COMIRB Protocol

Protocol #: 23-2559
Project Title: Antibiotic Concentrations after MassivE transfusion (ACME) study
Principal Investigator: Adit Ginde, MD, MPH
Version Date: 11-OCT-2024

Research Team:

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Research Locations:

Performance Site	Brooke Army Medical Center Site Investigator: Julie Rizzo, MD Email: Julie.a.rizzo.mil@health.mil
Lead Site **Performance Site**	University of Colorado Hospital Site Investigators: Adit Ginde, MD, MPH (administrative lead) Franklin Wright, MD David Douin, MD
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Multisite Research:
Function/Role of Lead Site: The University of Colorado will be the Lead Site with the above listed principal investigator as the overall project lead. The Lead Site is responsible for establishing and maintaining the master protocol in accordance with COMIRB and USAMRDC Office of Research (ORP), Office of Human Research Oversight (OHRO). The Lead Site in collaboration with the sponsor (Metis Foundation) will be responsible for all COMIRB and USAMRDC ORP, OHRO submissions. The Lead Site will be responsible for submitting all participating sites' OHRO submissions and maintain a record of all OHRO/IRB regulatory documents. Each site will submit all approval documents from their local regulatory office to the Lead Site for submission to the IRB.

The Lead Site will then submit the site's protocol documents to the USAMRDC OHRO for the DOD-required headquarters level administrative review (HLAR). Any revisions resulting from the headquarters level review will be communicated directly from the ORP OHRO to the performance site Principal Investigator (PI), Lead Site, and the DCC. Upon completion of the HLAR, an approval memo from ORP OHRO will be sent to the site PI, and the Lead Site.

Any revisions to the master protocols or supporting documents that are requested by the local regulatory office must be reviewed and approved by the Lead Site before the site resubmits the protocols to its IRB along with the COMIRB. In the event that the participating site IRBs require changes to the master protocols, the Lead Site will submit an amended master protocol and/or supporting document(s) to COMIRB for review and approval. Upon receipt of the COMIRB amendment approval, the Lead Site will provide all approval documents for participating sites. The Lead Site will disseminate the COMIRB approved documents to all participating sites for local regulatory office approval. All amendments made to the master protocols will be reported with the Lead Site's continuing review to ORP OHRO by the Lead Site

I. Hypotheses and Specific Aims:

Combat and civilian trauma frequently result in open wounds that are at risk for infection. Data from the Department of Defense Trauma Registry demonstrates that 74% of combat trauma casualties have an open wound. The Committee on Tactical Combat Casualty Care, the Prolonged Field Care Working Group, and the Joint Trauma System clinical practice guidelines recommend antibiotic prophylaxis for open wounds after trauma. The civilian setting has similar risks of open wound infection after trauma. In parallel, current practice guidelines recommend the aggressive use of balanced blood products during resuscitation. It remains unclear how the replacement of blood after hemorrhage through transfusion may affect antibiotic concentrations. Data is necessary to better understand this relationship to enhance wound prophylaxis antibiotic dosing, particularly in severely wounded casualties that receive blood products during massive transfusions. It remains unclear how these resuscitation methods may alter pharmacokinetics. Our hypothesis is that drug concentrations decrease with a direct relation to the amount of blood transfused during low volume, massive, and supermassive transfusion after trauma compared to patients that receive no blood products. We seek to understand the relationship between drug concentrations and blood product administration using a non-compartmentalized model in the setting of hemorrhage. Specifically, we will (1) obtain drug concentrations at regular intervals during the first 12-18 hours after administration of antibiotics, (2) determine how much blood products and fluids are transfused during the 12 hours prior to antibiotic and 24 hours post-administration, and (3) perform data modeling to understand the relationship between blood transfusions and drug concentrations to inform data-driven dosing models. Liquid chromatography methods will be developed to measure drug concentrations. We will conduct a prospective, multicenter study at two large trauma centers – Brooke Army Medical Center and the University of Colorado Hospital. We will seek to enroll any patient who is hospitalized or anticipated hospital admission for acute trauma and receives an antibiotic on our list during their index hospitalization. We will then model the drug levels against the amount of blood and fluid infused to create an understanding of the pharmacokinetics of antibiotic wound

prophylaxis during low-volume, massive, and supermassive transfusions compared to controls who receive no blood.

II. Background and Significance:

Trauma in both military and civilian settings can result in hemorrhage, which is a leading cause of potentially survivable death on the battlefield and the most common cause of death in the civilian setting after trauma.[1] Multiple previous studies from the military setting have demonstrated a survival benefit with early blood transfusions.[2] Studies from the civilian setting have similar findings.[3] Some casualties require a massive or supermassive transfusion which have varying definitions but are a unique subset of trauma patients that require extensive volumes of blood products.[4] Our previous study found that nearly 25% of combat casualties received blood during their course of care with nearly 3% reaching the supermassive transfusion threshold.[4] During such resuscitations, the casualty received so much blood that essentially their entire blood volume is 'turned over' by way of massive exsanguination followed by massive transfusion. Parallel to this, the resultant injury causing the massive hemorrhage is often an open wound that is at risk for infection (e.g., firearm injury). In unpublished data from the Department of Defense Trauma Registry (DODTR), of 25,897 casualties, 74% (n=19,096) had an open wound, highlighting the importance of wound prophylaxis.[5] While an open wound may not result in death in the first 24 hours, the potential resulting infection is a major cause of mortality for casualties that experience delayed death.[6] Such events are referred to as 'died of wounds.' To combat the development of wound infections, responders administer empiric antibiotics early in the course of combat casualty care with the intent of initiation in the field.[7,8] The Committee on Tactical Combat Casualty Care (CoTCCC), the Prolonged Field Care (PFC) Working Group, the and the Joint Trauma System (JTS) Clinical Practice Guidelines CPG all recommend antibiotic wound prophylaxis. What remains unclear is how the replacement of a casualty's blood with transfused blood because of massive hemorrhage alters the pharmacokinetics of antibiotic administration. Low antibiotic concentration in the plasma will lead to insufficient distribution of the antibiotics in the tissues. This is even more detrimental in the setting of devitalized tissue where significant concentrations are necessary in the plasma to reach effective therapeutic levels in the tissues.[9]

Currently there is no good data available to guide clinicians on dosing and re-dosing antibiotics in the setting of massive transfusion. Current dosing practices reflect the standard dosing regimen of antibiotics for wound prophylaxis or treatment of an infection, which are based on studies in non-hemorrhaging patients. The best available data at this time to guide medication dosing in the setting of volume loss and volume replenishment are extrapolated from studies on plasmapheresis, exchange transfusions, and hemodialysis.[10] Current data strongly suggest that antibiotic dosing should be adjusted based on renal function and liver function, with most of the data centered around reducing the dosing in the elderly and patients with chronic kidney disease.[11-14] This is the exact opposite of what is needed in the situation of massive hemorrhage. Unfortunately, data applied to massive hemorrhage is very limited, despite robust data for the dose-reducing practices. In the setting of continuous renal replacement therapy (CRRT) and hemodialysis, antibiotics with low levels of protein binding require significantly higher doses to achieve therapeutic levels as the drugs have a smaller volume of distribution, allowing more rapid removal.[15] Previous studies have found that antibiotic underdosing occurs frequently in the setting of hemodialysis and CRRT.[16-25] Based on this data, we can reasonably speculate that from a physiologic standpoint, significant blood loss would cause similar changes in antibiotic dosing requirements. However, the physiological changes that occur during CRRT or hemodialysis are substantially different than those caused by hemorrhage, given that renal replacement interventions do not rapidly remove fluid from the body. In the setting of massive hemorrhage, the replacement of lost blood with new blood is not a simple exchange process. Due to the rapid loss of blood volume, fluid rapidly redistributes across compartments from interstitial space into the vasculature to replenish the volume loss.[26] This further complicates the physiology compared when comparing to CRRT or hemodialysis. Separately, we must also highlight that hemodialysis is often used specifically for the purpose of drug removal in the setting of toxic ingestions.[27]

While there is a significant amount of literature evaluating antimicrobial dosing in the setting of CRRT or hemodialysis, markedly less literature is available for the setting of plasmapheresis.[28] Despite this lack of robust literature, drug dosing in plasmapheresis must also be explored as the physiology is somewhat similar to blood volume loss. In plasmapheresis, blood is removed from the body and the plasma component of the blood is separated out. The non-plasma components of the blood are then returned to the body along with another fluid such as saline or albumin. Somewhat similar processes are involved during massive transfusion in that plasma is lost and plasma is replaced, along with other blood components. However, during a massive transfusion all components are turned over, including the proteins that often bind to antibiotics. Limited studies of antibiotics in the blood and the effects of plasmapheresis exist, which further highlights the need for hemorrhage specific data.[29-35]

The lack of data focused on massive transfusion and supermassive transfusion highlights the need for studies specific to the trauma setting. Data specific to those practice patterns are greatly needed. In this project, we propose to fill this data gap.

III. Military Relevance:

Our previous study found that nearly 25% of combat casualties received blood during their course of care with nearly 3% reaching the supermassive transfusion threshold.[4] During such resuscitations, the casualty received so much blood that essentially their entire blood volume is 'turned over' by way of massive exsanguination followed by massive transfusion. The injuries causing the massive hemorrhage are often open wounds at risk for infection (e.g., firearm injury). In unpublished data from the Department of Defense Trauma Registry (DODTR), we found that out of 25,897 casualties within our dataset, 74% (n=19,096) had an open wound, highlighting the importance of wound prophylaxis.[5] While an open wound may not result in death in the first 24 hours, the potential resulting infection is a major cause of mortality for casualties that experience delayed death.[6] Such events are referred to as 'died of wounds.' To combat the development of wound infections, empiric antibiotics are administered. Antibiotics are administered early in the course of combat casualty care with the goal of initiation in the field.[7,8] The Committee on Tactical Combat Casualty Care (CoTCCC), the Prolonged Field Care (PFC) Working Group, the and the Joint Trauma System (JTS) Clinical Practice Guidelines CPG recommend antibiotic wound prophylaxis. What remains unclear is how the replacement of a casualty's blood with transfused blood as result of massive hemorrhage alters the pharmacokinetics of antibiotic administration. Insufficient antibiotic concentration in the plasma will lead to insufficient distribution of the antibiotics in the tissues. This is even more detrimental in the setting of devitalized tissue where significant concentrations in the plasma are necessary to reach effective therapeutic levels in the tissues.[9]

IV. Research Methods

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A. Outcome Measure(s):

Our hypothesis is that drug concentrations decrease with a direct relationship to the amount of blood transfused during low volume, massive, and supermassive transfusion after trauma. We seek to understand the relationship between antibiotic concentrations and blood product administration in the setting of hemorrhage. Specifically, we are seeking to do the following:

1. Obtain drug concentrations at regular intervals during the first 18 hours after antibiotic administration.
2. Determine the total volume of blood products and fluids transfused during the first 24 hours after antibiotic administration.
3. Perform data modeling to understand the relationship between blood transfusions and drug concentrations to inform data-driven dosing models.

A. Description of Population to be Enrolled:

Trauma patients brought to study sites who receive an antibiotic during their index hospitalization.

B. Study Design and Research Methods

We will enroll in a 1:2 ratio with 2 'controls' for each patient who receives massive transfusion. Control patients will ideally receive no blood but may be included with up to 2 units transfused. For every two control patients, one patient will be enrolled who receives at least 3 units of blood. Our enrollment will primarily be based off the maximal enrollment during the study period that meet inclusion. Since we cannot recruit for this study, the total size is not yet known but our subject enrollment will not exceed 208 with all draws completed at each site. Each research blood draw will not exceed 1mL at any timepoint for a maximum total of 6mL used for analysis per patient. Research draws will be completed using existing line(s). If existing lines are unavailable, research-only venipunctures may be performed at a maximum of 2 time points.

C. **Inclusion Criteria:**

Trauma Patient
Receives ampicillin/sulbactam, cefazolin, cefepime, ceftriaxone, clindamycin, ertapenem, levofloxacin, metronidazole or pipercillin/tazobactam at any dose
Hospitalized or anticipated hospital admission

D. **Exclusion Criteria:**

Received the same antibiotic within the past 5 half-lives of the drug (e.g. received the same antibiotic during a recent interval)
<18 years of age
Known pregnancy
Known prisoner

We will exclude known individuals under 18 years of age, pregnancy and prisoners on presentation as a trauma patient. However, these statuses may not be known until later in the patient's hospitalization. Therefore, if status is unknown we will enroll the patient. If the patient is later identified as under 18 years old, pregnant, or a prisoner, we would discard their blood and any data collected as soon as feasible.

E. **Research Procedures:**

Figure 1: Flow of study subjects and data

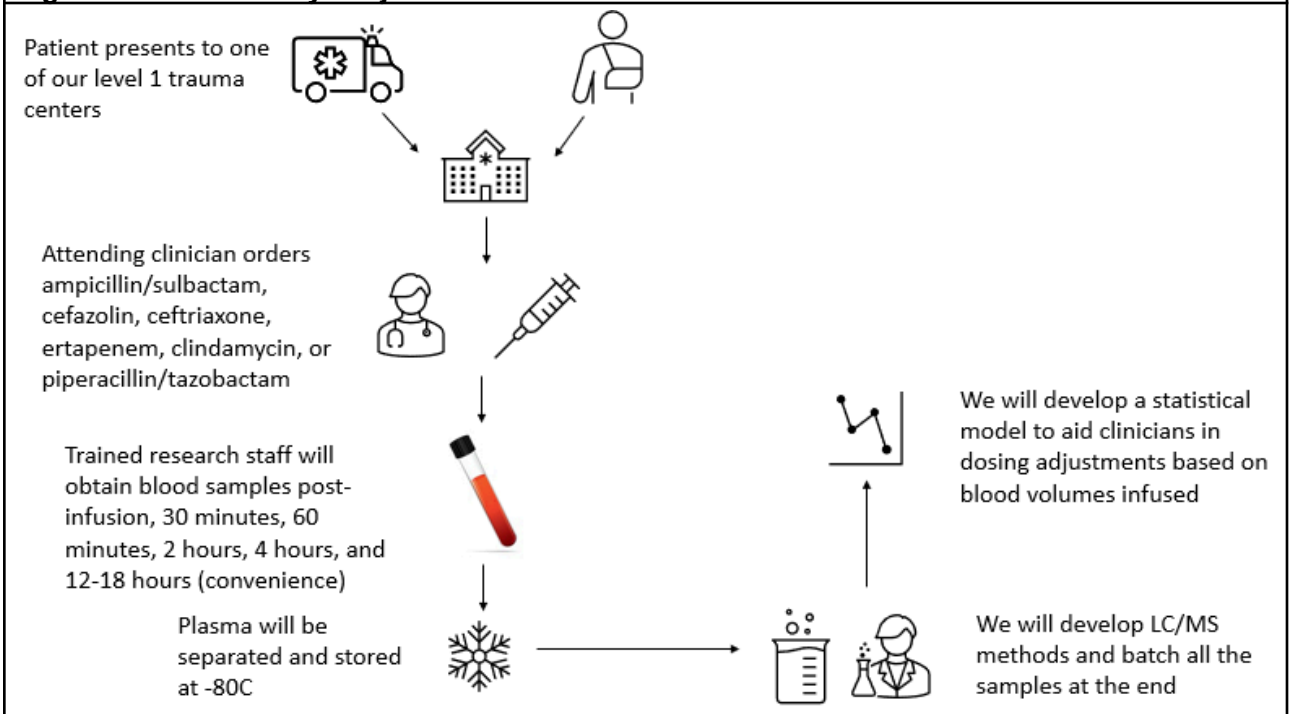

Table 1: Step-by-Step Study Procedures
1. **Identification of Trauma Subjects**
Acute Trauma patients for enrollment in the study will be identified using site-specific trauma alert and activation protocols in the emergency department with anticipated hospitalization or already hospitalized. Study members will seek out any patient that receives one of the antibiotics listed in the inclusion criteria during their index hospitalization through electronic alerts, provider engagement, research coordinator involvement, and ED/inpatient pharmacists. We will enroll a convenience sample. We will promote capture by way of staff education, staff reminders, staff-facing signage, and dissemination via routine department communications.
2. **Obtaining Trauma Subject Blood Samples**
Blood will be obtained for research in two ways: **Clinical Draws:** In clinical draws, which happen frequently in acute trauma patients, the patient is having blood drawn for clinical reasons. An additional blood sample may be obtained for research purposes at this time. Since this study only requires 1mL samples at six timepoints (6mL total volume) it is feasible to coordinate with the clinical team to obtain almost all of the research samples when clinical draws are being done. **Research Draws:** In research draws, no blood for usual clinical care coincides with the research time point. In this case, a credentialed study team member or member of the clinical team will perform or obtain the blood draw.
3. **Blood Sample Volume and Timepoints**
Blood draws will occur at six intervals after the antibiotic infusion: a. Immediately post-infusion (1mL) with a window of ±15 minutes b. 30 minutes post-infusion (1 mL) with a window of ±15 minutes c. 60 minutes post-infusion (1 mL) with a window of ±15 minutes d. 2 hours post-infusion (1 mL) with a window of ±1 hour

e. 4 hours post-infusion (1 mL) with a window of ±1 hour
f. 12-18 post-infusion (1 mL) with the draw occurring anytime inside this window or within ±1 hour of the window
g. Total research sample volume from all timepoints= 6mL

Whenever possible, research draws will be coordinated with the clinical team to happen with clinical draws and stand-alone research draws will be minimized. Given the unpredictable nature of trauma care, missed draws or draws outside of the goal time frame will not be considered protocol deviations. Research draws will not exceed 1mL per timepoint, for a maximum total volume of 6mL. *With the exception of these minimal risk blood draws, this study would otherwise meet exempt category 4 requirements as part of routine healthcare operations.*

4. **Storage of Blood Samples**

The whole blood will be collected in standard clinical sample tubes with anticoagulants and stored on ice or in a refrigerator (4°C) temporarily. As soon as feasible, the samples will be centrifuged for 10 min at 3000G and the plasma removed and frozen at -80°C by a study team member. The tubes will then be shipped to the laboratory at the USAISR for analysis in batches using approved shipping protocols for frozen biological specimens. Once the samples are at the USAISR, all handling will be at the direction of the relevant laboratory SOPs. The methodology for the analysis that will be performed at the USAISR will be provided to the regulatory office separately and adhere to the requirements for bench studies. The specimens will be numbered using assigned sequential study enrollment numbers. The PHI will not be transferred to the USAISR with the tubes and will remain at the local enrollment sites.

5. **Data Extraction**

Data extraction will occur by local study site personnel through the electronic medical records systems and/or the local trauma registry. Of note, each site has a participating trauma registry established as part of their level 1 trauma mission.

6. **Data Aggregation**

Data will be aggregated by a local study team member. The de-identified data will be uploaded to the REDCap system. Once the laboratory data is available from the USAISR analysis, that will be added to the REDCap data for final analysis.

F. **Data Collection:**

Data/Element	Source	Operational Specific
Demographics	Electronic medical record system, prehospital documentation, local trauma registry	Age, sex, military status, height, weight, body mass index, admission diagnoses, discharge diagnoses, past medical and past surgical history, social history
Injury Severity Scores (ISS)	Electronic medical record system, prehospital documentation, local trauma registry	Numeric
Timing of Events	Electronic medical record system, prehospital documentation, local trauma registry	Time of injury, time of hospital arrival, time of blood products transfused, time of fluids infused, time of prehospital and hospital drugs listed below

Sample collection	Blood draws at enrolling sites with laboratory analysis at the USIASR *Whenever possible, research blood collection will be timed to clinical labs to reduce the number of research blood draws and stay within the maximum of 2 research draws, consistent with guidelines for waiver of informed consent.*	Drug concentration
Routine clinical laboratory studies	Electronic medical record system, prehospital documentation, local trauma registry	Complete blood counts (hemoglobin, hematocrit, platelets, white blood cell counts), metabolic studies (electrolytes, blood urea nitrogen, creatinine, liver function studies), blood gas values, lactate, coagulation studies (prothrombin time, international normalized ratio, partial thromboplastic time), haptoglobin, thromboelastography (TEG)
Prehospital medications	Electronic medical record system, prehospital documentation, local trauma registry	Electrolytes, IV fluids, blood products (all), anti-coagulants, tranexamic acid
Hospital medications within ±12 hours of the antibiotic infusion	Electronic medical record system, local trauma registry	Electrolytes, IV fluids, blood products (all), anti-coagulants, tranexamic acid
Major procedures within ±24 hours of the antibiotic infusion	Electronic medical record system, prehospital documentation, local trauma registry	Hemorrhage control interventions, chest needle decompression, chest tube, thoracotomy, intubation, REBOA, central line placement, interventional radiology procedures, exploratory laparotomy, irrigation and debridement, fracture stabilization, open vascular procedures, compressive hemorrhage procedures (e.g., liver packing, etc.), estimated blood loss during each operative procedure and ICU stay
Blood products within ±12 hours of the antibiotic infusion	Electronic medical record system, prehospital documentation, local trauma registry	Whole blood, packed red cells, plasma, platelets, cryoprecipitate
Outcome data	Electronic medical record system, prehospital	Discharge status, time to death (if applicable), ventilator days, intensive care unit days, hospital

	documentation, local trauma registry	days; all truncated at 7 days if LOS exceeds

G. **Managing Data and/or Human Biological Specimens for this Research:**
We will manage all study data electronically. A study team member will assign subjects a study identifier number which will allow for easy removal of PHI after study completion. PHI (source documents) will be maintained at the participating sites for the purpose of data verification. De-identified data will be uploaded into REDCap with a goal of entry within 30 days of the subject hospitalization complete (truncated at 7 days post-enrollment if longer). The DCC utilizes the clinical research data management tool REDCap to manage clinical research studies. REDCap Data Management, which is a full clinical research electronic data capture application, compliant with HIPAA regulations for data storage. Use of study data in publications, presentations, grant proposals, and other uses will require approval of the principal investigator in consultation with the site PIs. The overall de-identified data will be stored at the direction of the overall PI for data verification and/or related sub-analyses indefinitely. Local site data will be stored based on institutional requirements and at the direction of the site PI. The local study keys linking the PHI to the data will be destroyed upon study closure. De-identified data may be shared with the sponsor at their request.

H. **Sample Size Estimation:**
Our sample size will be based off the maximal number of potential subjects during the timeframe of enrollment. Since we are performing an observational study, subjects cannot be assigned to a particular antibiotic as we must keep this study at the minimal risk level to obtain waiver of informed consent. We are planning to enroll in a 1:2 ration with two control patients for every one who receives at least three units of blood. We are not planning to enroll more than 208 subjects at each site. Patients who do not have all six draws completed will not count towards the enrollment cap. Partial samples may be used to enhance the statistical analysis but will not be considered towards maximum enrollment.

I. **Data Analysis:**
We will primarily use descriptive and inferential statistics along with regression modeling. We will summarize normally distributed continuous variables using means and standard deviations, non-normal continuous variables with medians and interquartile ranges, and nominal variables using frequencies and percentages. Continuous variables such as antibiotic plasma concentrations may be log-transformed prior to analysis to meet assumptions.

To determine the differences in antibiotic plasma concentrations between patients who do and do not receive blood transfusion, we will construct a general linear model (repeated measures analysis of variance/ANOVA) with blood transfusion (yes vs. no) as a between-subjects effect and time post-infusion as a within-subjects effect. We will obtain orthogonal polynomial contrasts to examine the trends in antibiotic plasma concentration over time. We will also calculate and report pairwise differences between the transfusion and no transfusion groups at each time point with the appropriate correction for multiple comparisons, as well as compare the changes in concentration between the groups. Currently, there is no relevant data to guide us for a sample size estimate.

In our secondary analyses, we will compare antibiotic plasma concentrations among patients who received blood transfusions based on the volumes of blood received (e.g., low volume, massive transfusion, supermassive transfusion, etc.). The model will be adjusted to account for fluctuations in acute changes in kidney function during treatment. We will construct a similar model as previously described and may include relevant covariates such as the timing of blood transfusion. We will obtain orthogonal polynomial contrasts to examine concentration trends over time, calculate and

report pairwise differences between the transfusion volume groups at each time point with the appropriate correction for multiple comparisons, and compare the change in concentration between the groups. Additionally, we will conduct a regression analysis with linear and polynomial terms to determine the relationship between the volume of blood transfused and antibiotic plasma concentration. We will analyze data using relevant statistical software including SAS (v9.4, Cary, North Carolina), JMP Statistical Discovery (v17, Cary, North Carolina), Microsoft Excel (v365, Redmond, Washington).

V. Human Research Protections

J. Recruitment and Consent

1. **Identification and Selection of Subjects**
   Subjects will be identified by clinical staff. Our study will result in minimal additional blood draws beyond routine clinical draws for trauma patients.
2. **Recruitment Process**
   All clinical care will remain at the direction of the attending clinician. All blood draws will occur by way of the clinical personnel or credentialed study team members. The study team members will work with clinical staff to coordinate research samples with clinical draws if at all possible.
3. **Eligibility**
   Eligibility will be determined by trained research staff and the attending clinician based on their determination that an antibiotic is indicated for the trauma patient.
4. **Consent Process**
   a. **Waiver of Informed Consent Until the Consent is Initiated**
   Given the emergent nature of our study during acute resuscitation of the trauma patients we plan to enroll, obtaining informed consent before patient enrollment is often not feasible and could potentially result in deleterious outcomes due to the delays in clinical care it would cause. Therefore, waiver of informed consent may often be required, at least initially.

   We will obtain written informed consent for all potential subjects only when the primary clinical team (attending clinician or designee) determines that obtaining consent will not interfere with the urgency of their care. In addition, the potential subject must not be decisionally challenged and/or have an established LAR. Decisionally challenged individuals may include those who are intubated and receiving invasive mechanical ventilation, sedated, have a traumatic brain injury, or are otherwise unable to provide informed consent. When feasible, we will make these attempts to obtain written informed consent prior to enrollment and after enrollment until the last blood draw (up to 18 hours after enrollment).

   For the small subset of patients who die in the hospital before informed consent can be obtained, we will analyze all collected plasma samples.

   b. **Obtaining Consent**
   Study protocol will be proposed to patients or LAR through face-to-face communication with the research team. The research team will screen patients via automated or manual alerts, EMR, in person, or via phone; if a patient is deemed eligible, a member of the research team will reach out via MR, in person, or via phone to the clinical staff regarding approaching the patient for study enrollment, patient consenting capability, and biospecimen collection.

   The study protocol will be proposed to patients in the UCHealth University of Colorado Hospital who meet the inclusion criteria. The investigator or designee will approach the

patient or LAR as soon as possible, inform of the study, and if the patient/LAR agrees, obtain signed informed consent form in compliance with the designated IRB/IEC and/or local law requirements. The patient or LAR will consent through electronic consent via REDCap or paper consent. Once a patient expresses interest in participating in this study, the research staff and patient will review the consent form, answer any questions, and confirm study comprehension before the patient signs the eConsent document. Written (paper) consent will be used if eConsent is unavailable or not feasible.

All patients (or their LAR) will have the right to refuse to participate in the study. All patients (or their LARs) will have the right to decline ongoing participation in the study if previously enrolled under the waiver of consent but become consentable. If consent is declined or withdrawn, we will cease data and sample collection going forward from that time point. We will use data and samples previously collected under waiver of consent, unless the patient or LAR specifically requests destruction, in which case the previously collected data and samples will be discarded. If a reason for withdrawing is offered, we will document such. Access to care or the choice of medical department is not changed by the approach. The participant remains free to withdraw their consent at any time. Under these circumstances, the patient will continue to receive the appropriate care in accordance with normal care practices. If the patient is unable to provide consent, the research team will approach the LAR to introduce the study and obtain consent. If the LAR is not located with good faith effort prior to the last blood draw (up to 18 hours), the patient may be enrolled under a waiver of informed consent (see below), give the study procedures meet criteria for no more than minimal risk under Federal regulation 45 CFR 46.116(d).

c. **Waiver of Informed Consent**

We will attempt to obtain written informed consent for every enrolled subject whenever possible. However, for some decisionally challenged patients, we may be unable to locate a LAR for consent, and the patient may not be able to consent for themselves due to the nature of their injuries, invasive mechanical ventilation, traumatic brain injury, sedation, or other issues. We anticipate some patients will meet such criteria. In these cases, we will complete a good-faith effort to locate a LAR. If no LAR is located prior to the last blood draw (up to 18 hours after enrollment), the patient will remain in the study under waiver of informed consent.

Patients enrolled in this fashion (waiver of informed consent (will receive the same number of research blood draws (maximum of six blood draws at 1mL each) as patients enrolled under waiver of informed consent until the consent is initiated (detailed in Section V). As an observational study, patients will experience no direct benefit.

All patients enrolled under waiver of informed consent will receive a patient information sheet/postcard detailing their involvement in the study and offering the opportunity to withdraw from further study participation (Attachment A).

All samples collected from patients enrolled under waiver of informed consent will be analyzed for study purposes only. Once this study is completed, samples from patients enrolled under a waiver of informed consent will be destroyed. No samples obtained for this study will be banked for future use.

d. **Justification for Waiver of Informed Consent for Decisionally Challenged Patients for whom a LAR Cannot be Identified within 18 hours of Hospital Arrival**

This research meets the federal definition and ethical standards for waiver of informed consent. Specifically, according to the Common Rule (45 CFR 46) that governs the ethical conduct and oversight of human subjects research, section 116(d) indicates that a waiver of informed consent can be obtained if the research involves no more than minimal risk to subjects.

There will be no randomization, study treatment, or intervention given during this study. The study will draw a maximum of 6mL of biospecimen blood over 12-18 hours from each eligible patient with an acute traumatic injury.

Hospitalized trauma patients experience frequent clinical blood draws as part of standard clinical care, as many as 10-12 per day. The volume of each clinical blood draw can be as much as 20mL. For example, a “rainbow” set of labs includes a basic metabolic panel (4.5mL), plasma lactate (0.5mL), complete blood count (6mL), coagulation studies (3mL), thromboelastogram (3mL), and arterial blood gas (3mL). Rainbow labs are usually obtained on arrival to the ED, on arrival to the ICU, and after trips to the operating room. Therefore, clinical blood draws for critically ill trauma patients frequently total 100-200mL daily. Therefore, the research itself (maximum 6mL research blood) introduces no more than minimal incremental risk beyond the condition and usual care in the absence of research, as defined by the Common Rule definition of minimal risk research.

K. **Risks of Harm**

We do not anticipate any additional risks of harm associated with the study beyond that of routine clinical care and the potential risk for a data breech. The subjects of the study are already undergoing routine clinical blood draws, and we are seeking an additional tube of blood in very small amount that is unlikely to have any physiologic effect. (URL: https://www.nimh.nih.gov/funding/clinical-research/nimh-guidance-on-risk-based-monitoring.shtml, last accessed 20 March 2021) The primary risk comes in the form of data breech, which we will utilize confidentiality measures as outlined in this protocol. There may be an additional risk from the study involving momentary and minor discomfort from blood draws and venipunctures, including bruising, redness, swelling, and rarely infection. Blood draws occur regularly as part of routine care of these patients.

L. **Potential Benefits**

Subjects will not derive any direct benefit because of this study. The benefit from this study will be society at large. Since trauma patients often experience future trauma (e.g., repeated visits for firearm wounds, interpersonal violence, etc.) it is plausible that they may benefit in the future from the science learned from this study.[37-40]

M. **Data and Safety Monitoring**

Subject records at the University of Colorado may be reviewed by COMIRB, Office of Human Research Protections (OHRP), and other applicable regulatory authorities responsible for human subject’s protections and the integrity of the data.

Subject records at Brook Army Medical Center may be inspected by the USAISR Quality Management and Research Regulatory Compliance Divisions, HQ USAMRDC IRB, the USAMRDC Army Human Research Protection Office and other applicable regulatory authorities responsible for human subject’s protections and the integrity of the data.

N. **Adverse Events**

The only expected adverse events related to the study are related to that of the blood draw. Common adverse events include pain during the procedure which will be minor, minor bleeding at the site, or development of hematoma. More significant risks include the possibility of a foreign body being retained or infection. We do not anticipate these events would be common. Since the blood draws are occurring as part of the clinical care by appropriately credentialed staff, the additional draws for the study are unlikely to alter that risk. Patients that are admitted to the hospital frequently have blood drawn several times a day, and thus the risk associated with drawing a small amount of extra blood is negligible. Any adverse events because of the blood draw will be managed at the direction of the attending clinician.

O. **Unexpected Adverse Events and Unanticipated Problems**

We do not anticipate unexpected adverse events as blood draws are routine clinical events. Any adverse event that occurs as part of the blood draw is the same as that of routine clinical care. If an adverse event occurs specific to the research, the adverse event will be reported to the PI or a member of the study team. If the event is determined to be related to the research the PI will follow standard site-specific reporting procedures for reporting the event to the regulatory office. All unanticipated problems involving risk to subjects or others, and serious adverse events that are unexpected and determined to be at least possibly or definitely related to study participation, will be reported to COMIRB within five working days by submission of a UAP document.

P. **References:**

1.Eastridge BJ, Mabry RL, Seguin P, et al. Death on the battlefield (2001-2011): Implications for the future of combat casualty care. *J Trauma.* 2012;73(6, Supplement 5):S431-S437.

2. Shackelford SA, Del Junco DJ, Powell-Dunford N, et al. Association of Prehospital Blood Product Transfusion During Medical Evacuation of Combat Casualties in Afghanistan With Acute and 30-Day Survival. *Jama.* 2017;318(16):1581-1591.

3. Oliveros Rodríguez H, Ríos F, Rubio C, et al. Mortality in civilian trauma patients and massive blood transfusion treated with high vs low plasma: red blood cell ratio. Systematic review and meta-analysis. *Colombian Journal of Anesthesiology.* 2020;48(3):126-137.

4. Fisher AD, Lavender JS, April MD, Hill R, Bynum J, Schauer SG. A Descriptive Analysis of Supermassive Transfusion Recipients Among US and Coalition Forces During Combat Operations in Afghanistan and Iraq. *Mil Med.* 2021.

5. Schauer SG, Naylor JF, Fisher AD, et al. An Analysis of 13 Years of Prehospital Combat Casualty Care: Implications for Maintaining a Ready Medical Force. *Prehosp Emerg Care.* 2021:1-15.

6. Eastridge BJ, Hardin M, Cantrell J, et al. Died of wounds on the battlefield: causation and implications for improving combat casualty care. *J Trauma.* 2011;71(1 Suppl):S4-8.

7. Schauer SG, Naylor JF, Ahmed YM, Maddry JK, April MD. Prehospital Combat Wound Medication Pack Administration in Iraq and Afghanistan: A Department of Defense Trauma Registry Analysis. *J Spec Oper Med.* 2020;20(3):76-80.

8. Naylor J, Burbank K, Wenke J, Maddry J, Schauer S. Effects of Prehospital Wound Prophylaxis in Iraq and Afghanistan on Mortality. *Journal of Trauma & Treatment.* 2018;07.

9. Burbank KM, Schauer SG, De Lorenzo RA, Wenke JC. Early application of topical antibiotic powder in open-fracture wounds: A strategy to prevent biofilm formation and infections. *OTA Int.* 2020;3(4):e091.

10. Murdock J, Watson D, Dorée CJ, Blest A, Roberts MM, Brunskill SJ. Drugs and blood transfusions: dogma- or evidence-based practice? *Transfus Med.* 2009;19(1):6-15.

11. Vilay AM. Antibiotic Dosing in Chronic Kidney Disease and End-Stage Renal Disease: A Focus on Contemporary Challenges. *Adv Chronic Kidney Dis.* 2019;26(1):61-71.

12. Aloy B, Launay-Vacher V, Bleibtreu A, et al. Antibiotics and chronic kidney disease: Dose adjustment update for infectious disease clinical practice. *Med Mal Infect.* 2020;50(4):323-331.

13. Chahine B. Antibiotic dosing adjustments in hospitalized patients with chronic kidney disease: a retrospective chart review. *Int Urol Nephrol.* 2022;54(1):157-163.
14. Chidambaram R. Optimal Antibiotic Dosage for Chronic Kidney Disease Patient: A Pharmacological Manual for Oral Clinicians. *Recent Pat Antiinfect Drug Discov.* 2015;10(2):113-123.
15. Trotman RL, Williamson JC, Shoemaker DM, Salzer WL. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clin Infect Dis.* 2005;41(8):1159-1166.
16. Li J, Rayner CR, Nation RL, et al. Pharmacokinetics of colistin methanesulfonate and colistin in a critically ill patient receiving continuous venovenous hemodiafiltration. *Antimicrob Agents Chemother.* 2005;49(11):4814-4815.
17. Tegeder I, Neumann F, Bremer F, Brune K, Lötsch J, Geisslinger G. Pharmacokinetics of meropenem in critically ill patients with acute renal failure undergoing continuous venovenous hemofiltration. *Clin Pharmacol Ther.* 1999;65(1):50-57.
18. Thalhammer F, Hörl WH. Pharmacokinetics of meropenem in patients with renal failure and patients receiving renal replacement therapy. *Clin Pharmacokinet.* 2000;39(4):271-279.
19. Keller E, Böhler J, Busse-Grawitz A, Reetze-Bonorden P, Krumme B, Schollmeyer P. Single dose kinetics of piperacillin during continuous arteriovenous hemodialysis in intensive care patients. *Clin Nephrol.* 1995;43 Suppl 1:S20-23.
20. Böhler J, Donauer J, Keller F. Pharmacokinetic principles during continuous renal replacement therapy: drugs and dosage. *Kidney Int Suppl.* 1999(72):S24-28.
21. Arzuaga A, Maynar J, Gascón AR, et al. Influence of renal function on the pharmacokinetics of piperacillin/tazobactam in intensive care unit patients during continuous venovenous hemofiltration. *J Clin Pharmacol.* 2005;45(2):168-176.
22. Ariano RE, Fine A, Sitar DS, Rexrode S, Zelenitsky SA. Adequacy of a vancomycin dosing regimen in patients receiving high-flux hemodialysis. *Am J Kidney Dis.* 2005;46(4):681-687.
23. Churchwell MD, Pasko DA, Mueller BA. Daptomycin clearance during modeled continuous renal replacement therapy. *Blood Purif.* 2006;24(5-6):548-554.
24. Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy.* 2009;29(5):562-577.
25. Klansuwan N, Ratanajamit C, Kasiwong S, Wangsiripaisan A. Clearance of vancomycin during high-efficiency hemodialysis. *J Med Assoc Thai.* 2006;89(7):986-991.
26. Ryan ML, Thorson CM, Otero CA, et al. Initial hematocrit in trauma: a paradigm shift? *J Trauma Acute Care Surg.* 2012;72(1):54-59; discussion 59-60.
27. Bayliss G. Dialysis in the poisoned patient. *Hemodial Int.* 2010;14(2):158-167.
28. Ibrahim RB, Liu C, Cronin SM, etSamtleben W, Mistry-Burchardi N, Hartmann B, Lennertz A, Bosch T. Therapeutic plasma exchange in the intensive care setting. *Ther Apher.* 2001;5(5):351-357 al. Drug removal by plasmapheresis: an evidence-based review. *Pharmacotherapy.* 2007;27(11):1529-1549.
29. Bertino JS, Jr., Kliegman RM, Myers CM, Blumer JL. Alterations in gentamicin pharmacokinetics during neonatal exchange transfusion. *Dev Pharmacol Ther.* 1982;4(3-4):205-215.
30. Keller F, Wagner K, Faber U, et al. Elimination kinetics of plasma exchange. *Klin Wochenschr.* 1983;61(22):1115-1122.
31. Bakken JS, Cavalieri SJ, Gangeness D, Kubat T, Pollack JR. Influence of therapeutic plasmapheresis on elimination of ceftiaxone. *Antimicrob Agents Chemother.* 1993;37(5):1171-1173.
32. Fauvelle F, Lortholary O, Tod M, et al. Pharmacokinetics of ceftriaxone during plasma exchange in polyarteritis nodosa patients. *Antimicrob Agents Chemother.* 1994;38(7):1519-1522.
33. Bakken JS, Cavalieri SJ, Gangeness D. Influence of plasma exchange pheresis on plasma elimination of ceftriaxone. *Antimicrob Agents Chemother.* 1990;34(6):1276-1277.
34. .
35. McClellan SD, Whitaker CH, Friedberg RC. Removal of vancomycin during plasmapheresis. *Ann Pharmacother.* 1997;31(10):1132-1136.

36. Mendez J, Jonas RB, Barry L, et al. Clinical Assessment of Low Calcium In traUMa (CALCIUM). *Med J (Ft Sam Houst Tex).* 2023(Per 23-1/2/3):74-80.
37. Strong BL, Greene CR, Smith GS. Trauma Recidivism Predicts Long-term Mortality: Missed Opportunities for Prevention (Retrospective Cohort Study). *Ann Surg.* 2017;265(5):847-853.
38. Heimke IM, Connelly M, Clarke A, et al. Trauma recidivism is pervasive and is associated with mental and social health opportunities. *Injury.* 2023;54(2):519-524.
39. Kao AM, Schlosser KA, Arnold MR, et al. Trauma Recidivism and Mortality Following Violent Injuries in Young Adults. *J Surg Res.* 2019;237:140-147.
40. Dixon SD, Como JJ, Banerjee A, Claridge JA. Trauma recidivists: surprisingly better outcomes than initially injured trauma patients. *Am J Surg.* 2014;207(3):427-431; discussion 431.