

Protocolized Care for Early Septic Shock (ProCESS)

Summary

Objective and specific aims

The study objective is to improve the management of septic shock by exploring the clinical, biological, and economic aspects of alternative resuscitation strategies. This will be done by comparing two alternative resuscitation strategies, Early Goal Directed Therapy (EGDT) or Protocolized Standard Care (PSC), to usual care in subjects with septic shock.

Aim #1: To compare the clinical efficacy of alternative resuscitation strategies for septic shock

Aim #2: To better understand the mechanisms by which resuscitation strategies affect clinical outcomes.

Aim #3: To assess the costs and cost-effectiveness of the alternative resuscitation strategies.

Background and significance

Rivers et al¹ carried out a single-center randomized controlled trial (RCT) comparing usual care in the Emergency Department (ED) to protocolized resuscitation during the first 6 hours of management for subjects with suspected infection and shock (septic shock). Mortality was reduced from 46.5% in the usual care arm to 30.5% in the protocolized care arm. While these data are compelling, widespread adoption of protocolized resuscitation for septic shock would require a stark departure from current practice.

This proposal will provide new, important and comprehensive data on the clinical, biologic, and pragmatic aspects of a key therapy for a common and serious medical condition. Sepsis and septic shock affects over 750,000 people yearly in the U.S. and is the cause of death for 215,000. The findings will aid scientists, clinicians, families and policymakers and will immediately affect care of the critically ill. As the number of Americans dying with sepsis is similar to that of acute myocardial infarction, the proposed study has enormous implications for the public health of the country and is consistent with the recent NIH emphasis on translational research.

Research design and methods

ProCESS is a prospective, randomized, open-label, three-arm parallel-group trial of alternative resuscitation strategies for early septic shock, looking at not only clinical efficacy but biologic mechanisms and cost effectiveness. Data will be collected and analyzed on an intent-to-treat basis. The study will enroll 1935 subjects, with 645 subjects per treatment arm. Subjects will be randomized to receive one of two resuscitation protocols – EGDT (based on the Rivers protocol) or PSC, or will be randomized to usual care. The duration of the study is approximately 5 years with active enrollment and data collection for up to 2 ½ years.

The study will enroll 1935 subjects at approximately 19 hospitals during a 27 month enrollment period. The University of Pittsburgh will serve as the Coordinating Center.

The study population is expected to mirror the US adult sepsis population. Subjects will be enrolled without regard to race, sex or age.

Inclusion criteria: At least 18 years of age, suspected infection, two or more systemic inflammatory response syndrome (SIRS) criteria, and refractory hypotension (a systolic blood pressure <90 mmHg despite an IV fluid challenge of at least 20ml/kg over a 30 period (ideal body weight), or evidence of hypoperfusion (a blood lactate concentration \geq 4mmol/L).

Exclusion criteria: Known pregnancy; primary diagnosis of acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, major cardiac arrhythmia, active gastrointestinal hemorrhage, seizure, drug overdose, burn or trauma; requirement for immediate surgery; CD4 < 50/mm³; do-not-resuscitate status, advanced directives restricting implementation of the protocol; contraindication to central venous catheterization; contradiction to

blood transfusion (i.e. Jehovah's Witness); attending physician deems aggressive care unsuitable; participation in another interventional study; transferred from another in-hospital setting.

Study Treatment Arms

Early Goal Directed Therapy (EGDT) - The study team will insert a PreSep® central venous catheter (FDA approved and routinely used) to monitor the subject's blood pressure and blood oxygen. The study team will use this information to give fluid, blood and other medications in a structured fashion. At the end of 6 hours, the subject returns to standard care and continuous ScvO₂ monitoring is no longer mandated.

Protocolized Standard Care (PSC) - The study team will monitor blood pressure and blood oxygen with standard equipment. The study team will use this information to give fluid and medications in a structured fashion. Central lines will only be used when standard IV access is inadequate to give the proper amount of fluids and medicines. Blood transfusions will be given according to currently recommended guidelines. At the end of 6 hours, the subject returns to usual care.

Usual care - The attending physician(s) will treat the subject according to their standard treatment plan and without any influence from the study team. A member of the study team will simply observe and records what happens.

Other potential sepsis therapies

With regards to use of other potential sepsis therapies such as Xigris, steroids, and antibiotics; all sites support the recent international consensus statement on sepsis management, and appropriate use of these therapies is expected. However, the choice of these drugs will not be regulated by the protocol.

Study Procedures

Initial screening - Patients arriving in the ED will first be assessed by the clinical team. Should a patient be suspected of infection and occult shock, a blood lactate will be drawn (standard of care). For patients with suspected infection and overt hypotension, the clinical team will administer a fluid challenge of at least 20cc/kg to test for presence of refractory hypotension (standard of care). Diagnosis of suspected infection will be left to the discretion of the patient's attending physician.

Recruitment and consent procedures - All patients who enter the study site's ED with a diagnosis of severe sepsis will be approached about study participation. Each site will follow their IRB's guidelines regarding HIPAA authorization, informed consent (including those guiding the use of genetic material) and use of the *Emergency Research Consent Waiver*. Prior to obtaining consent (whether subject, proxy or waiver), all potential subjects will undergo standard of care management procedures.

Randomization and initiation of study - Each site's ProCESS Study Team will be led by a designated Principal ProCESS Trainer and a SC/nurse. The site SC (or other member of the study team) will assure that protocol-certified physicians and nurses (members of the study team) are available to perform the study interventions in the ED and the ICU, and will be responsible to assure that study required documentation of authorization and consent, or the Emergency Research Consent Waiver have been properly completed prior to enrollment in the study. Randomization will be 1:1:1 into each arm and will be done by computer via a web-based randomization system.

Once a treatment allocation is assigned, the site SC informs the clinical team (ED physician(s), nurse(s), and charge nurse). If assigned to usual care, no care changes are made. If assigned to either EGDT or PSC, the study team is informed, and the intervention begins, while the clinical team continues to provide all other aspects of care to the subject (i.e. admission, consults, etc. will remain the responsibility of the clinical team).

Protocol delivery - When a subject is assigned to either EGDT or PSC, the study team receives a packet of intervention materials. These will include the ScvO₂-capable CVC (when appropriate), an instruction sheet that outlines the protocol arm and a documentation forms (flowsheet). A similar documentation form, but without instructions or prompts, will be used by the site SC for subjects in the 'usual care' arm to ensure equivalent data collection. Initial measurements will be obtained and recorded. If a CVC is required (either assignment to EGDT or subject is judged to have inadequate peripheral access) the CVC will be inserted, connected to the appropriate monitor, and the initial measurements taken. These initial measures, together with other relevant clinical parameters, will trigger specific protocol instructions.

If transfer from the ED occurs within 6 hours, subjects will be admitted to the ICU and the protocol will continue. At the end of the 6-hour intervention, study devices will be removed to the extent possible. The CVC may be left in place, but the ScvO₂ monitor will be disconnected.

Data Collection, Storage and Analysis

Following recruitment of subjects meeting all study eligibility criteria, the site SC will enter subject information and receive from the randomization system a study ID # and treatment assignment. Baseline and follow-up clinical data will be collected and entered into the DCF described earlier. Each DCF will be identified by study ID number. Data will be entered by the site SC into a secure web-based data entry system and uploaded to the study database server via a secure internet connection.

Data management will be coordinated by the CRISMA Laboratory DCC at the University of Pittsburgh. The Data Coordinating Center will monitor enrollment, track follow-up rates, and perform routine data edit checks for consistency. Once edited, the DCC will merge temporary files to generate analysis files.

The primary analysis is an intent-to-treat analysis of hospital mortality with two interim analyses and a final analysis. The primary end-point is hospital mortality, defined as the rate (number of deaths) prior to discharge or 60 days, whichever comes first. Secondary end-points include: duration of survival and clinical evidence of organ dysfunction. Resource use end-points, such as hospital and ICU length of stay will also be considered.

The trial is designed to test the primary hypothesis: protocolized resuscitation is superior to usual care). If the null hypothesis is rejected (protocolized care is better), then hypothesis 2 (EGDT is superior to PSC) will be tested.

- 1). Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, for the Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-1377.