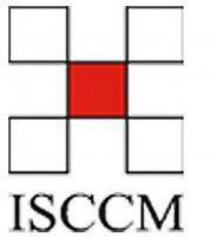
Study Protocol

HEmodynamic Resuscitation and Monitoring in Early Sepsis (HERMES Study)

An ISCCM research project



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INTRODUCTION

Septic shock is the most commonly occurring of all types of shock. (1) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defines septic shock as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%.

The "sepsis bundle" has been central to the implementation of the Surviving Sepsis Campaign (SSC) from the first publication of its evidence-based guidelines in 2004 through subsequent editions (2−7). Developed separately from the guidelines publication by the SSC, the bundles have been the cornerstone of sepsis quality improvement since 2005 (8−12). An updated version was published in 2016 "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock" (13, 14). There is compelling nature of the evidence in the literature which demonstrates an association between compliance with bundles and improved survival in patients with sepsis and septic shock. This has led to the adoption of the SSC measures by the National Quality Forum (NQF) and other departments (15, 16). The important relationship between the bundles and survival was confirmed in a publication from this initiative (17).

The Surviving Sepsis Campaign released an updated one-hour sepsis bundle, which combines recommendations listed in the three-hour and six-hour bundles. This includes 5 elements:
1. measuring lactate levels 2. obtaining blood cultures before administering antibiotics 3. administering broad-spectrum antibiotics 4. fluid resuscitation for hypotension or lactate level ≥ 4 mmol/L and 5. use of vasopressors for hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg.

Presently there is no data from Indian ICUs on the way patients in early sepsis are resuscitated and monitored. There may exist a wide variation in clinical practice. We would like to conduct an observational study in various levels of Indian ICUs, to prospectively collect data on adult patients admitted to ICU with early sepsis in a 60-day window period. We would like to study the hemodynamic resuscitation and monitoring performed in these patients. In addition, we would like to identify factors associated with improved outcomes and fulfilling the goals of the one hour SSC bundles in one, three and six hours in patients with sepsis and septic shock.

OBJECTIVES

- To capture the patient characteristics and hemodynamic resuscitation and monitoring practices in patients presenting with early sepsis and hypotension to Indian ICUs
- To determine various factors associated with improved survival in patients with sepsis and septic shock
- To determine factors associated with achieving the goals of the one hour SSC sepsis bundle in one, three and six hours in patients with sepsis and septic shock.

METHODS

Study design

Prospective observational multi–center national cohort study.

Patient Recruitment

ISCCM members across India will be contacted to register their ICUs in the study, through emails sent from the ISCCM Research committee. Repeated emails will be sent over a two-month period. Hospitals with more than one ICU can enroll each of their ICUs separately. Each ICU will need to contribute a minimum of 10 adult patients with sepsis and hypotension in a 60 day window period. Each center will designate a maximum of two local coordinators (PI and Co-PI) who will provide scientific and structural leadership in their centers. They will ensure that all local necessary ethical and regulatory approvals are obtained before the start of patient inclusion.

Local coordinators will guarantee the integrity of data collection and ensure timely completion of the case record forms.

Each center will select a start date anytime between **1st August to 1st October 2019** and will collect data within 60 days of the start date. The study will end anytime between **30th September and 29th November 2019,** depending on the start date. All consecutive patients in the 60-day period will be screened and those eligible will be enrolled.

Proposed Study Timelines

- First email invitation - **11th July 2019**
- Earliest date to start recruitment **-1st August 2019**
- Last date to start recruitment **- 1st October 2019**
- Window period **- 60 days from the start date of recruitment**
- Last date of recruitment – **29th November 2019**
- Data cleaning/analysis **- December 2019**
- Presentation to ISCCM Research committee – **January 2020**
- Presentation at CRITICARE 2020 – **February 2020**
- **Publication in 2020**

Inclusion criteria

1. Adult patients (≥ 18 years old)
2. Presenting to ICU with suspected sepsis
3. Presence of hypotension (Systolic BP ≤ 90 mmHg / Mean arterial pressure (MAP) ≤ 65mmhg or patient with Systolic BP > 90 mmHg / MAP >65mmHg on vasopressor.

Exclusion Criteria

1. Patient likely to be in shock due to reason other than sepsis (e.g. cardiogenic, hemorrhagic shock etc.)

2. Decision taken for not intubating / ventilating /aggressive resuscitation prior to ICU admission
3. Patient transferred from another ICU/ another hospital (admission >7 days)

Data Collection

There will be no direct patient contact or intervention. Local coordinators will guarantee the integrity of data collection and ensure timely completion of CRFs. Date related to the following will be collected prospectively from the charts:

1. Patient demographic data e.g. age, sex, comorbidities, likely source of sepsis
2. Total number of ICU patients, patients with sepsis and septic shock admitted to the ICU in the 60 days period
3. Patient clinical examination findings and severity of illness
4. Details of hemodynamic monitoring and other systemic monitoring and therapy performed in ICU e.g. fluid bolus, vasopressor agents, monitoring devices used, hemodynamic variables measured, mechanical ventilation, dialysis etc. in the first 3 days of ICU admission
5. Antibiotics administered and details of microbiology examinations
6. Adjunct therapies initiated for sepsis
7. ICU, hospital and 28-day mortality

Primary outcome

- ICU Mortality
- Completing the elements of the one hour SSC sepsis bundle in one 1 hour

Secondary outcomes

- Hospital mortality
- 28-day mortality
- Completing the elements of the one hour SSC sepsis bundle in one three hour

- Completing the elements of the one hour SSC sepsis bundle in six hour

Sample size

The primary endpoint of study was to determine the incidence of ICU mortality in patients with septic shock admitted to Indian ICUs. The sample size calculation was done on the basis of INDICAPS I Study data (IJCCM April 2016). In this study the ICU mortality incidence was found to be 45% in patients with septic shock. Assuming the incidence rate found in this study, a sample size of 401 produces a two-sided 95% confidence interval with a width equal to 0.100 when the sample proportion is 0.450. Sample size calculation was done using PASS software. To account for attrition, we will take a sample size of at least 450 patients. We plan to recruit 50 - 100 centers nationwide. Each center will be asked to collect data from at least 10 patients, hence we should be able to meet this target of >450 patients.

Statistical analysis

The primary objective of the study is to determine the patient characteristics and hemodynamic resuscitation and monitoring practices in patient presenting with early sepsis and hypotension to Indian ICUs which will be analyzed using descriptive statistics. To determine various factors associated with improved survival in patients with septic shock we will use the Fisher's exact test or Pearson's $\chi 2$ test. Univariable and Multivariable logistic regression models will be developed to assess the independent effects on ICU mortality. To determine factors associated with achieving the 1 hour SSC Sepsis resuscitation bundle in 1 hour, 3 hours and 6-hours in patients with sepsis and septic shock will be assessed by Fisher's exact test or Pearson's $\chi 2$ test. Univariable and Multivariable logistic regression models will be developed to assess the independent effects on ICU mortality of the 1 hour, 3 hour and 6-hour resuscitation goals of the sepsis bundle in patients with sepsis and septic shock. The overall performance of the internally validated model will be assessed using Nagelkerke's R2. The higher Nagelkerke's R2, the greater the strength of the model. The ability of the models to identify ICU mortality will be quantified as the area under the receiver operating characteristic curve (AUC). The AUC ranges from 50% to 100%, indicating no discriminative capacity to perfect discriminative capacity. The agreement

between predicted probabilities and observed frequencies of the outcome will be assessed by visually inspecting the calibration plot. Last, the Hosmer and Lemeshow goodness-of-fit statistic will be computed as a quantitative measure of accuracy. A high outcome of this statistic is related to a low p-value, which indicates a poor fit. All analysis will two sided, and significance will set at a p-value of 0.05. Statistical analyses will be performed using SPSS (the statistical package for social sciences) IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp and R studio (version 1.2).

STUDY REGISTRATION

The Principle Investigator (PI) will register the study on **clinical trials.gov** on behalf of all the investigators. The registration number will be provided to all investigators as soon as it is available.

INSTITUTIONAL ETHICS COMMITTEE (IEC) APPROVAL

The local hospital investigators should ensure that all necessary local ethical and regulatory approvals are obtained if required, before the start of the study in their institution

CONSENT FOR DATA COLLECTION

This is an observational study and involves capture of data from the patient charts. There is no direct patient contact or intervention, hence written, informed consent is not mandatory. However, if required by the institution, consent may be taken from the patients legally accepted representative (LAR). Sample short consent forms for patient data capture will be provided by the PI in English, Hindi and Marathi. This may be translated in various regional languages as required by the local investigator

STUDY FUNDING

This is an ISCCM Research Committee funded study. The ISCCM will fund the PI institution for all expenses related software development, website hosting, secretarial assistance and miscellaneous expenses related to the conduct of the study, data analysis and publication (against actual bills). No funding will be given to the investigators from the various participating centres for contributing data.

DATA STORAGE AND OWNERSHIP

The PI will have ownership of the data. The data will be stored in the PIs department at Tata Memorial Hospital, Mumbai for 10 years.

PUBLICATION AND AUTHORSHIP POLICY

The main results of study will be published in a peer–reviewed medical journal.
Authorship policy will follow the International Committee of Medical Journal Editors (ICMJE) recommendations. Authorship will be considered based on contributions the study design and protocol development, recruitment of patients, data acquisition and cleaning, analysis and interpretation of the data, manuscript writing AND final approval of the version to be published AND agreement to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Steering Committee - Members of the Steering Committee will include 7 members from the PIs center, 8 -10 experts from across the country and PIs from the top 3 centers with highest number of patient recruitment. The members of the steering committee will be on the main author list.

The PI and Co PI from each participating ICU will be in the list of study collaborators and their names will be in the publication. **The names of all the investigators will be indexed in PubMed.**

SECONDARY ANALYSES

After publication of the primary results, on request, the pooled dataset will be available for investigators for secondary analysis, after judgment and approval of scientific quality and validity by the steering committee. Before submission, the final version of all manuscripts related to the study dataset must be approved by the steering committee. The members of the writing committee will be authors of the publications derived from the study dataset.

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