Protocol

Project Title: Persistent Inflammation, Immunosuppression and Catabolism Syndrome (PICS): A New Horizon for Surgical Critical Care

Subtitle. Kidney Response to Sepsis Affects Angiogenic Balance and Likelihood of CCI and PICS

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3. Abstract:

Approximately a third of those patients who survive an early sepsis episode linger in the intensive care unit with manageable organ dysfunction without meeting criteria for established late multi-organ failure. Their clinical course is characterized by ongoing protein catabolism with poor nutritional status, poor wound healing, and recurrent infections. These patients are commonly discharged to long-term, acute care facilities, but due to excessive loss of lean body mass and their immunosuppressed state, they often develop secondary nosocomial infections and are rarely able to return to a fully functional state. The overall hypothesis of this program grant is that persistent inflammation, immunosuppression and catabolism (PICS) are the hallmark of pathophysiologic processes leading to a decrease in long-term survival and functional capacity in patients with chronic critical illness. This study investigates the mechanism by which kidney dysfunction perpetuates inflammation, immunosuppression, and catabolism in chronic critical illness. In a prospective, longitudinal, case-control study of sepsis patients with one year follow-up using iohexol clearance we will measure glomerular filtration rate in patients with chronic critical illness and controls (sepsis patients discharged from ICU before day 14) to determine to what extent degree of kidney dysfunction contributes to decreased survival and increase in chronic kidney disease at year one after sepsis onset.

4. Background:

Approximately a third of those patients who survive an early sepsis episode linger in the intensive care unit with manageable organ dysfunction without meeting criteria for established late multi-organ failure. Their clinical course is characterized by ongoing protein catabolism with poor nutritional status, poor wound healing, and recurrent infections. These patients are commonly discharged to long-term, acute care facilities, but due to excessive loss of lean body mass and their immunosuppressed state, they often develop secondary nosocomial infections and are rarely able to return to a fully functional state. The overall hypothesis of this program grant is that persistent inflammation, immunosuppression and catabolism are the hallmark of pathophysiologic processes leading to a decrease in long-term survival and functional capacity in patients with chronic critical illness. This study investigates the mechanism by which kidney dysfunction perpetuates inflammation, immunosuppression, and catabolism in chronic critical illness. We will test the working hypothesis that persistent kidney dysfunction in sepsis associated chronic critical illness contributes to decreased survival through the development of persistent inflammation, immunosuppression and catabolism. In chronic critical illness, the persistence of inflammatory state may lead to capillary rarefication in the kidney causing accelerated chronic kidney disease. Progression of chronic kidney disease during chronic critical illness can drive persistent inflammation, immunosuppression and catabolism. Indeed, many of the features of chronic critical illness are consistent with the protein-energy malnutrition and muscle wasting associated with chronic kidney disease. Thus the kidney can play a contributory role in chronic critical illness and PICS, respectively.

The main goal of this project is to measure kidney filtration function at day 14 of the ICU stay or the day of discharge from the ICU (whichever occurs first), in order to determine the presence and *magnitude of persistent kidney dysfunction after sepsis episode and to longitudinally assess* further decline of kidney function at one year follow-up. In our initial IRB protocol we have proposed to use iohexol clearance as a gold standard that provides most accurate determination of glomerular filtration rate (GFR). Unfortunately we have not been able to recruit patients into the study as designed due to the complexity of this procedure and need for a dedicated IV line. Since one of the main goals of the overall project is to determine the decline in glomerular filtration rate from the sepsis episode to the one year follow up, we have considered different approaches, in order to be able to obtain this valuable data.

<u>We propose to offer patients four complementary ways for GFR assessment, both at approximately day 14 or approximately at the day of discharge from the ICU and at the one year follow up :</u>

1. Determine clearance of Iohexol from blood after Iohexol injection and/or
2. Determine appearance of Iohexol in urine after Iohexol injection (this would be the same injection as in one, and would not require two injections) and/or
3. A timed urine collection to determine clearance of urea and creatinine and/or
4. Estimated GFR using calculations with serum creatinine, if performed clinically if not we will draw it specifically for the study, and cystatin C, performed specifically for the study. Currently any patient that is enrolled in this protocol will already be a part of IRB201400611 and will already be getting serum creatinine, cystatin C and a urine microalbumin/creatinine ratio drawn at the one year appointment.

This approach will allow us to maximize recruitment of patients into the study by providing flexibility, but it also provides an important opportunity to validate the different measurements against the gold standard, Iohexol clearance. For all patients we will also obtain a urine microalbumin/creatinine ratio as another important determinant of structural kidney damage.

We also propose to include stage 3 AKI patients on renal replacement therapy, who were previously excluded. Some of these patients do recover after initial episode and will present at one year follow up. It will be very valuable for us to understand factors leading to recovery. For these patients we will use only methods 2 and/or 3 for estimation of GFR, both of which are safe. Even patients who are dialysis dependent have some level of residual renal function and even if they make even a minimal amount of urine this may be an important determinant of renal recovery.

The assessments will be performed approximately 72 hours within day 14 or the anticipated discharge from the ICU and at 1 year follow-up.

Given the loss of muscle mass in chronic critical illness, we will measure, rather than estimate glomerular filtration rate, to determine whether unrecognized kidney dysfunction in late sepsis drives inflammation and catabolism, contributing to poor long term survival and development of chronic kidney disease. For the assessment of glomerular filtration rate, the most frequently used clinical test is serum creatinine, despite the fact that its accuracy depends on a constant muscle mass, which is almost never the case with patients with chronic critical illness. We have previously demonstrated that sepsis and chronic critical illness are associated with a rapid and significant loss of lean muscle mass over time. Even a small fall of 25% in muscle mass should lead to a fall in serum creatinine of 25%. Thus in a chronic critical illness patient hospitalized for 4 weeks, the persistent increase in serum creatinine from a baseline of 1.0 mg/dl to 1.5 mg/dl implicates a significant drop in glomerular filtration rate; assuming a 50% reduction in muscle mass, in this individual a serum creatinine of 1.5 would reflect glomerular filtration rate of ~37 mL/min/1.73 m^2, consistent with stage 3 chronic kidney disease. To determine whether unrecognized decline in kidney function contributes to persistent inflammation, decreased protein intake, and muscle wasting in chronic critical illness it is necessary to measure glomerular filtration rate rather than estimate it.

5. Specific Aims:

The goal of this study is to determine to what extent persistent kidney dysfunction contributes to inflammation, catabolism and long-term mortality in chronic critical illness. We will test the working hypothesis that persistent kidney damage in chronic critical illness contributes to decreased survival through persistent inflammation, immunosuppression and catabolism.

6. Research Plan:

Study overview and design

This is a prospective, longitudinal, case-control study involving a subset of the initial cohort of 400 sepsis subjects enrolled in IRB STUDY #2014-611 who agree to measurement of glomerular filtration rate using iohexol clearance and the amended measurements listed above. Assuming a minimum 70% recruitment rate, we expect to enroll minimum of 230 patients and maximum of 400.

Identifying patients and consent

All sepsis patients who consent to enroll in the IRB Project #2014-611 and meet inclusion/exclusion criteria will be asked for enrollment in this study after they are consented for the IRB Project #2014-611. The informed consent will be obtained by the same research staff

within the Human Subject Core of the University of Florida P50 Center. Since many sepsis patients in the surgery and trauma ICUs may have altered mental status or pharmacologic sedation, but would be regarded as prospective research subjects a legal authorized relative (LAR) or next of kin would be approached for informed consent. The research nurse will monitor the patient's progress and once they regain capacity, the patient will be reconsented.

Inclusion Criteria
a) Presence in the surgery or trauma ICU where clinical care can be managed by surgical critical care guided by standard operating procedures.
b) Age of ≥18 years
c) First entrance into our sepsis protocol at Shands/UF on index admission.
d) Ability to obtain informed consent.

Exclusion criteria
Expected lifespan of the patient is less than 3 months due to severe pre-existing comorbidities (ex. recurrent, advanced or metastatic cancer).
b) Severe traumatic brain injury (evidence of neurologic injury on
CT scan and a GCS <8)
c) refractory shock (i.e., patients who die within 12 hours)
d) uncontrollable source of sepsis (e.g., irreversible disease state such as unresectable dead bowel)
e) Patient or patient's family are not committed to aggressive management of the patient's condition.
f) severe CHF (NY Heart Association Class IV)
g) Child-Pugh Class C liver disease or pre-liver transplant.
h) known HIV infection with CD4 count <200 cells/mm_3
i) organ transplant recipient on immunosuppressive agents
j) known pregnancy and mother's that are breastfeeding
k) prisoners
l) Institutionalized patients
m) inability to obtain informed consent.
n) Chemotherapy or radiotherapy within 30 days prior to sepsis.
o) End stage renal disease on admission

Determination of Glomerular Filtration Rate and Proteinuria

For all patients we will measure and estimate GFR and urinary microalbumin/creatinine ratio at day 14 of ICU admission or at hospital discharge (if prior to day 14) and one year follow-up.

We propose to offer patients four complementary ways for GFR assessment, both at approximately day 14 or approximately at the day of discharge from the ICU and at the one year follow up :

1. Determine clearance of Iohexol from blood after Iohexol injection and/or
2. Determine appearance of Iohexol in urine after Iohexol injection (this would be the same injection as in 1 and would not require another injection.
3. A timed urine collection to determine clearance of urea and creatinine and/or
4. Estimated GFR using calculations with serum creatinine, if performed clinically, if not we will draw specifically for the study, and cystatin C, performed specifically for the study. Currently any patient that is enrolled in this protocol will already be a part of

IRB201400611 and will already be getting serum creatinine, cystatin C and a urine microalbumin/creatinine ratio drawn at the one year appointment.

For all patients we will also obtain urine microalbumin/creatinine ratio as another important determinant of structural kidney damage. If a patient is of childbearing potential at the one year follow up appointment, they will be given a pregnancy test. If they test positive, they will not be given the iohexol injection.

1. Iohexol clearance.

Iohexol clearance will not be performed in patients with a known allergy to contrast. All patients will need two IVs for this procedure. If the subject does not have 2 intravenous catheters (IVs) as a part of their routine clinical care during sepsis episode they will be placed by someone from the research team. We will attempt to place a 22 gauge or larger IV as indicated by the patients veins. We will inject iohexol 0.5-1 ml of iohexol diluted in normal saline through an existing IV catheter, and we will collect no more than 3 ml of blood prior to the injection and and at approximately 1, 2, 3 and 4 hours after injection. The concentration of iohexol in the blood will be measured by ELISA (Biopal Inc). The GFR will be calculated by the blood clearance method:

The concentration of iohexol (µg/ml) in each blood sample will be plotted as a function of time. The data will be fit to a one exponential decay function, i.e., Y = B e-bX. The function will be integrated over the limits zero to infinity to obtain the area-under-the-curve (AUC), i.e., AUC = B/b (mg·min/ml). The GFR value (ml/min) is then obtained by dividing the administrated dose by the AUC (REF:

2. Timed urinary collection for combined urea and creatinine clearance.

The urine will be collected for at least 4 hours to as long as 24 hours or more. The urine volume determined and a sample sent to the lab for determination of creatinine and urea concentration. We will not place a foley if there is not a foley and the person will only be asked to collect their urine for the indicated time.

3. Estimation of GFR using serum creatinine and cystatin C. We will estimate GFR using both serum creatinine and cystatin C and average the two values using CKD-EPI equation.

The glomerular filtration rate at 1 year will be compared to the measured glomerular filtration rate at discharge and the rate of change in glomerular filtration rate over time will be determined. The measured iohexol glomerular filtration rate will be compared to the estimated glomerular filtration rate, as determined by the in order to correlate the equation after adjusting for loss of muscle mass.

The patients will be asked to return for a one year follow up appointment that will occur with the one year appointment from IRB protocol #2014-611 at the Institute on Aging. The patients will receive a $25 compensation for the inpatient portion of the study and a $75 compensation for their time when they return for the one year follow up visit. At one year follow-up all measurements for iohexol clearance, will be performed in CTSI. Timed urine collection at one year follow up will be performed at home and all necessary supplies will be mailed to patient. If the patient did not do a timed collection, but is still willing to perform timed urine at the time of the CTSI visit, we will time the urine collection during their CTSI visit. For patients who opt only for serum creatinine/cystatin C measurement and spot urine microalbumin/creatinine ratio, urine and blood will be collected in the CTSI as a part of the IRB protocol #2014-611.

Primary Outcomes

We will compare:

a) The decline in glomerular filtration rate at 1-year follow-up between chronic critical illness and control groups.

b) Correlation between iohexol glomerular filtration rate and estimated glomerular filtration rate using previously validated equation applied to serum creatinine.

c) Development of de novo albuminuria or progression of existing albuminuria.

Data Collection and Analyses

All relevant clinical and laboratory variables for this cohort will be uploaded directly into the REDCap case report form (CRF) from the EPIC EMR for the main STUDY IRB#2014-611.

Sample size and feasibility. Assuming that chronic critical illness patients have at least a two-fold decline in glomerular filtration rate as compared to the average glomerular filtration rate decline of 6 ± 16 ml/yr, the sample size of 150 chronic critical illness and 80 control subjects will offer 80% power at a two-sided significance of P=0.05.

Data analyses and interpretation. The parametric and non-parametric tests for difference between two independent samples will be used to compare decline in glomerular filtration rate between chronic critical illness. Using the Cox survival model we will test the multivariate relationship between glomerular filtration rate at day 14 and survival status at year 1.

Protection of Privacy and Confidentiality

Confidentiality is maintained through use of the Department of Surgery offices, anonymous data files, and password access protection. Physical data security is maintained by after-hours door lock to Department of Surgery offices. All electronic data will be stored on REDCap (Research Electronic Data Capture). It is a secure, Web-based application designed to support traditional case report form data capture maintained by the CTSI. UF Health firewall functions maintained by UF Health Information Technology are constantly in effect as basic electronic data protection. As a part of informed consent and IRB requirement, the prospective patient or proxy are informed of the database process, that clinical data will be regarded as confidential and maintained anonymous for use in publications, and that participation is voluntary. Blood samples for project-proposed studies will be obtained at patient bedside with standard of clinical care by research nurses (clinically current, licensed RNs). Blood and urine sample collection tubes will be labeled with a unique study number and without a patient identifier. The samples will be initially processed and delivered directly to the research lab. After analysis, data will be transferred to the REDCap database. Research-related blood or urine samples are patient-identified, but stored samples are barcode-labeled and contained in separate, ascension-number-labeled boxes for frozen storage.

7. Possible Discomforts and Risks:

Collection of blood is central to carrying out the specific aims. There are no alternatives to the proposed research strategy of blood sampling, short of not pursuing these aims. Study blood draws across Projects have been coordinated and collated to minimize the number of blood draws and overall blood volume required for each individual study patient

Blood draws: In some cases removing blood and blood loss may leave the patient feeling faint. If too much blood is taken too often, the patient may become anemic. All of these complications are very uncommon, and care will be taken to avoid them.

Intravenous Catheters: The patient may experience pain and bruising during the insertion of the intravenous catheters (IV). Having these IVs could cause redness or cause an infection. After removal of the IVs the patient may have a bruise and experience pain that could last for 3 days. Tape will be used to keep the catheter in the arm from moving around. The tape can cause a skin rash. If this happens, it should go away in a short time.

Urine collection: The patient, if they do not have a foley may be inconvenienced in having to urinate in a collection vehicle but there is no risk associated with this procedure.

In general, the reactions which occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Reactions to iodinated contrast agents are mild-moderate although severe life threatening complications have occurred. Approximately 95 percent of adverse reactions accompanying iodinated contrast agents are classified as mild to moderate. Reported incidences of death range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 (0.01 percent). Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005 percent) patients. Other side effects include: 1) Allergic reactions: ranging from mild flushing and hives that only lasts a short time to death. 2) Common side effects: warmth and flushing of the skin. 3) Less common side effects: chills; dizziness or lightheadedness; headache; nausea or vomiting; pain or burning at the place of injection; sweating; unusual or metallic taste; or unusual thirst. Iohexol may have risks to the embryo, fetus, or newborn if the subjects are breastfeeding. Therefore, women of childbearing potential will have a pregnancy test as part of the study. If it is positive, no GFR studies will be performed during the subject's pregnancy. If the subjects are breastfeeding no GFR studies will be performed as well.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy are twice that of the general population, and thus in this study we will not inject iohexol into subjects who have a "contrast allergy." Importantly, sensitivity to contrast media does not appear to increase with repeated examinations.

There is a minimal risk of an unauthorized disclosure of patient's protected health information during the conduct of this study. However, due to the use of our Honest Broker certification program, the risk of unauthorized disclosure is not significantly greater than the risk of an unauthorized disclosure during normal health care operations at the UFH.

If a serious adverse event requiring medical intervention were to occur due to the proposed research, then the ICU intensivist team is available at all times to provide necessary care. Adverse events will be reviewed by UF intensivist faculty not directly involved with ongoing studies (David Mozingo, M.D., Brenda Fahy, M.D.) reported by the investigator team to the HSC and overall P50 Program PI (Scott Brakenridge who will report to UF IRB, as required by policy.

***Data and safety monitoring plan*.**

The proposed study is an integral part of P50 Program Grant (all recruited subjects will participate in the main observational study approved by IRB #). Accuracy and quality of collected data is monitored through the Human Subject Core and Data and Biostatistics Core of the P50 Center. Monitoring of all subjects involved in this study and parent observational study IRB# will involve: 1) individual research subject review by Dr.

Brakenridge, (PD) and the investigator team at weekly SCIRC SOP and Adjudication meetings; 2) review of the data record of each research subject by internal medical monitors (D.W. Mozingo, M.D., Professor of Surgery; B.G. Fahy, M.D., Professor of Anesthesiology, UF (Gainesville)), reporting of adverse events, and annual (or more frequent) review of study progress; 3) interim review by PIs, and statistician at 10 randomized patient intervals, to include prepared reports that describe individual and mean interventions and clinical responses of hemodynamic, clinical laboratory, and biomarker data, and comparison with previously accrued trajectory data.

For the current study we have developed additional data and safety monitoring plan. The study involves more than minimal risk related to intervention for the routine standard measurement of glomerular filtration rate using iohexol. In addition, the study includes patients with a highly morbid pre-existing medical disease (sepsis), some of who are vulnerable subjects (chemically sedated in ICU due to primary disease sepsis). Thus physical, social, psychological, or financial events that are anticipated due to subjects' pre-existing disease including debilitated state, acute kidney injury, prolonged hospitalization, incapacity and death are possible and will be treated by the standard clinical care.

Safety and data integrity for this study will be assessed by PIs and the P50 investigator team led by program director Dr. Brakenridge at weekly Adjudication meetings, IRB, GCRC Data Safety Monitoring Subcommittee and Internal Medical monitors for entire P50 program (D.W. Mozingo, M.D., Professor of Surgery; B.G. Fahy, M.D., Professor of Anesthesiology, UF (Gainesville). Accumulating study-wide data across all subjects will be monitored weekly and discussed at the weekly P50 meeting. Accumulated data will be discussed every three months at the P50 safety meeting. The following safety endpoints are in place: An MD is required to perform every injection and observe the patient for at least 15 minutes. If a side effect occurs as a result of the injection, we will formally present the case at the P50 weekly meeting. Importantly, the iohexol used for GFR measurement is routinely used clinically and we are using a 1/10 to 1/100 of the dose that is routinely used clinically, thus risks of side effects are greatly reduced. In addition the majority of these patients would have already received at least one contrast study during their hospitalization making it extremely unlikely to have undetected allergy to contrast. With any side effect suspected to occur as the result of the GFR determination, we will stop further GFR studies until the event can be presented and discussed at the weekly P50 meeting. Following adverse events will be observed: shortness of breath, itching, hives, vomiting, swelling, breathing difficulties, hypotension or any other noted problem related to the injection. They will be identified and monitored using advance monitoring system in ICU and GCRC as summarized in the table below

Safety Assessment	Special conditions/equipment	Personnel responsible for assessment
Vital signs	*Automated sphygmomanometer, ICU advance monitoring in place for routine care*	*MD and Nurse*
SOB, breathing difficulties	*Talking with the patient, pulse oxymetry.*	*MD and Nurse*
Itching, hives	*Talking with the patient*	*MD and Nurse*
Severe vomiting	*Observation*	*MD and Nurse*
Swelling	*Talking with the patient observation*	*MD and Nurse*

Acute kidney injury	*Routine labs*	*MD*

Adverse events will be evaluated by PIs, P50 co-investigators and Internal Medical monitors for entire P50 program. We will use standard NIH and IRB definitions. All adverse events will be reviewed by the PIs and investigator team to identify and implement changes in study protocol to correct problems. The Project PIs (Dr. Segal and Dr. Bihorac) will report adverse events to P50 Program Executive Committee, P50 Internal monitors and IRB, as required by policy. Serious adverse events are required to be reported immediately; adverse events are reviewed annually.

8. Possible Benefits:

There will be no benefit to the participating subjects. The potential knowledge gained from this research may ultimately prove beneficial to the health and wellbeing of future patients with sepsis.

9. Conflict of Interest:

No conflict of interest exists for the PI or sub-investigators.

References

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