22 randomized controlled trials of a variety of injury prevention interventions in clinical settings suggested a strong improvement in safety practices, which included child safety seat and safety belt restraint use [51].

Research shows that parents and children are often receptive to injury prevention counseling during a sick

visit, especially if it is related to an injury, a recent emergency department visit, or injury to a sibling [55]. Due to the fact that pediatricians come into contact with parents a great deal in the first 5 years of a child's life for routine care, the American Academy of Pediatrics and Bright Futures recommends that clinicians use this opportunity to provide injury prevention counseling [56,57]. The Injury Prevention Program, developed in 1983 by the American Academy of Pediatrics, includes a safety counseling schedule, age-appropriate safety sheets for families, and interventions that have been proven to effectively improve safety practices among parents and caregivers [53,58,59].

*Recommendation*: Physicians and health-care providers should use routine doctor visits, emergency department visits, and other health-care visits as teachable moments to educate the patient and their parent on age-appropriate injury prevention.

*Grade of recommendation*: A

## 2.7 What Is the Effectiveness of Injury Prevention and Medication Safety Counseling Delivered by a Health-Care Provider in Improving Safety Practices among Geriatric Patients?

As our population continues to grow, the number of older adults is on the rise. Older adults are at an increased risk for various types of unintentional injuries [60,61]. Unintentional injures rank among the top 10 leading causes of death and disability among adults aged 65 years and older with falls and motor vehicle crashes as leading causes [60]. According to Rosen et al., falls are the most common cause of injury death, hospitalization, and emergency department visits in this population with various injuries such as hip fractures and traumatic brain injuries [61]. The study suggests that injury prevention counseling be conducted by emergency physical and primary care physicians regarding fall prevention strategies such as asking about environmental circumstances surrounding an incident and suggesting potential modifications [61]. In 2010, the CDC published a compendium of effective fall interventions for older adults recommending exercise interventions to maintain or improve balance and mobility and home environment modifications [62].

Furthermore, injury prevention counseling to older adults on medication safety can be used as a strategy to reduce unintentional poisoning exposures to this population. Health-care providers are in a position to educate patients on medication safeguards such as how to read and follow prescriptions, importance of taking medications on time, and discarding old unused medications. Health-care providers should also use medication reviews to assess potential issues that may lead to falls [61]. A combination of strategies such as medication discharge summaries coupled with medication safety counseling, and reminder cards can lead to improved patient outcomes [63]. A study conducted by Shields et al. provides evidence that the majority of older adults are not aware of vital safety information needed to protect themselves adequately [64]. As trusted providers health-care providers must maximize encounters with this population to increase awareness and reduce injury risks (Table 2.2).

**TABLE 2.2**

Evidence-Based Injury Prevention Summary

| No. | Question | Answer | Grade | Reference |
|---|---|---|---|---|
| 1 | Do state-based primary enforcement safety belt laws save lives in the United States? | Evidence supports the benefit of primary belt laws in reducing injuries and fatalities. | A | [8,10,11] |
| 2 | What evidence exists on the effectiveness of SBI for alcohol problems for reducing subsequent injury among emergency room patients? | Evidence supports SBI to reduce short-term recidivism, but additional research on long-term effects is needed. | A | [16,18–26] |
| 3 | What are the applications of preventive medicine to the control of domestic violence? | Screening programs increase victim identification however evidence on intervention effectiveness is limited. | B | [30–36] |
| 4 | What is the evidence for the effectiveness of clinician counseling regarding firearm safety? | Evaluation of gun safety programs in primary care settings have resulted in inconsistent outcomes. | B | [41–45] |
| 5 | What is the effectiveness of injury prevention counseling delivered by a health-care provider in improving safety practices among pediatric patients? | There is sufficient evidence to suggest that injury prevention counseling improves safety practices among the pediatric population. | A | [51–55] |
| 6 | What is the effectiveness of injury prevention and medication safety counseling delivered by a health-care provider in improving safety practices among geriatric patients? | There is sufficient evidence to support educating aging patients on injury prevention and medication safety. | A | [60–64] |

*Recommendation*: Physicians and health-care providers should use routine doctor visits, emergency department visits, and other health-care visits as teachable moments to educate aging patients on injury prevention and medication safety.

*Grade of recommendation*: A

## 2.8 Conclusions

Physicians in office-based practices, hospital outpatient/follow-up clinics, and emergency departments all have a unique opportunity to educate patients on injury prevention. Major influences in physicians' decisions to incorporate injury prevention counseling into routine care include physicians' confidence in their ability to counsel, perceptions regarding counseling effectiveness, training, practice setting, and office time constraints. Injury prevention counseling does not have to be very time-consuming and extensive, but rather substantive enough to increase knowledge. Effective prevention programs can include physician or nurse counseling, the use of computerized education materials, public service announcements, and educational videos in waiting areas. Due to the fact that physicians and health-care providers have time constraints, the most efficient strategy is to educate patients or caregivers on specific topics that are appropriate for the patient's age, time of year, and other common injuries seen in that population.

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