Guidance of Ultrasound in Intensive Care to Direct Euvolemia: A Cluster Randomized Crossover Comparative Effectiveness Trial (GUIDE Trial)

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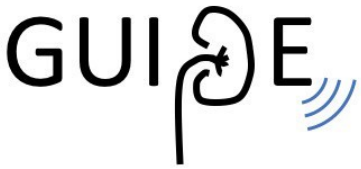

Study Protocol

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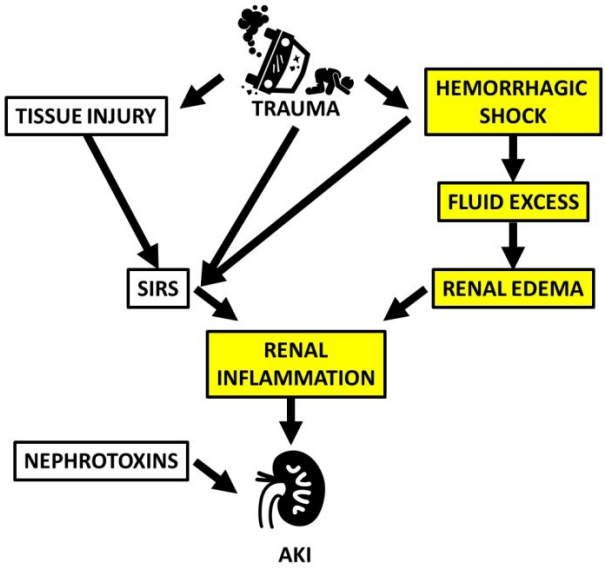
Significance:

Severe injury, which occurs in approximately one quarter of the 2 million annual trauma patients in the United States, [1] is a known risk factor for acute kidney injury, which is independently associated with increased morbidity and mortality. [2] Prevention of post-traumatic AKI has been identified by the International Kidney Diseases Improving Global Outcomes (KDIGO) group as a top research priority. [3]

Background and Preliminary Observations:

AKI complicating severe trauma is associated with increased morbidity and mortality. Trauma patients are subjected to multiple, additional renal insults early after trauma such as tissue injury resulting in rhabdomyolysis, systemic inflammatory response, and exposure to nephrotoxins such as intravenous contrast agents **(Figure)**. Renal inflammation and subsequent AKI can be worsened and prolonged by inadequate resuscitation of hemorrhagic shock and/or from excess fluid administration leading to renal edema. [4, 5] Therefore, prevention and recovery from AKI requires optimization of fluid management and early identification of high-risk patients.



In 2018, 46% of severely injured trauma patients developed AKI within one week of admission to the Trauma Intensive Care Unit (ICU) at our institution. AKI was defined according to the KDIGO guidelines **(Table 1)**. [3] AKI-free days is a novel metric of time without AKI during the first week of admission. In 2018, AKI-free days of less than 6 was observed in 39% of ICU patients. A diagnosis of AKI and fewer AKI-free days were associated with increased risk of mortality, prolonged ICU length-of-stay, prolonged hospital length-of-stay, and discharge location other than home. Positive fluid balance was also common among this population with 49% of patients having a fluid balance greater than 2L after 48-hours. A positive fluid balance is an independent risk factor for AKI development and mortality. [6, 7] This is despite the fact that euvolemia, or

Stage	Serum creatinine
1	1.5-1.9 times baseline OR ≥0.3 mg/dL (≥26.5 µmol/L) increase
2	2.0-2.9 times baseline
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL (≥353.6 µmol/L) OR Initiation of renal replacement therapy, OR in patients <18 years, decrease in eGFR to <35 mL/min/1.73 m^2

Table 1: KDIGO guideline for AKI diagnosis

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maintaining a fluid balance near zero, is a usual goal of care for the trauma patient.

Goal-directed therapy (GDT)-based fluid resuscitation is hemodynamic resuscitation targeting the achievement of pre-determined end-points, which include: (1) correction of coagulopathy guided by rapid thromboelastography (rTEG), (2) expedient hemorrhage control, and (3) restoration of end-organ perfusion with balanced transfusion guided by hemodynamic measurements, lactic acid, and base excess. GDT has been studied in the peri-operative setting as part of enhanced recovery pathways and has been reported to decrease the incidence of AKI. [8] Given that laboratory values are only obtained every few hours and hemodynamic abnormalities can persist despite adequate fluid resuscitation, ***the optimal strategy for ensuring optimal fluid administration during GDT remains unknown.***

Dynamic evaluation of volume status complements traditional measurements used in GDT to improve resuscitation once a patient arrives to the ICU. A number of dynamic and static tests have been evaluated in assessment of fluid responsiveness, all with various limitations (**Table 2**).

Method	Threshold	Requires invasive measurements	Limitations
Pulse Pressure/Stroke volume variation [9]	12%	Yes	Inaccurate with spontaneous breathing, arrhythmias, or low Vt
IVC diameter variations [10]	12%	No	Inaccurate with spontaneous breathing or low Vt
SVC diameter variations [10]	36%	Yes	Requires transesophageal doppler, inaccurate with spontaneous breathing or
Passive Leg Raising [11]	10%	Yes*	Cannot be used if mobility limitations, requires direct CO measurement
End-expiratory occlusion test [12]	5%	Yes	Requires patient to be intubated
Mini-fluid challenge (100mL) [13]	6%	Yes	Requires precise CO measurement, irreversible fluid administration
Conventional fluid challenge (500mL) [14]	15%	Yes	Requires direct CO measurement

Table 2: Tests for assessing fluid responsiveness. Thresholds indicate validated percent change from baseline that is consistent with fluid responsiveness. [15]
Vt=tidal volume, CO=cardiac output.
*Passive leg raising is accurate with concurrent bedside echocardiography

Ultrasound assessment of volume status is appealing because it is non-invasive, rapidly accessible, inexpensive, and easily learned. Guidelines from the Society of Critical Care Medicine endorses assessment of preload responsiveness by measuring inferior vena cava (IVC) collapsibility by ultrasound (Grade 1B). [16] Kanji, et al. found a lower incidence of AKI after incorporating volume assessment by intensivist-performed limited bedside echocardiography for patients with shock of mixed etiologies. [17] Notably, volume assessment in their study frequently resulted in decreased fluid administration.

However, the *effectiveness* of routine ultrasound assessments for GDT in reducing AKI incidence and duration in trauma patients in a teaching institution is unknown.

Rationale for Clinical Trial:

Ultrasound assessment of volume status and fluid responsiveness is a technique frequently utilized in the trauma ICU at our institution and is performed by the ICU physicians. Residents are taught this technique during their clinical rotation on service, as well as during other intensive care rotations. Physicians utilize the information gathered from the IVC ultrasound for resuscitation feedback. However, obtaining *repeated* IVC measurements for feedback is uncommon and many physicians obtain resuscitation feedback from additional adjuncts, as listed in the table above. These practices are inconsistently documented in the medical record, making it difficult to retrospectively ascertain if and how these practices impact clinical outcomes. Furthermore, implementation of a protocol without proof of effectiveness would risk inappropriate energy expenditure by the care team. And finally, there may be risks of increased physician feedback.

Design:

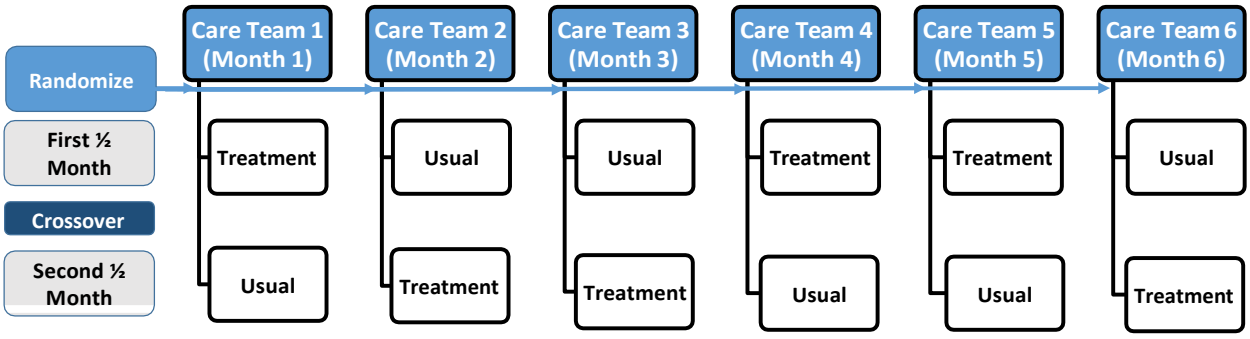
Hypothesis: Ultrasound-guided GDT results in adult trauma patients with more AKI-free days when compared to usual care in the trauma ICU at a teaching hospital.

Design: This is a single-center, pragmatic, cluster randomized crossover trial to be performed at The Red Duke Trauma Institute, Texas Medical Center, an academic, level-1 trauma center.

Study Participants: Primary participants are the care providers in the Shock Trauma ICU. All providers will be included in this study. The care structure is comprised of post-graduate year 1-3 surgical, anesthesia, and emergency medicine residents, a surgical critical care fellow, and a surgical critical care faculty member. Secondary participants will include injured patients at least 16 years of age that are admitted to the Shock Trauma ICU will be assessed for eligibility. Exclusion criteria of secondary participants include prisoners and pregnancy. Prisoners will be excluded due to their vulnerable status. Because pregnancy results in an increase in circulating blood volume up to 50%, there is a high likelihood of clinical misinterpretation of ultrasound findings. [18] Therefore, pregnant patients will be excluded as well. Both of these exclusions are expected to minimally impact secondary participant enrollment.

Randomization: Care teams will be clustered according to resident and fellow rotation schedule. Rotations occur on the first of the month with a new care team and therefore

one month is considered a cluster. Clusters will be randomized at the first of the month using variable permuted blocks using a computer-generated random sequence. Clusters will be randomized by a study coordinator using sequentially numbered, opaque sealed envelope. Care assignment will continue until the 15th of each month, at which point the cluster will cross over and provide the alternative assignment.



Procedures:

During the assigned intervention period, a care team member will perform IVC ultrasound to assess volume status and fluid responsiveness upon patient arrival to the ICU, and two more times over a 24-hour period. Assessments will be completed at least three hours apart. IVC diameter and collapsibility index (IVCCI) will be measured. Use of the results to guide care will be at the discretion of the primary team. Usual goals of resuscitation include lactate concentration <1 mmol/L, base excess +2 to -2, normal rTEG values, mean arterial pressure >60 mmHg after hemorrhage control has been obtained. The goal for volume management in this study will be euvolemia, most consistent with <18% IVCCI and IVC diameter 15 - 25 mm. [19] Measurements are to be interpreted by the physician within the clinical context. Results of the ultrasound and subsequent management will be recorded in a study notebook by the physician at time of ultrasound.

Usual Care: No changes to usual care will be made. Physicians will record results of IVC ultrasound, if utilized.

Quality Assurance: Accuracy of technique of all care team physicians will be assessed during an ultrasound training session provided the day prior to the intervention arm of the cluster. Additional training will be provided until proficiency deemed adequate by the session leaders. Session leaders will include the Trauma ICU faculty and the study PI who has been independently certified in modified echocardiography for Critical Care, which includes IVC Ultrasound techniques (GH). The dedicated training session will be new to the rotating resident education, but represents a similar training to prior, individual training sessions that occur between a resident and faculty throughout an ICU rotation.

Troubleshooting Opportunities: At least three care team members are present in the STICU at all times and US for the same patient may be performed by different physicians, based on individual care demands within the unit. If the physician is having difficulty with US technique, another physician is available to attempt the ultrasound prior to indicating that the ultrasound was unable to be performed.

Outcomes:
Primary outcome: AKI-free days within 7 days of injury. AKI will be defined by the KDIGO criteria. All stages will be considered AKI.

Secondary outcomes: AKI incidence within the first 7 days of ICU admission, stage of AKI, need for renal replacement therapy, quantity and type of fluids administered at 24 and 48 hours, quantity and type of diuretics admisnistered at 24 and 48 hours, time to lactate normalization, time to creatinine concentration <1.5 mg/dL or to prehospital baseline, time to base excess normalization, ventilator-free days, ICU-free days within first 30 days. Adverse events determined *a priori* include transfusion-related acute lung injury, acute respiratory distress syndrome, abdominal compartment syndrome, new onset congestive heart failure, and re-bleeding requiring unscheduled intervention. Data measurement will occur according to the schedule outlined in **Table 3**.

Data and Collection Method	24 Hours	48 Hours	7 Days	30 Days
IVC Measurements and Physician Actions – Data Forms	x			
AKI-Free Days – Chart Review			x	
AKI Incidence and Highest Stage – Chart Review			x	
Fluid Administration – Chart Review	x	x		
Creatinine Trend – Chart Review			x	
Lactate Trend – Chart Review			x	
Base Excess Trend – Chart Review			x	
Ventilator-Free Days – Chart Review			x	x
ICU-Free Days – Chart Review			x	x
Mortality – Chart Review			x	x
Potential Adverse Events: transfusion-related acute lung injury, acute respiratory distress syndrome, abdominal compartment syndrome, and re-bleeding requiring unscheduled intervention, need for and duration of renal replacement therapy – Chart Review			x	x

Table 3: Process measures and clinical outcome collection schedule

Pre-planned subgroup analyses include:

1. Resuscitation indication: hemorrhage, post-traumatic SIRS, rhabdomyolysis, other, and none.
2. Ventilation Type: Spontaneous, mechanical
3. Order of intervention: Intervention first, intervention second

Statistical Analysis:
The largest feasible study will be completed over the course of 12 months with an estimated enrollment of 30 secondary subjects per cluster, resulting in 360 patients enrolled in each treatment group and 720 total patients in the study.

No interim analysis will be completed. Multilevel Bayesian analysis will be performed to assess the effectiveness of the intervention to account for care team cluster. Neutral, conservative priors will be used to estimate the probability of both benefits and harms.

Safety Assessment:
Ultrasound imaging uses high-frequency sound waves to create images from wave reflection from internal body structures. It has been utilized routinely for over 20 years, has an excellent safety record, and is considered safe when utilized by a healthcare provider. [20]

Data Collection and Confidentiality:
Clinical data and laboratory data will be prospectively collected as part of an ongoing, prospective trauma registry. Findings from both scheduled and unscheduled volume assessments by any modality will be recorded in a study notebook kept in a locked cabinet at the charge nurse's station and transferred to a secure, Microsoft Access database daily. The database will be accessible only to study personnel, as approved by the institutional review board.

Future directions:
The results of this study will inform the feasibility and effectiveness of implementing scheduled ultrasound-guided fluid resuscitation for AKI prevention.

Ethical Considerations:

The protocol proposed aims to increase physician feedback of resuscitation by means of a non-invasive ultrasounds and improve healthcare delivery. This study poses minimal risk to subjects and will not adversely affect the rights and welfare of patients or physicians. The investigators seek approval through the institutional review board for waiver of individual consent and qualify as a quality improvement initiative.

Personnel Roles:

Dr. Gabrielle Hatton is a research fellow in the Department of Surgery. She is responsible for protocol development, physician training, troubleshooting, protocol

implementation, data collection, data merging and cleaning, statistical analysis, interpretation of the results and any other primary study requirements.

Dr. Lillian Kao is a Professor in the Department of Surgery. She will assist with protocol development, outcome measure assessment, troubleshooting, protocol implementation, interpretation of the results, and mentorship to the primary PI.

Dr. Charles Wade is a Professor in the Department of Surgery and Director of the Center for Translational Injury Research (CeTIR). He will assist with protocol development, outcome measure assessment, troubleshooting, protocol implementation, interpretation of the results, and mentorship to the primary PI.

Dr. Kevin Finkel is a Professor in the Department of Renal Diseases and Hypertension. He provides expertise in fluid management and kidney disease. He will assist with protocol development, outcome measure assessment, and interpretation of the results.

Dr. John Harvin is an Associate Professor in the department of Surgery. He provides expertise in comparative effectiveness trials and will assist with protocol development, implementation, and interpretation of the results.

Dr. Timothy Donahue is a Surgical Critical Care Fellow in the Department of Surgery. He will assist with protocol development, troubleshooting, process improvement, and implementation.

Dr. Jessica Hudson is an Assistant Professor in the Department of Emergency Medicine. She has expertise in use of point-of-care ultrasound in clinical care for critically ill patients. She will assist with protocol development, physician training, and protocol implementation.

Drs. Shuyan Wei and Kayla Isbell are research fellows in the Department of surgery. They will assist in physician training, protocol implementation, process improvement, troubleshooting, data collection, statistical analysis, and results interpretation.

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