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Sepsis and Critical Illness Research Center Investigators: standard operating procedures for a prospective cohort study of sepsis in critically ill surgical patients

Short title: SCIRC standard operating procedures

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Abstract

Introduction: Sepsis is a common, costly, and morbid cause of critical illness in trauma and surgical patients. Ongoing advances in sepsis resuscitation and critical care support strategies have led to improved in-hospital mortality. However, these patients now survive to a enter state of chronic critical illness (CCI), persistent low-grade organ dysfunction, and poor long-term outcomes driven by the persistent inflammation, immunosuppression, and catabolism syndrome (PICS). The Sepsis and Critical Illness Research Center (SCIRC) was created to provide a platform by which the prevalence and pathogenesis of CCI and PICS may be understood at a mechanistic level across multiple medical disciplines, leading to the development of novel management strategies and targeted therapies.

Methods: Here we describe the design, study cohort, and standard operating procedures used in the prospective study of human sepsis at a level 1 trauma center and tertiary care hospital providing care for over 2,600 critically ill patients annually. These procedures include implementation of an automated sepsis surveillance initiative, augmentation of clinical decisions with a computerized sepsis protocol, strategies for direct exportation of quality-filtered data from the electronic medical record to a research database, and robust long-term follow-up.

Ethics and dissemination: This study has been registered at Clinicaltrials.gov and is actively enrolling subjects. Dissemination of preliminary results is forthcoming.

Strengths and limitations of this study

- Computerized decision support will minimize the influence of variability in management practices
- Robust long-term follow-up will allow for deeper understanding of functional recovery following sepsis
- Investigation of targeted therapies is currently limited by deficiencies our understanding of sepsis pathophysiology

Introduction

Sepsis as both a cause and complication of surgical intensive care unit admission is common, costly, and morbid. Hospitalization with sepsis has become more common than hospitalization with myocardial infarction, with annual costs over $20 billion in the United States [1 2]. Mortality rates for sepsis range from 18-28%, and remain unacceptably high despite more than 30 years of intensive research [3 4]. Recent advances in resuscitation strategies have improved in-hospital mortality, but sepsis survivors often enter a state of chronic critical illness (CCI) driven by the persistent inflammation, immunosuppression, and catabolism syndrome (PICS) [5 6] (Figure 1). However, the pathophysiology of these conditions remains incompletely understood. The Sepsis and Critical Illness Research Center (SCIRC) was created to provide a platform by which the prevalence and pathogenesis of PICS may be understood at a mechanistic level across multiple medical disciplines, leading to the development of novel management strategies and targeted therapies.

Methods and analysis

Setting

The University of Florida Health Shands Hospital (Gainesville, Florida; U.S.A.) is a Level 1 Trauma and tertiary care center with two trauma/surgical intensive care units (ICU) totaling 48 beds, which serve as the recruitment base for this cohort study. UF Health is the sole tertiary care center for a greater than 90-mile radius catchment area, including over 1.5 million

people. Together, the trauma and surgical ICU teams manage over 2,600 critically ill patients annually. Each ICU has a dedicated surgical critical care team including a board certified attending intensivist, critical care fellows, surgical and anesthesia residents, and advanced practice providers (physician assistants and nurse practitioners). These teams collaborate with unit-dedicated pharmacists, respiratory therapists, physical therapists, occupational therapists, nutritionists, and social workers. Board certified attending acute care surgeons and critical care fellows provide in-hospital coverage 24 hours per day, 7 days per week.

Study design and population

This is a prospective, longitudinal cohort study of surgical intensive care unit (ICU) patients that develop surgical sepsis. Based on preliminary data and *a priori* power analyses, 400 patients will be enrolled over a period of 4 years, with subsequent 12-month individual follow-up. Inclusion criteria are presence in the trauma/surgical intensive care unit, age ≥ 18 years, and diagnosis with sepsis, severe, sepsis or septic shock with subsequent initiation of the computerized clinical decision support (CCDS) directed sepsis protocol [7 8]. Septic patients are initially identified by a modified version of the Modified Early Warning Score (MEWS-SRS) [9], which screens for sepsis based on temperature, heart rate, respiratory rate, blood pressure, and level of consciousness (Figure 2). In the emergency department and on surgical wards, this score is calculated for each patient on arrival, every time vital signs are recorded, and any time a patient has an acute change from their baseline physiologic status, prompting further investigation. Patients identified by the MEWS screening protocol are then directly assessed by a physician or advance practice provider for bedside clinical adjudication of the presence of

sepsis (a systemic inflammatory response with a source of infection), severe sepsis (sepsis-induced tissue hypoperfusion or organ dysfunction), or septic shock (severe sepsis with persistent arterial hypotension despite volume resuscitation) based on consensus definitions [10-13]. This screening and diagnostic process has been automated and embedded within the UF Health electronic medical record (Epic Systems, Verona, WI).

Exclusion criteria are age <18 years, severe traumatic brain injury (i.e. CT evidence of neurologic injury and Glasgow Coma Scale score <8), spinal cord injury resulting in permanent sensory and/or motor deficits, sepsis with an uncontrollable source (e.g. unresectable bowel ischemia), NY Heart Association class IV heart failure, Child-Pugh Class B or C liver disease, known HIV infection with CD4 count <200 cells/mm^3, organ transplant recipient on an immunosuppressant agent, chemotherapy or radiotherapy within 30 days prior to onset of sepsis, expected lifespan <3 months due to severe pre-existing comorbidities, active Do Not Resuscitate or Do Not Intubate order, pregnancy, incarceration, or institutionalization.

Computerized clinical decision support (CCDS) sepsis protocol

Patients who are diagnosed with sepsis, severe sepsis, or septic shock are started on a computerized clinical decision support protocol, as previously described [7]. This system was modified from a sepsis management protocol originally implemented at the Methodist Hospital in Houston, Texas [8]. In brief, mobile bedside computer workstations were programed with sepsis protocol algorithm logic that interacts with the patient and clinician by mapping clinical workflow and recommendations to patient physiology and clinical interventions. The sepsis protocol algorithm logic was developed by a multidisciplinary team of surgeons, intensivists,

advanced practitioners, nurses, respiratory therapists, pharmacists, pathologists, and computer engineers, based on Surviving Sepsis Campaign guidelines [13]. The algorithm produces a recommendation; the clinician may accept or modify the recommendation, tailoring care to individual patient-specific factors. The selected intervention is then imputed, and the computerized clinical workflow and recommendations continue to evolve.

The computerized sepsis protocol is the platform for clinical decisions regarding initial volume resuscitation and antibiotic therapy initiation. For all other clinical decisions, the SCIRC developed protocols based on standard operating procedures from the Inflammation and the Host Response to Injury Collaborative Research Program [14-23]. SCIRC protocols include a traumatic brain injury management protocol, sedation and analgesia protocol, delirium protocol, mechanical ventilation protocol, ventilator associated pneumonia prevention bundle, blood product transfusion protocol, nutritional support protocol, stress ulcer prophylaxis protocol, electrolyte replacement protocol, subcutaneous and continuous infusion insulin protocol, venous thromboembolism prophylaxis protocol, and progressive upright mobility protocol.

Subject recruitment

When a patient diagnosed with sepsis, a page notification is sent to a team of research nurses who respond to evaluate for study enrollment 24 hours per day, 7 days per week. The research nurse on-call evaluates inclusion and exclusion criteria. If the patient qualifies, the research nurse seeks to obtain informed consent from the patient (if able) or legally authorized representative. Similar to the Inflammation and Host Response to Injury program, a 96-hour waiver of informed consent exists for initial sample and data collection based upon previous precedent at this institution, and approved by the institutional review board (IRB) [14-16]. If

consent is not able to be obtained after 96 hours, all initial blood samples and patient data are destroyed. If consent is initially obtained from the legally authorized representative and the patient regains decision-making capacity, the patient has the opportunity to withdraw from the study at that time. Study subjects may choose to participate during hospital admission with or without long-term follow-up, though long-term follow-up is encouraged, per study objectives.

Within the first seven days, all study subjects undergo prospective clinical adjudication to confirm proper diagnosis, source identification, and severity classification of sepsis during weekly SCIRC adjudication and retention committee meetings. As this study was designed and initiated prior to the Sepsis-3 consensus statement, sepsis severity is classified by previously established consensus definitions [10-13]. However, data collected during the course of the study will allow for subsequent classification and comparison to the subsequently released Sepsis-3 consensus statement [24].

Data procurement and management

Data describing baseline characteristics, management, and outcomes for each study subject are prospectively collected, recorded, and managed using the REDCap™ (REDCap consortium; www.projectredcap.org) research electronic case report form platform [25]. In collaboration with the University of Florida Clinical and Translational Science Institute (CTSI), our center developed an automated data collection and integration system that extracts clinical data from the electronic medical record and uploads the data to REDCap over a secure server on a daily basis. Raw data from the electronic medical record (EMR), including information on patient laboratory results, vital signs, medications, and information related to hospital and ICU

admission and discharge are directly uploaded to the SCIRC database by the University of Florida Health Integrated Data Repository (IDR). The SCIRC database includes over 800 data fields describing the vital signs, clinical signs and symptoms of sepsis, medical history, laboratory values, microbiologic analyses, cardiopulmonary resuscitation parameters, procedural interventions, medications, infusions, and outcomes for each patient. Parameters available in the EMR are transferred to the SCIRC database after compilation and quality filtering via the IDR system. Data from biologic sampling analyses performed by the Bioanalytical Core (e.g. flow cytometry, ELISA, multiplex, and gene analyses) are also transferred to the SCIRC drive as they are completed. The SCIRC database gives each project access to its own protected folder and to a bridge folder in which data can be placed for transfer to the Database Management and Biostatistics Core personnel for quality control and statistical analyses. The quality and accuracy of the transferred data is validated at regular intervals by the Database Management and Biostatistics Core. Parameters that are not available in the electronic medical record are manually extracted and entered into the REDCap case report form platform. Data regarding the inpatient hospital course prior to protocol initiation are also collected. For patients transferred from another facility, this includes records from the outside facility regarding the initial signs and symptoms of sepsis, microbiologic findings, antibiotic administration parameters, and source control procedures.

Biomarker sampling, processing, and analysis

Tissue samples are collected at scheduled intervals for biomarkers analyses of inflammation (e.g. plasma tumor necrosis factor-alpha, interleukin (IL)-1, IL-2, IL-3, IL-5, IL-6,

IL-10, IL-12, interferon-gamma, macrophage inflammatory protein 1-alpha), immunosuppression (e.g. granylocytic and monocytic myeloid-derived suppressor cells in whole blood) and catabolism (e.g. serum prealbumin, urine 3-methylhistidine, skeletal muscle high-resolution respirometry *in situ*) from 12 hours out to 42 days or inpatient discharge. For purposes of sample collection, time zero coincides with initiation of the sepsis protocol. Blood samples and laboratory measurements are obtained at the following time points, relative to sepsis protocol and study initiation: 12 hours, 1 day, 4 days, 7 days, 14 days, 21 days, 28 days, 35 days, and 42 days. Initial sample processing, including centrifugation, labeling, and freezing of patient samples, is performed 24 hours per day, 7 days per week at an on-site sample processing laboratory located within the trauma ICU. All samples are susbsequently transported to the Bioanalytics core or individual project laboratories as appropriate. Analytic methods include flow cytometry, enzyme-linked immunosorbent assay, multiplex, and gene expression array (NanoString Technologies, Seattle, WA, and Affymetrix, Cleveland, OH). The analytic plan followed the STROBE recommendations for observational cohort studies [26].

Subject retention, clinical assessments, and long-term follow-up

During the index hospitalization, clinical assessments focus on host factors (e.g. age, gender, comorbidities, hospital course prior to ICU admission), infection characteristics (e.g. presumed type of infection, microbiologic data, antibiotic therapy), sepsis severity (e.g. hemodynamic parameters, vasopressor support, laboratory measures of hypoxemia and tissue ischemia, Sequential Organ Failure Assessment (SOFA) scores [27], APACHE II scores [28]), volume status by protocolized bedside echocardiography, procedural interventions to obtain

source control, nutritional parameters (e.g. caloric and protein goals, nitrogen balance, metabolic cart for energy expenditure), and short-term outcomes (e.g. infectious complications, non-infectious complications, ICU length of stay, days on mechanical ventilation, change in SOFA score over time, in-hospital mortality, discharge disposition).

A retention committee creates an individualized follow-up plan for each study subject prior to discharge from the hospital. The retention committee meets twice per week to discuss all active study subjects, with special attention to subjects for whom long-term follow-up may be jeopardized by geographic and social impediments. Phone contact encounters are scheduled and used to predict retention problems. Parking and transportation costs are provided to the study subjects to maximize access to the research center. Members of the retention committee are trained to recognize and address psychosocial issues and provide emotional support as needed. When medical and/or mental health problems necessitating further treatment are identified, the retention committee provides referrals to the appropriate specialists, and ensures that care is provided in a timely fashion.

Long-term follow-up outpatient clinic visits occur at 3 months, 6 months, and 12 months at the facilities of the University of Florida Institute on Aging. Clinical assessments at these time points will focus on functional recovery from sepsis by performing a battery of tests including the Rand 36 Item SF health Survey [29], Mini Nutritional Assessment [30], EQ-5D-3L Health Questionnaire [31], Hopkins Verbal Learning Test [32], Controlled Oral Word Association test [33], Modified Mini-Mental State Exam [34], ECOG/WHO/Zubrod score [35], Short Physical Performance Battery [36], hand grip strength measurement, and body composition measurements with the BIA 450 bioimpedance analyzer (Biodynamics Corporation, Shoreline, WA). If patients are

unwilling or unable to return for outpatient clinical follow-up, home-visits are scheduled (up to 2-hour drive radius), or subjective data is collected via telephone interview.

To identify and evaluate the progression of sarcopenia, we will perform computed tomography (CT) morphometric assessments of psoas and abdominal wall lean muscle mass at baseline, 3 months, and 12 months, using SliceOmatic software (version 5.0 rev 6a; Tomovision, Magog, Quebec, Canada). Standard of care CT scans of the abdomen and pelvis conducted for diagnostic purposes while the patient was hospitalized were used for this analysis. Two of these CT scans were used: the baseline scan was performed within three days of sepsis protocol onset; the second scan was performed within seven to fourteen days of the baseline scan. To calculate the total skeletal muscle cross-sectional area (cm^2), trained investigators identified and quantified all skeletal muscles (psoas, paraspinal, and abdominal wall muscles) at the level of the third lumbar (L3) vertebra where both transverse processes were visualized using established Hounsfield unit (-29 to 150) attenuation thresholds for skeletal muscle tissue [37]. The L3 vertebral level was chosen because skeletal muscle visualized at this axial plane has been shown to correlate with whole-body muscle mass [38]. Skeletal muscle index (SMI, cm^2/m^2) was then calculated by normalizing the total skeletal muscle cross-sectional area (cm^2) to patient height squared (m^2). Psoas muscle index (PMI, cm^2/m^2) was also calculated by normalizing only the psoas muscle cross-sectional area (cm^2) to patient height squared (m^2).

Outcome definitions and analytic design

The primary outcomes of interest are the development of chronic critical illness (CCI) and 1-year mortality rates after the development of sepsis. CCI is defined as an extended course

of critical illness with persistent organ dysfunction requiring intensive care resources. Extended course of illness requiring intensive care resources is defined as total ICU days >14 days or being discharged to another hospital, long term acute care hospital, or hospice. Persistent organ dysfunction is defined as having a SOFA score of at least 2 in any organ system with the exception of at least 1 for cardiovascular system on day 14 in ICU after protocol onset or last SOFA score available, whichever comes first. Subjects are deemed to have developed CCI if they are discharged to dispositions associated with poor outcomes (e.g. long term acute care facility, skilled nursing facility) prior to ICU day 14 with ongoing evidence of organ dysfunction, as described above. Mortality at 1-year will be determined by prospective follow-up, or from the United States Social Security Death Index for those lost to follow-up.

Secondary outcomes of interest include changes in health, function and quality of life assessments at 1-year after sepsis onset. Analyses will include the development of biomarker and clinical prediction models for the development of CCI, as well as prediction models and the development of a "CCI score" at ICU day 14 to predict 1-year mortality and poor functional outcomes. Additionally, biomarker analyses at day 14 will seek to characterize the presence of persistent inflammation, immunosuppression and catabolism in subjects who have developed CCI, consistent with the PICS pathophysiologic phenotype.

Ethics and dissemination

This study has been registered at Clinicaltrials.gov. The University of Florida IRB approved this study. All investigators will complete annual training modules regarding the ethical conduct of research and Health Insurance Portability and Accountability Act (HIPAA)

compliance, per IRB requirements. All investigators also complete National Institutes of Health conflict of interest disclosure training. Results will be presented at national and international conferences and reported in peer-reviewed journals. Dissemination of preliminary results is forthcoming.

Summary

Better strategies are needed to improve care for millions of critically ill patients with sepsis and septic shock. While in-hospital mortality has decreased, a new phenotype of CCI driven by PICS physiology has emerged, and appears to be associated with a substantial burden of morbidity and late mortality. Therefore, further investigation is needed to elucidate pathophysiology and identify therapeutic approaches for CCI and PICS. Through prospective multidisciplinary investigation augmented by automated sepsis surveillance, clinical decision support with a computerized sepsis protocol, advanced data management strategies, and robust long-term follow-up, the SCIRC seeks to develop novel management strategies and targeted therapies for critically ill septic patients.

Author contributions

TO, BAB, AB, MSS, SDA, CL, AMM, PAE, LLM, FAM and SCB contributed to study design. TJL, JCM, and TO contributed to manuscript composition. LLM, FAM, and SCB provided critical revisions.

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Table 1: The modified early warning signs (MEWS) – sepsis recognition score (SRS) grading scale, adapted from Croft et al.[7] was used as a screening tool to identify patients who may be developing sepsis. The provider is notified if the patient has a total score ≥ 6, 3 points in any single category, worsening mental status, or an increase in fraction of inspired oxygen (FiO_2).

Points	3	2	1	0	1	2	3
Temp	< 32	< 35	< 36	36.0-38.4	38.5-38.9	39.0-40.9	≥ 41
HR	< 40	40-44	45-50	51-100	101-110	111-129	≥ 129
RR	≤ 7	8	9	10-14	15-20	21-29	≥ 30
SBP	≤ 70	71-80	81-100	101-160	161-180	181-199	≥ 200
Mental status[a]	unresp-onsive	responds to noxious stimuli	responds to voice or tap	alert, coop-erative	mildly agitated, confused	very agitated, requires restraints	extremely agitated, danger to self or others
WBC	< 1.0[b]	1.0-2.9[b]	-	3.0-14.9	15.0-19.9	20.0-39.9	≥ 40

Temp: temperature (°C), HR: heart rate, RR: respiratory rate, SBP: systolic blood pressure (mmHg), WBC: white blood cell count ($x10^9$/L). [a]Do not score if the patient is receiving a sedating medication or has a general medical condition affecting mental status (e.g. traumatic brain injury, stroke). [b]Do not score if the patient is receiving oncolytic therapy.

Figure legend

Figure 1: The persistent inflammation, immunosuppression, and catabolism syndrome (PICS), adapted from Rosenthal et al.[6] and Mira et al.[39] MOF: multiple organ failure, SIRS: systemic inflammatory response syndrome, CARS: compensatory anti-inflammatory response syndrome, LTAC: long-term acute care facility.

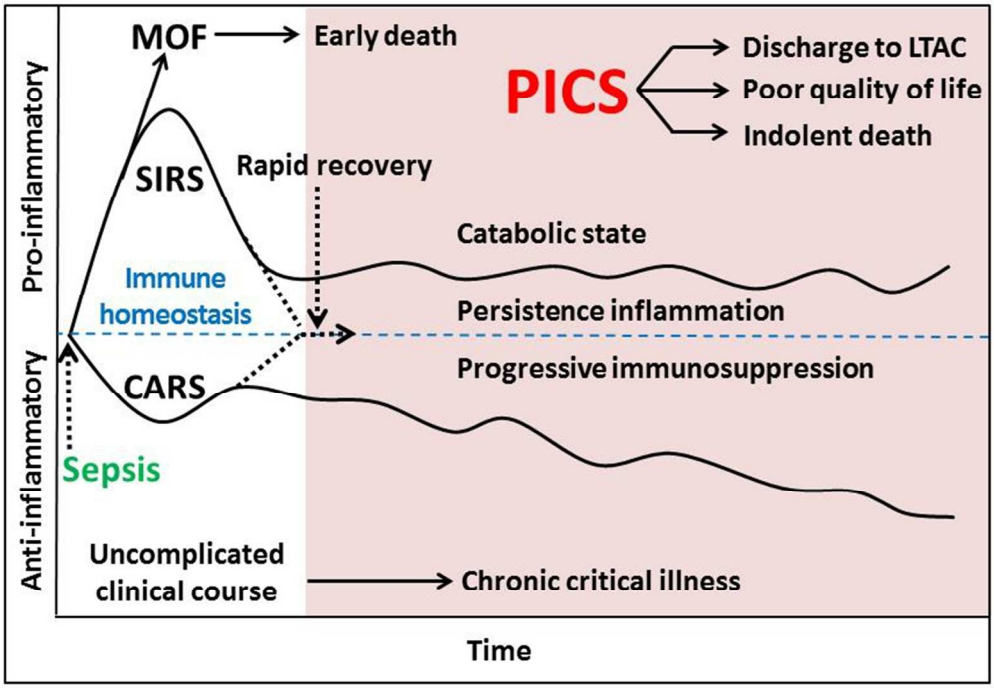

Figure 1: The persistent inflammation, immunosuppression, and catabolism syndrome (PICS), adapted from Rosenthal et al.6 and Mira et al.39 MOF: multiple organ failure, SIRS: systemic inflammatory response syndrome, CARS: compensatory anti-inflammatory response syndrome, LTAC: long-term acute care facility.

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Sepsis and Critical Illness Research Center Investigators: protocols and standard operating procedures for a prospective cohort study of sepsis in critically ill surgical patients

Short title: SCIRC standard operating procedures

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Abstract

Introduction: Sepsis is a common, costly, and morbid cause of critical illness in trauma and surgical patients. Ongoing advances in sepsis resuscitation and critical care support strategies have led to improved in-hospital mortality. However, these patients now survive to enter state of chronic critical illness (CCI), persistent low-grade organ dysfunction, and poor long-term outcomes driven by the persistent inflammation, immunosuppression, and catabolism syndrome (PICS). The Sepsis and Critical Illness Research Center (SCIRC) was created to provide a platform by which the prevalence and pathogenesis of CCI and PICS may be understood at a mechanistic level across multiple medical disciplines, leading to the development of novel management strategies and targeted therapies.

Methods: Here we describe the design, study cohort, and standard operating procedures used in the prospective study of human sepsis at a level 1 trauma center and tertiary care hospital providing care for over 2,600 critically ill patients annually. These procedures include implementation of an automated sepsis surveillance initiative, augmentation of clinical decisions with a computerized sepsis protocol, strategies for direct exportation of quality-filtered data from the electronic medical record to a research database, and robust long-term follow-up.

Ethics and dissemination: This study has been registered at Clinicaltrials.gov, approved by the University of Florida Institutional Review Board, and is actively enrolling subjects. Dissemination of results is forthcoming.

Strengths and limitations of this study

- Computerized decision support will minimize the influence of variability in management practices
- Robust long-term follow-up will allow for deeper understanding of functional recovery following sepsis
- Investigation of targeted therapies is currently limited by deficiencies in our understanding of sepsis pathophysiology

Introduction

Sepsis as both a cause and complication of surgical intensive care unit admission is common, costly, and morbid. Hospitalization with sepsis has become more common than hospitalization with myocardial infarction, with annual costs over $20 billion in the United States [1 2]. Mortality rates for sepsis range from 18-28%, and remain unacceptably high despite more than 30 years of intensive research [3 4]. Recent advances in resuscitation strategies have improved in-hospital mortality, but sepsis survivors often enter a state of chronic critical illness (CCI) driven by the persistent inflammation, immunosuppression, and catabolism syndrome (PICS) [5 6] (Figure 1). However, the pathophysiology of these conditions remains incompletely understood. The Sepsis and Critical Illness Research Center (SCIRC) was created to provide a platform to better understand the pathophysiology of PICS. The objective of this prospective cohort study of sepsis in critically ill surgical patients is to understand the prevalence and pathogenesis of PICS at a mechanistic level across multiple medical disciplines, leading to the development of novel management strategies and targeted therapies.

Methods and analysis

Setting

The University of Florida Health Shands Hospital (Gainesville, Florida; U.S.A.) is a Level 1 Trauma and tertiary care center with two trauma/surgical intensive care units (ICU) totaling 48 beds, which serve as the recruitment base for this cohort study. UF Health is the sole

tertiary care center for a greater than 90-mile radius catchment area, including over 1.5 million people. Together, the trauma and surgical ICU teams manage over 2,600 critically ill patients annually. Each ICU has a dedicated surgical critical care team including a board certified attending intensivist, critical care fellows, surgical and anesthesia residents, and advanced practice providers (physician assistants and nurse practitioners). These teams collaborate with unit-dedicated pharmacists, respiratory therapists, physical therapists, occupational therapists, nutritionists, and social workers. Board certified attending acute care surgeons and critical care fellows provide in-hospital coverage 24 hours per day, 7 days per week.

Study design and population

This is a prospective, longitudinal cohort study of surgical intensive care unit (ICU) patients that develop sepsis. Based on preliminary data and *a priori* power analyses, 400 patients will be enrolled over a period of 4 years, with subsequent 12-month individual follow-up. Enrollment began in January 2015 and will continue through January 2019, and beyond if funding permits. Inclusion criteria are presence in the trauma/surgical intensive care unit, age ≥ 18 years, and diagnosis with sepsis, severe sepsis, or septic shock with subsequent initiation of the computerized clinical decision support (CCDS) directed sepsis protocol [7-9]. Septic patients are initially identified by a modified version of the Modified Early Warning Score (MEWS-SRS) [10], which screens for sepsis based on temperature, heart rate, respiratory rate, blood pressure, and level of consciousness (Table 1). In the emergency department and on surgical wards, this score is calculated for each patient on arrival, every time vital signs are recorded, and any time a patient has an acute change from their baseline physiologic status, prompting further

investigation. Patients identified by the MEWS screening protocol are then directly assessed by a physician or advance practice provider for bedside clinical adjudication of the presence of sepsis (a systemic inflammatory response with a source of infection), severe sepsis (sepsis-induced tissue hypoperfusion or organ dysfunction), or septic shock (severe sepsis with persistent arterial hypotension despite volume resuscitation) based on consensus definitions [11-14]. This screening and diagnostic process has been automated and embedded within the UF Health electronic medical record (Epic Systems, Verona, WI). All cases that are deemed to have sepsis, severe sepsis, or septic shock by the physician or advanced practice provider at the bedside are then reviewed in detail by a faculty member of the SCIRC to ensure that the diagnosis was appropriate, and are reviewed again at weekly SCIRC sepsis adjudication meetings for the same purpose.

Exclusion criteria are age <18 years, severe traumatic brain injury (i.e. CT evidence of neurologic injury and Glasgow Coma Scale score <8), spinal cord injury resulting in permanent sensory and/or motor deficits, sepsis with an uncontrollable source (e.g. unresectable bowel ischemia), NY Heart Association class IV heart failure, Child-Pugh Class B or C liver disease, known HIV infection with CD4 count <200 cells/mm^3, organ transplant recipient on an immunosuppressant agent, chemotherapy or radiotherapy within 30 days prior to onset of sepsis, expected lifespan <3 months due to severe pre-existing comorbidities, active Do Not Resuscitate or Do Not Intubate order, pregnancy, incarceration, or institutionalization. Demographics, comorbidities, illness severity, length of stay, and discharge disposition for patients who have been enrolled in the study are listed in Table 2.

Within the study population, cohort analyses will include comparisons between patients who develop CCI versus patients who experience early recovery from sepsis. Among CCI

patients, patients who develop PICS will be compared to patients who do not. In addition, inflammatory, immunosuppression, and catabolism biomarkers will be measured in age-matched healthy control for comparison to CCI, non-CCI, and PICS patients.

Computerized clinical decision support (CCDS) sepsis protocol

Patients who are diagnosed with sepsis, severe sepsis, or septic shock are started on a computerized clinical decision support protocol, as previously described [7]. This system was modified from a sepsis management protocol originally implemented at the Methodist Hospital in Houston, Texas [8]. In brief, mobile bedside computer workstations were programed with sepsis protocol algorithm logic that interacts with the patient and clinician by mapping clinical workflow and recommendations to patient physiology and clinical interventions. The sepsis protocol algorithm logic was developed by a multidisciplinary team of surgeons, intensivists, advanced practitioners, nurses, respiratory therapists, pharmacists, pathologists, and computer engineers, based on Surviving Sepsis Campaign guidelines [14]. The algorithm produces a recommendation; the clinician may accept or modify the recommendation, tailoring care to individual patient-specific factors. The selected intervention is then imputed, and the computerized clinical workflow and recommendations continue to evolve.

The computerized sepsis protocol is the platform for clinical decisions regarding initial volume resuscitation and antibiotic therapy initiation. For all other clinical decisions, the SCIRC developed protocols based on standard operating procedures from the Inflammation and the Host Response to Injury Collaborative Research Program [15-24]. SCIRC protocols include a daily spontaneous breathing trial protocol (Supplementary figure 1), delirium protocol (Supplementary

table 1) [25 26], product transfusion protocol (Table 3), and a nutritional support protocol (Supplementary table 2) [27].

Subject recruitment

When a patient is diagnosed with sepsis, a page notification is sent to a team of research nurses who respond to evaluate for study enrollment 24 hours per day, 7 days per week. The research nurse on-call evaluates inclusion and exclusion criteria. If the patient qualifies, the research nurse seeks to obtain informed consent from the patient (if able) or legally authorized representative. Similar to the Inflammation and Host Response to Injury program, a 96-hour deferral of informed consent exists for initial sample and data collection based upon previous precedent at this institution, and approved by the institutional review board (IRB) [15-17]. If consent is not obtained within 96 hours, all initial blood samples and patient data are destroyed. If consent is initially obtained from the legally authorized representative and the patient regains decision-making capacity, the patient has the opportunity to withdraw from the study at that time. Study subjects may choose to participate during hospital admission with or without long-term follow-up, though long-term follow-up is encouraged, per study objectives.

Within the first seven days, all study subjects undergo prospective clinical adjudication to confirm proper diagnosis, source identification, and severity classification of sepsis during weekly SCIRC adjudication and retention committee meetings. As this study was designed and initiated prior to the Sepsis-3 consensus statement, sepsis severity is classified by previously established consensus definitions [11-14]. However, data collected during the course of the study will allow for subsequent classification and comparison to the subsequently released Sepsis-3 consensus statement, including assessment of qSOFA scores [28 29].

Data procurement and management

Data describing baseline characteristics, management, and outcomes for each study subject are prospectively collected, recorded, and managed using the REDCap™ (REDCap consortium; www.projectredcap.org) research electronic case report form platform [30]. In collaboration with the University of Florida Clinical and Translational Science Institute (CTSI), our center developed an automated data collection and integration system that extracts clinical data from the electronic medical record and uploads the data to REDCap over a secure server on a daily basis. Raw data from the electronic medical record (EMR), including information on patient laboratory results, vital signs, medications, and information related to hospital and ICU admission and discharge are directly uploaded to the SCIRC database by the University of Florida Health Integrated Data Repository (IDR). The SCIRC database includes over 800 data fields describing the vital signs, clinical signs and symptoms of sepsis, medical history, laboratory values, microbiologic analyses, cardiopulmonary resuscitation parameters, procedural interventions, medications, infusions, and outcomes for each patient. Parameters available in the EMR are transferred to the SCIRC database after compilation and quality filtering via the IDR system. Data from biologic sampling analyses performed by the Bioanalytical Core (e.g. flow cytometry, ELISA, multiplex, and gene analyses) are also transferred to the SCIRC drive as they are completed. The SCIRC database gives each project access to its own protected folder and to a bridge folder in which data can be placed for transfer to the Database Management and Biostatistics Core personnel for quality control and statistical analyses. The quality and accuracy of the transferred data is validated at regular intervals by the Database Management and Biostatistics Core by identifying potential outlier values and reviewing the source data with

SCIRC faculty. Parameters that are not available in the electronic medical record are manually extracted and entered into the REDCap case report form platform. Data regarding the inpatient hospital course prior to protocol initiation are also collected. For patients transferred from another facility, this includes records from the outside facility regarding the initial signs and symptoms of sepsis, microbiologic findings, antibiotic administration parameters, and source control procedures.

Biomarker sampling, processing, and analysis

Tissue samples are collected at scheduled intervals for biomarkers analyses of inflammation (e.g. plasma tumor necrosis factor-alpha, interleukin (IL)-1, IL-2, IL-3, IL-5, IL-6, IL-10, IL-12, interferon-gamma, macrophage inflammatory protein 1-alpha), immunosuppression (e.g. granylocytic and monocytic myeloid-derived suppressor cells in whole blood, expression of PD-1[31] and PDL-1 on blood monocytes and $CD66b^+$ neutrophils) and catabolism (e.g. serum prealbumin, urine 3-methylhistidine, skeletal muscle high-resolution respirometry *in situ*, assessment of muscle morphology and myosin/actin ratio by histochemistry, and measurement of FoxO3A, MuRF1, MAFBx, BNIP, calpains, and 20S proteasome activity) from 12 hours out to 42 days or inpatient discharge for non- muscle samples. Muscle samples are obtained 28 days after sepsis protocol initiation. Skeletal muscle samples weighing 150-250 mg are obtained from the vastus lateralis at the midpoint between the patella and the greater trochanter of the femur by trained practitioners using sterile technique under local anesthesia, as previously described [32]. A portion is immediately permeabilized for high resolution respiration

measurements, a portion is mounted in embedding medium and frozen in isopentane for histochemical analysis, and the remaining tissue is frozen in liquid nitrogen and stored at -80°C.

For purposes of sample collection, time zero coincides with initiation of the sepsis protocol. Blood samples and laboratory measurements are obtained at the following time points, relative to sepsis protocol and study initiation: 12 hours, 1 day, 4 days, 7 days, 14 days, 21 days, 28 days, 35 days, and 42 days. Initial sample processing, including centrifugation, labeling, and freezing of patient samples, is performed 24 hours per day, 7 days per week at an on-site sample processing laboratory located within the trauma ICU. This laboratory contains a -80° freezer, a microfuge, a refrigerated centrifuge, and an environmental hood. Flow cytometry is performed on fresh samples, and all other samples are stored in the -80° freezer, and susbsequently transported to the Bioanalytics core or individual project laboratories as appropriate. Collected specimens are annotated, labeled, and stored according to best practice guidelines [33]. Stored samples are maintained in a biobank that will remain available for future testing. Standard training is provided to all laboratory staff regarding machine calibration, sample processing, operator safety, and quality control. Serum and plasma samples are collected in a fully filled collection tube, inverted 5-10 times, and then maintained in a closed tube in vertical position until centrifugation. Samples are analyzed in parallel with reagents from the same batch by the same technician. Analytic methods include flow cytometry, enzyme-linked immunosorbent assay, multiplex, and gene expression array (NanoString Technologies, Seattle, WA, and Affymetrix, Cleveland, OH). The analytic plan followed the STROBE recommendations for observational cohort studies [34].

Subject retention, clinical assessments, and long-term follow-up

During the index hospitalization, clinical assessments focus on host factors (e.g. age, gender, comorbidities, hospital course prior to ICU admission), infection characteristics (e.g. presumed type of infection, microbiologic data, antibiotic therapy), sepsis severity (e.g. hemodynamic parameters, vasopressor support, laboratory measures of hypoxemia and tissue ischemia, Sequential Organ Failure Assessment (SOFA) scores [35], APACHE II scores [36]), volume status by protocolized bedside echocardiography, procedural interventions to obtain source control, nutritional parameters (e.g. nutrition provided by gastric, post-pyloric, and parenteral routes, weekly caloric and protein goals versus actual calories and protein administered, 24-hour urine collection to assess nitrogen balance, indirect calorimetry, and changes in body mass index and ideal body weight), and short-term outcomes (e.g. infectious complications, non-infectious complications, ICU length of stay, days on mechanical ventilation, change in SOFA score over time, in-hospital mortality, discharge disposition).

Bedside echocardiography is performed by the transesophageal approach for intubated patients with an intact esophagus and stomach, no known or suspected gastroesophageal variceal disease, and low risk for pathologically increased intracranial pressures. Echocardiography is performed by the transthoracic approach for all other patients. Assessments include the presence of pericardial fluid, characterization of the right ventricle size as normal, collapsible, or enlarged, characterization of right and left ventricle contractility as normal, poor, or hyperdynamic, description of the superior vena cava collapsibility index as less than or equal to 36%, quantification of fractional area change (the difference in left ventricular area at end-diastole versus end-systole, divided by end-diastolic area), an interpretation of the findings as representing euvolemia, hypovolemia, or hypervolemia, and a plan to start, discontinue, increase,

or decrease intravenous fluid therapy, vasopressor therapy, and inotrope therapy based on echocardiography findings.

A retention committee creates an individualized follow-up plan for each study subject prior to discharge from the hospital. The retention committee meets twice per week to discuss all active study subjects, with special attention to subjects for whom long-term follow-up may be jeopardized by geographic and social impediments. Phone contact encounters are scheduled and used to predict retention problems. Parking and transportation costs are provided to the study subjects to maximize access to the research center. Members of the retention committee are trained to recognize and address psychosocial issues and provide emotional support as needed. When medical and/or mental health problems necessitating further treatment are identified, the retention committee provides referrals to the appropriate specialists, and ensures that care is provided in a timely fashion.

Long-term follow-up outpatient clinic visits occur at 3 months, 6 months, and 12 months at the facilities of the University of Florida Institute on Aging. Clinical assessments at these time points will focus on functional recovery from sepsis by performing a battery of tests including the Rand 36 Item SF health Survey [37], Mini Nutritional Assessment [38], EQ-5D-3L Health Questionnaire [39], Hopkins Verbal Learning Test [40], Controlled Oral Word Association test [41], Modified Mini-Mental State Exam [42], ECOG/WHO/Zubrod score [43], Short Physical Performance Battery [44], hand grip strength measurement, and body composition measurements with the BIA 450 bioimpedance analyzer (Biodynamics Corporation, Shoreline, WA). If patients are unwilling or unable to return for outpatient clinical follow-up, home-visits are scheduled (up to 2-hour drive radius), or subjective data is collected via telephone interview.

To identify and evaluate the progression of sarcopenia, we will perform computed tomography (CT) morphometric assessments of psoas and abdominal wall lean muscle mass at baseline, 3 months, and 12 months, using SliceOmatic software (version 5.0 rev 6a; Tomovision, Magog, Quebec, Canada). Standard of care CT scans of the abdomen and pelvis conducted for diagnostic purposes while the patient was hospitalized were used for this analysis. Two of these CT scans were used: the baseline scan was performed within three days of sepsis protocol onset; the second scan was performed within seven to fourteen days of the baseline scan. To calculate the total skeletal muscle cross-sectional area (cm^2), trained investigators identified and quantified all skeletal muscles (psoas, paraspinal, and abdominal wall muscles) at the level of the third lumbar (L3) vertebra where both transverse processes were visualized using established Hounsfield unit (-29 to 150) attenuation thresholds for skeletal muscle tissue [45]. The L3 vertebral level was chosen because skeletal muscle visualized at this axial plane has been shown to correlate with whole-body muscle mass [46]. Skeletal muscle index (SMI, cm^2/m^2) was then calculated by normalizing the total skeletal muscle cross-sectional area (cm^2) to patient height squared (m^2). Psoas muscle index (PMI, cm^2/m^2) was also calculated by normalizing only the psoas muscle cross-sectional area (cm^2) to patient height squared (m^2).

Outcome definitions and analytic design

The primary outcomes of interest are the development of chronic critical illness (CCI) and 1-year mortality rates after the development of sepsis. CCI is defined as an extended course of critical illness with persistent organ dysfunction requiring intensive care resources. Extended course of illness requiring intensive care resources is defined as total ICU days >14 days or being

discharged to another hospital, long term acute care hospital, or hospice. Persistent organ dysfunction is defined as having a SOFA score of at least 2 in any organ system with the exception of at least 1 for cardiovascular system on day 14 in ICU after protocol onset or last SOFA score available, whichever comes first. Subjects are deemed to have developed CCI if they are discharged to dispositions associated with poor outcomes (e.g. long term acute care facility, skilled nursing facility) prior to ICU day 14 with ongoing evidence of organ dysfunction, as described above. Mortality at 1-year will be determined by prospective follow-up, or from the United States Social Security Death Index for those lost to follow-up.

Secondary outcomes of interest include changes in health, function and quality of life assessments at 1-year after sepsis onset. Analyses will include the development of biomarker and clinical prediction models for the development of CCI, as well as prediction models and the development of a "CCI score" at ICU day 14 to predict 1-year mortality and poor functional outcomes. Additionally, biomarker analyses at day 14 will seek to characterize the presence of persistent inflammation, immunosuppression and catabolism in subjects who have developed CCI, consistent with the PICS pathophysiologic phenotype.

Ethics and dissemination

This study has been registered at Clinicaltrials.gov (NCT02276417). The University of Florida IRB approved this study. This work was supported by P50 GM111152–01 awarded by the National Institute of General Medical Sciences (NIGMS). TJL, JCM, and JAS were supported by a post-graduate training grant (T32 GM-08721) in burns, trauma, and perioperative injury from the NIGMS. The authors have read and understood BMJ policy on declaration of

interests and declare that the authors have no competing interests. All investigators will complete annual training modules regarding the ethical conduct of research and Health Insurance Portability and Accountability Act (HIPAA) compliance, per IRB requirements. All investigators also complete National Institutes of Health conflict of interest disclosure training. Results will be presented at national and international conferences and reported in peer-reviewed journals. Dissemination of preliminary results is forthcoming.

Summary

Better strategies are needed to improve care for millions of critically ill patients with sepsis and septic shock. While in-hospital mortality has decreased, a new phenotype of CCI driven by PICS physiology has emerged, and appears to be associated with a substantial burden of morbidity and late mortality. Therefore, further investigation is needed to elucidate pathophysiology and identify therapeutic approaches for CCI and PICS. Through prospective multidisciplinary investigation augmented by automated sepsis surveillance, clinical decision support with a computerized sepsis protocol, advanced data management strategies, and robust long-term follow-up, the SCIRC seeks to develop novel management strategies and targeted therapies for critically ill septic patients.

Author contributions

TO, GG, ZW, BAB, AB, MSS, SDA, CL, AMM, PAE, LLM, FAM and SCB contributed to study design. TJL, JCM, and TO contributed to manuscript composition. LLM, FAM, and SCB provided critical revisions.

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Table 1: The modified early warning signs (MEWS) – sepsis recognition score (SRS) grading scale, adapted from Croft et al.[7] was used as a screening tool to identify patients who may be developing sepsis. The provider is notified if the patient has a total score ≥ 6, 3 points in any single category, worsening mental status, or an increase in fraction of inspired oxygen (FiO_2).

Points	3	2	1	0	1	2	3
Temp	< 32	< 35	< 36	36.0-38.4	38.5-38.9	39.0-40.9	≥ 41
HR	< 40	40-44	45-50	51-100	101-110	111-129	≥ 129
RR	≤ 7	8	9	10-14	15-20	21-29	≥ 30
SBP	≤ 70	71-80	81-100	101-160	161-180	181-199	≥ 200
Mental status[a]	unresp-onsive	responds to noxious stimuli	responds to voice or tap	alert, coop-erative	mildly agitated, confused	very agitated, requires restraints	extremely agitated, danger to self or others
WBC	< 1.0[b]	1.0-2.9[b]	-	3.0-14.9	15.0-19.9	20.0-39.9	≥ 40

Temp: temperature (°C), HR: heart rate, RR: respiratory rate, SBP: systolic blood pressure (mmHg), WBC: white blood cell count ($x10^9$/L). [a]Do not score if the patient is receiving a sedating medication or has a general medical condition affecting mental status (e.g. traumatic brain injury, stroke). [b]Do not score if the patient is receiving oncolytic therapy.

Table 2: Characteristics of enrolled patients.

Demographics	**All patients** n=216
Age in years, mean (SD)	59.3 (15.2)
Male, n (%)	116 (53.7)
Race, n (%)	
Caucasian (White)	191 (88.4)
African American	20 (9.3)
Asian	1 (0.5)
Pacific Islander	0 (0)
Other	3 (1.4)
BMI, median (25^{th}, 75^{th})	29.3 (24.8, 35.8)
Charlson comorbidity index, mean (SD)	4.3 (3.0)
APACHE II score (24 hrs), mean (SD)	18.0 (8.1)
Inter-facility hospital transfer, n (%)	95 (44.0)
Hospital-acquired sepsis*, n (%)	88 (40.7)
ICU LOS, median (25^{th}, 75^{th})	7 (3.5, 18)
Hospital LOS, median (25^{th}, 75^{th})	17 (8, 29)
Discharge disposition, n (%)	
"Good" disposition	117 (54.2)
Home	38 (17.6)
Home healthcare services	69 (31.2)
Rehab	10 (4.6)
"Poor" disposition	99 (45.8)
Long term acute care facility	30 (13.9)
Skilled nursing facility	37 (17.1)
Another Hospital	9 (4.2)
Hospice	7 (3.2)
Death	16 (7.4)

SD: standard deviation, BMI: body mass index, APACHE: Acute Physiology and Chronic Health Evaluation, ICU: intensive care unit, LOS: length of stay. *Sepsis onset ≥48 hours after hospital admission.

Table 3: Indications for blood product transfusion.

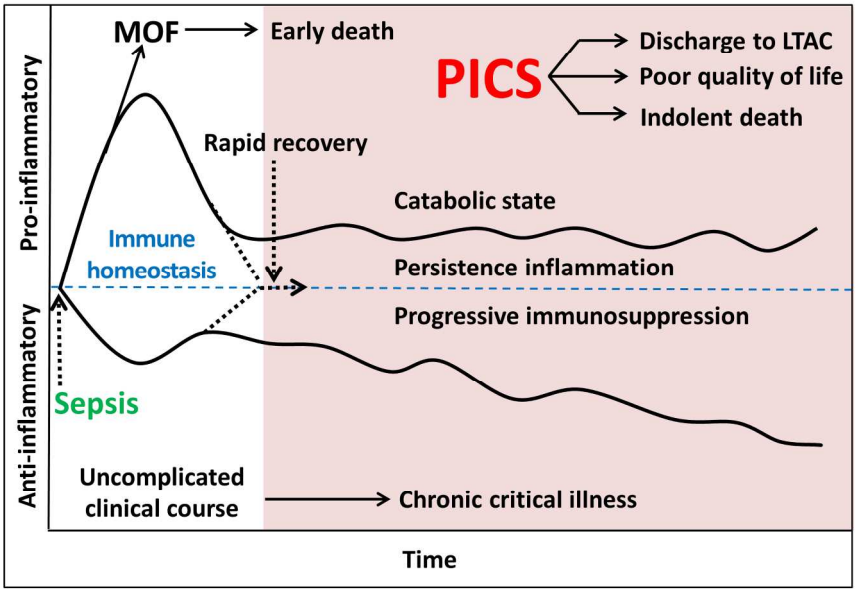
Blood product	Indications for transfusion
Red blood cells	Hb <7 g/dL or HCT <21% Hb <10 g/dL or HCT <30% and symptomatic cardiovascular disease Acute blood loss >30% of total blood volume
Plasma (minimum dose 10-20 mL/kg)	INR >1.7 and active bleeding or immediately prior to a procedure Thrombotic thrombocytopenic purpura Factor deficiency for which no specific concentrate is available
Cryoprecipitate	Fibrinogen <100 mg/dL Factor XIII deficiency Perioperative management

Hb: hemoglobin, HCT: hematocrit, INR: international normalized ratio.

Figure legends

Figure 1: The persistent inflammation, immunosuppression, and catabolism syndrome (PICS), adapted from Rosenthal et al.[6] and Mira et al.[47] MOF: multiple organ failure, SIRS: systemic inflammatory response syndrome, CARS: compensatory anti-inflammatory response syndrome, LTAC: long-term acute care facility.

Supplementary figure 1: Protocol for daily spontaneous breathing trials.



MOF –multiple organ failure; PICS – persistent inflammation, immune suppression, and catabolism syndrome; LTAC – long term acute care facility

Figure 1: The persistent inflammation, immunosuppression, and catabolism syndrome (PICS), adapted from Rosenthal et al.6 and Mira et al.44 MOF: multiple organ failure, SIRS: systemic inflammatory response syndrome, CARS: compensatory anti-inflammatory response syndrome, LTAC: long-term acute care facility.

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Supplementary table 1: Delirium protocol.

Step 1: Non-pharmacological interventions for delirium prevention and treatment

General

- Perform daily sedation holidays, unless contraindicated
- Avoid over-treatment and under-treatment of pain

Orientation

- Encourage communication
- Have familiar objects from the patient's home in the hospital room
- Frequently re-orient the patient to date, time, and caretakers
- Attempt consistency in staff
- Provide visual and auditory aids
- Allow television during the day with daily news or non-verbal music

Environment

- Encourage early mobilization (e.g. ambulation, range of motion exercises, minimize use of immobilizing equipment, ensure timely removal of catheters, order physical therapy and occupational therapy consults)
- Optimize sleep hygiene
  - Minimize noise and interruption
  - Keep lights on and window shades up during the day
  - Keep lights off and window shades closed at night

Clinical parameters

- Maintain euvolemia
- Maintain adequate systolic blood pressure
- Maintain adequate oxygen saturation
- Treat underlying metabolic derangements and infections

Step 2: Patient assessment

Nursing responsibilities

- Assess delirium using Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[45] every nursing shift, during sedation holidays if applicable
- Document screening results in the electronic medical record
- Report delirium positive results to the physician or advanced practitioner
- Assess for other causes of neurological status changes (e.g. hypoxia, vasospasm, stroke, seizure, infection, hypoglycemia, myocardial

infarction, pulmonary embolism)

- Assess patient for extra-pyramidal symptoms (e.g. acute dystonia, akathisia, parkinsonism, tardive dyskinesia), drug-induced rigidity, and high fever at least twice daily (every nursing shift) and when there is a change in clinical status

Physician or advanced practitioner responsibilities

- Assess the patient for non-delirium causes of neurological status changes
- Order appropriate delirium intervention(s) if applicable (Step 3)

Step 3: Interventions by CAM-ICU assessment result

Unable to assess delirium (Richmond Agitation Sedation Scale (RASS)[46] score -4 or -5)

- Lighten sedation, if applicable, to obtain goal level of sedation
- Continue non-pharmacological interventions for delirium prevention
- Continue daily sedation holidays, unless contraindicated

CAM-ICU delirium negative

- If applicable, continue sedation and analgesia protocols for treatment of anxiety and pain
- Continue non-pharmacological interventions for delirium prevention
- Continue twice daily delirium assessments

CAM-ICU delirium positive

All delirium positive patients

- Implement non-pharmacologic interventions for the prevention and treatment of delirium
- Assess patient for non-delirium causes of neurological status changes
- Ensure adequate pain control
- Discontinue or minimize use of potentially deliriogenic drugs
  - Avoid the use of benzodiazepines
  - Consider the use of propofol if sedation is required

-AND-

Tailored delirium treatment based on RASS score

- Delirium positive and RASS +2 to +4 [agitated]

- Assess pain
  - Pain: treat with analgesics and reassess for delirium
  - No pain: consider treatment with an antipsychotic agent (see next section)
- Provide adequate sedation for protection of the patient and staff

- Delirium positive and RASS 0 or +1 [awake and alert]
  - Ensure adequate pain control
  - Consider treatment with an antipsychotic agent (see next section)

- Delirium positive and RASS -1 to -3 [sedated]
  - Reassess sedation goal and consider adjustment of sedation regimen
  - Perform daily sedation holidays

Treatment of delirium with antipsychotic medications

General considerations

- For patients with alcohol withdrawal delirium (delirium tremens) or traumatic brain injury, use protocols specific for those disease processes
- For transplant patients, discuss with the transplant service before ordering medications
- For pregnant patients, carefully assess risks and benefits of medications and discuss with the Obstetrics and Gynecology service prior to ordering medications
- Use lower antipsychotic doses for elderly patients
- Prior to initiation of antipsychotics, obtain baseline QTc and monitor regularly thereafter
  - If QTc >490 mSec on bedside monitor, obtain 12-lead electrocardiogram
  - If QTc >500 mSec on 12-lead electrocardiogram
    - Alert physician or advanced practitioner
    - Hold all non-essential QTc prolonging medications and do not administer atypical antipsychotics
    - Repeat electrocardiogram in 6-12 hours
    - Consider supplemental magnesium administration
- Perform regular assessments for extra-pyramidal symptoms, drug-induced rigidity, and high fever
- Obtain liver function tests at baseline and at regular intervals according to the pharmacologic profile of the medication in use
- Consider consultation with the Psychiatry service if:

- Antipsychotic agents are ineffective
- The patient has a contraindication to antipsychotic use
- The patient has a baseline psychiatric disorder for which the patient is already receiving antipsychotics

Antipsychotic discontinuation

Once delirium has resolved, taper to the minimum effective dose over 3 to 5 days. Therapy should be discontinued approximately two weeks after discharge from the ICU or prior to discharge home to avoid the development of long-term adverse effects, including:

- Sedation/fatigue
- Weight gain
- Glucose intolerance
- Dyslipidemia
- Sudden cardiac death
- Increased mortality among elderly patients with dementia

Supplementary table 2: Nutrition protocol.

Feeding initiation and advancement parameters

- For intubated patients with NUTRIC[47] score =5 with severe malnutrition per clinical assessment, unless contraindicated (see below) enteral access should be obtained and tube feeds initiated within 48 hours of admission
- For non-intubated severely malnourished patients or patients with NUTRIC score =5 who remain NPO or on a clear liquid diet on ICU day 5, get enteral access and initiate feeds unless contraindicated (see below)
- After resuscitation is complete (as defined by the resuscitation protocol), start tube feeds at 20 mL/hour and if no moderate or severe intolerances exist, advance by 10 mL/hour every 4-6 hours until the targeted goal is reached
- If post-pyloric enteral access is unavailable after multiple attempts, gastric feeds via a nasogastric tube may be initiated with aspiration precautions and gastric residual volume checks every 4 hours, tube feeds should only be held for residuals >500 mL or other signs of intolerance (e.g. emesis, distension)
- Enteral feeds should be no greater than 10ml/hour for the following high vasopressor requirements:
  - Norepinephrine or Epinephrine >0.1mcg/kg/min
  - Phenylephrine >1mcg/kg/min
  - Dopamine >10mcg/kg/min
  - Multiple vasopressors

Contraindications for tube feeds (risk for non-occlusive bowel necrosis)

- Active shock resuscitation
- Mean arterial pressure <60 mmHg for >60 minutes
- Acute respiratory distress syndrome with prone position
- Moderate or severe distention for >48 hours on an elemental diet
- Ischemic heart disease requiring vasopressors
- Bladder pressure >20 mmHg
- Vasopressin use
- Paralytic use

Tube feed formula	Kcal/mL	Protein g/L
Immune enhancing	1.5	94
Polymeric	1.5	63
Semi-elemental	1.2	75

Additives	Kcal/pack	Contents/pack
Juven®	80	7g glutamine, 7g arginine
Benefiber®	15	3g soluble fiber
Protein liquid	60	15g protein

Indications for immune enhancing formula

(administer for 10 days following surgery or trauma)

1. Non-trauma patients

- Moderately or severely malnourished patients undergoing major gastrointestinal surgery should receive immune enhancing formulas for 5-7 day preoperatively and 10 days postoperatively

2. Trauma patients

- Major torso trauma
  - Combined flail chest/pulmonary contusion anticipated to require prolonged mechanical ventilation
  - Thoracotomy with lung resection, aortic repair, or diaphragm repair
  - Patients >45 years old with 4 or more rib fractures or flail chest
- Major abdominal trauma
- Two or more of the following:
  - >6 unit transfusion requirement
  - Major pelvic fracture (acetabular, vertical shear, open book)
  - Two or more long bone fractures

Indications for polymeric formula

- Patients who do not meet the criteria for immune enhancing formula but have normal digestive and absorptive capacity of the gastrointestinal tract
- Patients who have received 10 days of immune enhancing formula administration

Indications for semi-elemental formula

- Pancreatitis
- Intolerance to the first formula used
- Short gut syndrome
- High output distal colonic or ileal fistula
- Persistent, severe diarrhea for >48 hours on polymeric formula

Indications for Juven®*

- After intraoperative ischemia/reperfusion injury (systolic blood pressure <90 mmHg for >1 hour or serum lactate >4 mmol/L)
- After cardiac arrest or burn injury
- Thoracoabdominal radiation and/or chemotherapy
- Major torso trauma with Injury Severity Score >17
- Post-operative patients at high risk for poor wound healing
- Prolonged mechanical ventilation

*Do not use Juven® if the patient is status post solid organ transplantation

Indications for total parenteral nutrition

- Massive small bowel resection refractory to enteral feeds
- High output fistula after failure of elemental diet
- Unable to meet >60% caloric and protein goals enterally by ICU day 7
- Unable to meet >85% caloric and protein goals enterally by ICU day 10
- High risk for non-occlusive bowel necrosis after ICU day 7

- TPN may be considered earlier in patients with severe malnutrition or NUTRIC =5 and contraindications to enteral nutrition feeding

- Lipids should not be given to critically ill patients who require parenteral nutrition during their first week of hospitalization

Weekly indirect calorimetry assessments

- For mechanically ventilated patients with FiO2 <60%, PEEP <10 mmHg, no leaky chest tubes or leaky endotracheal tubes, bronchopleural fistula, or renal replacement therapy within 12 hours and are receiving enteral or parenteral nutrition at goal rate

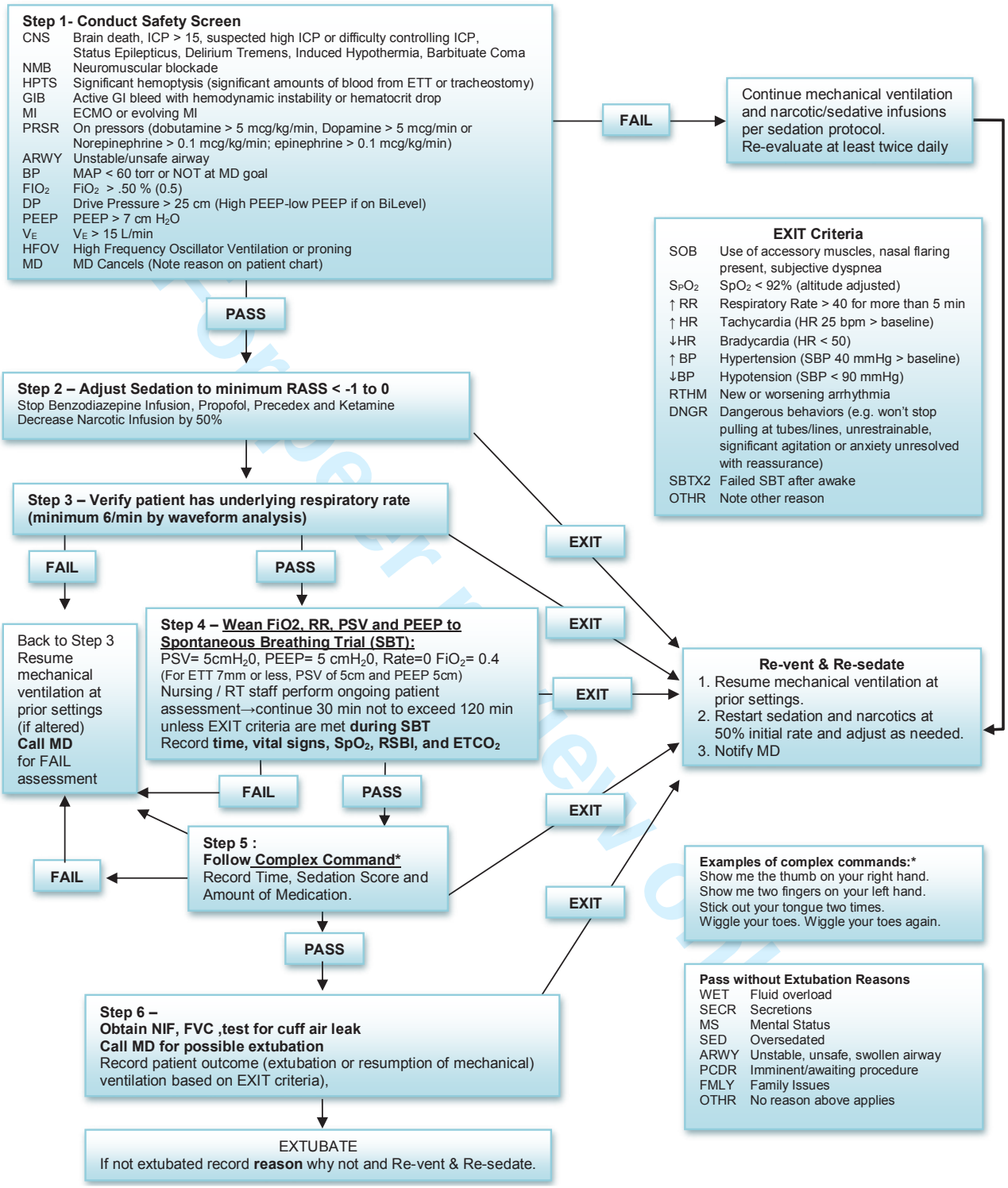
- Measure 24-hour urine urea nitrogen weekly for patients who are not receiving renal replacement therapy or diuresis

NPO: nothing by mouth, ICU: intensive care unit, FiO2: fraction of inspired oxygen, PEEP: positive end-expiratory pressure

Daily Wake Up Plus BEST

(Breathing to Extubate Spontaneous Trial)

(To occur for endotracheally intubated patients: 4E/4W between 0330-0430; MICU between 0800-0930)



Do not file in Medical Record after Discharge

Patient Name: Patient Identification #:

UFHealth SHANDS