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IRB Proposal

A Protocol for Early Goal Directed Therapy in the Emergency Department: Can we change compliance?

Study Purpose and Rationale

The systemic inflammatory response syndrome (SIRS) is the systemic activation of the innate immune response that can be caused by a generalized infection, trauma, thermal injury or an inflammatory response (1). SIRS is classified in a patient that has more than one of the following: a body temperature, >38^{o}C or <36^{o}C; respiratory rate > 20 or $PaCO_2$ of <32mm Hg; and a white blood cell count of >12,000 cells µL or <4000 µL. When SIRS occurs secondary to an infection, it is known as sepsis (1). Sepsis can be a self-limited disease process with the appropriate treatment, however, it can progress to severe sepsis, septic shock and can eventually result in death if it is not treated appropriately (2).

Progression to severe sepsis and septic shock predicts an extremely poor outcome. An observational cohort study of 847 hospitals in seven states of patients with severe sepsis, found a mortality of 28.6%, with an average cost of $22,100 (in 2001), correlating to national estimates of 215,000 deaths annually and annual total cost of 16.7 billion dollars(3). Sepsis is a prolific problem that plagues hospitals with high costs, both financially and in terms of patient outcomes.

Early goal-directed therapy, characterized by early antibiotics(4,5) and aggressive volume resuscitation(2,6) based on hemodynamic and laboratory monitoring have become the mainstays of treatment for patients with sepsis. In a landmark study in the 2001 by Rivers et al., patients were assigned to early goal directed therapy (EGDT) consisting of central venous pressure (CVP) measurement and central venous O2 saturation monitoring as a means of guiding IV fluid volume repletion vs standard therapy as guided by the physician in the ED. Patients undergoing EGDT had a dramatic reduction in the in-hospital mortality and secondary markers of severity of illness. Other studies have demonstrated that antibiotic therapy is critical to survival for patients with sepsis, in a time dependent manner, with mortality increasing with every hour that passes without appropriate antibiotic therapy (4,5).

Despite the extensive evidence for EGDT and the guidelines from the Surviving Sepsis Campaign, hospitals still fail to initiate EGDT frequently(7-9), . There are multiple barriers of EGDT, including nursing knowledge, nurse staffing, feasibility of inserting a central venous catheter in the ED and monitoring CVP/SvO2 in the ED(7). In a recent analysis of 340 patients at

a premier academic hospital that had a sepsis protocol in place, EGDT was only initiated in 58% of patients who had severe sepsis(8,9). Other studies have demonstrated similar success rates after implementing EGDT protocols and additionally, these studies have reported dramatic reductions in mortality when the protocol was followed compared to when the protocol was not followed. (10,11).

The inability to translate evidence into practice is a challenge of modern medicine. Studies in critically ill patients have demonstrated that protocols and check lists, such as those for catheter insertion(12,13) and acute lung injury(14) improve patient centered outcomes. Currently, the Surviving Sepsis Campaign is attempting to follow this trend, and the 2008 guidelines recommend "the protocolized resuscitation of a patient with sepsis induced shock(6)."

At Columbia Presbyterian Medical Center, there is no Emergency Department €D protocol to facilitate the triage, recognition or treatment of patients with sepsis. The purpose of this study is to investigate the effectiveness of an EGDT protocol for severe sepsis in the ED at CPMC. Extensive evidence demonstrates that a protocol will improve compliance and patient outcomes. This study will investigate how often EGDT is achieved after a formal protocol is started in the ED

Objectives and Hypothesis:

Objective: To determine if a Sepsis protocol for Early Goal Directed Therapy implemented in the ED will increase the frequency that EGDT is initiated

Hypothesis: A sepsis Protocol for EGDT will increase the frequency that EGDT is initiated in the Emergency Department

Study Design:

Retrospective Cohort Study

Study Groups:

Eligible patients prior to the use of the EGDT Protocol (Cohort 1) and eligible patients after the implementation of the EGDT Protocol (Cohort 2)

Subject Selection:

Inclusion Criteria:

Patients must have sepsis defined as SIRS (at least 2/4 of temperature >38°C or <36.0°C; heart rate of >90 beats/min; respiratory rate of >20 breaths/min or $PaCO_2$ of <32 mm Hg; and WBC count of >12,000 cells/mL, <4000 cells/mL **AND** a documented infection.

AND

Patients must have SBP < 90 mmHg or a blood lactate of 4mmol or more

Exclusion Criteria:

Age less than 18 years old, pregnancy, emergent surgery, contraindication to central venous catheterization, do-not-resuscitate status, patient or proxy refusal of central venous catheter or advanced directives not allowing antibiotics or aggressive intravenous fluids.

Study Description:

Primary Outcome Variable

Placement of Central Venous Catheter with CVP measurement and/or SvO2 measurement within 6 hours of documented SBP <90 or lactate > 4mmol

Secondary Outcomes Variable

1) Proportion of Patients who received IV antibiotics within 6 hours of SBP < 90mmHg or lactate >4mmol
2) Proportion of patients who received IV antibiotics within 2 hours of SBP drop/lactate
3) Proportion of patients who have 2 recorded lactates within 3 hours of SBP drop/lactate
4) Blood Cultures prior to administration of Antibiotics
5) Time to Central venous catheter placement
6) Proportion of Patients with Effective Antimicrobial therapy
7) Time to IV Antibiotics
8) Total Volume Resuscitation within the first 6 hours
9) Blood pressure at 6 hours
10) In-hospital 30- day Mortality

This will be a retrospective cohort study evaluating patients who meet the clinical criteria for severe sepsis as explained by the pre-specified inclusion criteria above. Patients will be identified as potential candidates by reviewing admitting diagnosis for sepsis (including urosepsis), additionally, the charts of all patients admitted to MICU A, MICU B and the SICU will be reviewed for the inclusion and exclusion criteria. Vital signs in the ED will be used to classify

SIRS, Sepsis and the first documented SBP < 90mm Hg.

Intervention:

The intervention is the implementation of a protocol to provide clear guidance and instructions how to identify and treat a patient who has severe sepsis. The protocol has 3 parts: a protocol for the triage nurse; a protocol for the ED floor nurse; and a protocol for the MD.

Additionally, prior to implementation of the protocol, nursing staff, attendings and ED residents will require education regarding the importance of diagnosis and treatment of sepsis.

Please see Appendix A, B and C

Statistical Analysis:

A chi square analysis for categorical values comparing proportions (primary outcome) and an unpaired T-test to evaluate continuous data such as total volume resuscitation, time to antibiotics, blood pressure, and time to central venous catheter placement.

Sample Size:

The Power analysis was done to detect a 20% difference between the two cohorts for the primary outcome variable.

$N = 8 (p1q1 + p2q2)/ effect^2 + 2/effect + 2$

N= 108

Study Drugs: None

Medical Devices: None

Study Questionnaires: None

Confidentiality of Study Data:

Patients with be identified by a unique number which will be located on a secured file on a secured computer by the primary investigator of the study. Patient data will only be associated with the identifying number in all analysis. Patients will not be identified by name, address, or date of birth in any analyses or published reports.

Risks: The risk of this study is that the instituted protocols will diminish the frequency of EGDT in the ED, however, this is exceedingly unlikely and near impossible given the clinical data regarding protocol success. Additionally, the protocols merely explain early goal directed therapy and attendings/residents can opt not to continue with early goal directed therapy if they feel it is not clinically indicated.

The more substantial risk is to the other patients that arrive in the ED, this protocol forces a reallocation of resources to patients with sepsis or suspected sepsis and this will subtract from resources available to other patients. These risks can be minimized by the hiring of an extra RN per shift. The increase work load on the ED physicians can be offset by the early activation of ICU triage to help with care.

Benefit:

- Concrete Evidence that a protocol for EGDT in the ED will improve compliance with EGDT guidelines
- A protocol that demonstrates an improvement in EGDT compliance at a busy urban medical center will indicate that enacting EDGT protocol is possible at busy urban medical centers.
- Insight into improving Protocols for EGDT, specifically, the secondary outcome variables with reveal multiple areas for improvement in EGDT protocols

Confounding Variables/Bias:

The primary confounding variable is recall bias and identifying all the patients who might meet criteria for severe sepsis. A retrospective trial relying on admission diagnosis and MICU/SICU admissions will likely underestimate the number of patients who present to the hospital with severe sepsis. Additionally, after administration of the EGDT protocol, it will be significantly easier to identify persons at risk of sepsis and consequently there will likely be more persons identified with severe sepsis, this will likely make it more difficult to demonstrate increased compliance EGDT.

Why A Retrospective Trial? Why not a prospective trial?

The ideal study would be a randomized control trial of patients admitted with severe sepsis, however, this is unethical, because there is significant evidence available that suggests the superiority of using protocols for EGDT.

Another possible study would be a prospective cohort study of CPMC Emergency Department versus the Cornell Medical Center Emergency department. However, different physicians,

different nursing and different environments are too dissimilar to aptly compare the improvement of that occurs with the implementation of a protocol.

A retrospective protocol will offer the before and after perspective to demonstrate superiority of an Emergency Department EGDT protocol.

Appendix A

Triage Protocol

Does the patient have the following 3 of the following criteria?

[] Temp >38
[] HR>90
[] RR > 20
[] Altered Mental Status
[] O2 sat <90%
[] SBP < 90
[] Suspected Infection?

If 3 Criteria are met:

[] Notify clinician
[] Draw CBC
[] Draw BMP
[] Draw Lactate
[] Draw **Blood** cultures
[] Vital signs q1hr

* adapted from the NYC sepsis initiative http://nycsepsis.org

Appendix B

RN in ED

- Vital Signs q 1 hour
- Does SBP fall to < 90, MAP <65?
    - notify MD immediately
- Lactate result > 4
    - Notify MD immediately
- Place on continuous O2 monitoring
- Supplemental O2 for O2 saturation <90%

If SBP < 90, MAP <65 or Lactate >4, IV antibiotics within 1 hour of recorded BP/Lactate or Physician signature acknowledging no antibiotics

Appendix C

Sepsis Protocol for MD

SIRS criteria (HR>90, RR>20, PaCO2 <32, Temp >38 or <36 C, WBC <12,000 or <4,000

Does this patient have a suspected infection and meet the SIRS criteria? (2/4))

- If No -> continue ED therapy
- If Yes, continue with Protocl

Is the lactate > 4mmHg or SBP < 90 mmHg?

- If No -> continue ED therapy
- If Yes, **Begin Early Goal Directed Therapy**

PROTOCOL FOR Early Goal Directed Therapy for SEPTIC Patients

Initial resuscitation:

- Send Blood cultures
- Administer IV antibiotics immediately **within 1 hour of high lactate or hypotension**
- Bolus 20-30ml/kg of crystalloid Immediately over 20 minutes

Continued Resuscitation:

- Obtain repeat Lactate in 1 – 2 hours
- Place Central Venous Catheter to measure CVP, SvO2 to guide fluid resuscitation
- Resuscitation Goals
  - Goal SvO2 >70%
  - Goal CVP 8-12 mmHg
  - MAP > 65 mmHg and SBP >90 mmHg
  - Lactate Clearance >10% after fluid resuscitation
- Consider Measuring Dynamic US of IVC: Bolus IVF in 500-1000 mL until there is less <30% change in IVC with Inspiration
-

If Crystalloid IV fluid fails to maintain Resusitation Goals and Tissue Perfusion Goals:

- Consider transfusion (if Hb < 7) OR additional IVF OR Inotropes/vasoactive agents

* adapted from the NYC sepsis initiative http://nycsepsis.org

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