IMPRESS

INTERNATIONAL MULTICENTRE PREVALENCE STUDY ON SEPSIS

Surviving Sepsis Campaign

An International Multicentre Prevalence Study on Sepsis.

Project Protocol

Table of Contents

1. Trial Coordination and Management

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2. Introduction

2.1. The Surviving Sepsis Campaign

As the Surviving Sepsis Campaign marks 10 years of progress with the publication of the third edition of its "International Guidelines for Management of Severe Sepsis and Septic Shock," we are gratified to reflect on what has been achieved through committed participation in the Campaign by clinicians worldwide. Despite these achievements, sepsis remains a disorder of epidemic incidence and severe consequences with an unacceptably high death rate and devastating long-term effects (1-2). Application of sepsis care bundles has reduced mortality in hospitals that signed up to the Surviving Sepsis Campaign, but the number of hospitals involved has remained low. We also recognize the possibility that the guidelines may not be applicable for those patients whose care is delivered in under-resourced environments. We are, therefore, compelled to delineate new steps that will save many more lives.

The original goal of the Campaign was to reduce mortality from severe sepsis and septic shock by 25%. Activities toward this goal included:

- Developing evidence-based guidelines for appropriate care
- Improving diagnosis
- Educating healthcare professionals
- Increasing the use of appropriate treatment
- Building awareness of sepsis

The Campaign proceeded in three phases:

Phase I: Introduction of the Campaign--Following the announcement of the target in 2002, awareness of the incidence and prevalence of the condition became heightened. Although clinicians were more attuned to the signs of sepsis, a need to enhance the recognition among patients and their families was observed (3).

Phase II: Publication of the Guidelines--In June 2003, representatives from 11 international societies convened to develop an evidence-based set of guidelines for the management of severe sepsis and septic shock. With publication of this document in 2004 (4), the Campaign initiated an educational effort to disseminate the knowledge and recommendations widely. An updated set of guidelines,

published in 2008, was sponsored by 26 professional societies (5). The current, third, edition, which reflects the latest evidence related to sepsis treatment and involves 30 organizations, appears in the February 2013 issues of *Critical Care Medicine* and *Intensive Care Medicine* (6). The Surviving Sepsis Campaign Guidelines have become the gold standard for sepsis care as they are incorporated into hospital protocols and regulatory mandates internationally.

Phase III: Guideline Implementation, Data Collection, and Behavior Change-- Drawing on the expertise in quality improvement gained through partnering with the Institute for Healthcare Improvement, we constructed the Surviving Sepsis Campaign Care Bundles from key guideline recommendations. Subsequent development and distribution of a data collection tool along with a website, online discussion forum, implementation manual, newsletter, and a series of educational meetings enabled local and regional networks of hospitals worldwide to document and improve performance.

The Significant Results

A recent analysis of more than 25,000 patient charts from 186 hospitals over a 5-year period confirms the initial statement that ongoing hospital participation in the Campaign is associated with continuous quality improvement and a sustained, linear decrease in mortality (7,8). Despite the evidence demonstrating the value of using performance metrics for maintaining standards of care for the management of sepsis, marked differences remain between hospitals in the delivery of care for septic patients (9). Published data clearly show that delays in the recognition and treatment of sepsis are associated with worse outcomes while early treatment improves survival (10). Reviewing the inconsistent application of measures identifies an important opportunity to reduce sepsis-induced mortality further. In particular, earlier identification of patients who develop sepsis on the wards and improvements in the timely application of evidence-based, validated therapies represents a unique opportunity to save additional lives.

Future Needs

Despite the successes, it is recognized that the penetration of the campaign to hospitals around the world and the patients they treat is not good. To inform current and future quality improvement efforts in sepsis globally, there is a need to better understand how patients presenting with severe sepsis are treated, how the individual elements of the evidence-based Surviving Sepsis Campaign bundles are used in different geographic areas and how these may relate to outcome. A critical step in quality improvement efforts is a thorough assessment of current practice in order to identify ongoing gaps in clinical practice. This project is designed to address this need.

2.2. Project Aims

1. Establish an estimate of the global burden of sepsis by determining the prevalence of sepsis, severe sepsis and septic shock throughout the world presenting to critical care units
2. Assess practice gaps in care of patients with sepsis by measuring compliance with SSC sepsis guidelines and bundles in sites in both community and academic hospitals internationally.
3. To evaluate the impact of sepsis, severe sepsis and septic shock on outcome
4. Estimate sample size requirements to detect meaningful differences in patient-centered outcomes for clinical trials performed in a large, international research network.

2.3. Rationale

Previously collected data on sepsis and septic shock is now old (11,12) and with recent changes in clinical practice together with the impact of the SSC, the data needs updating. Identification of practice gaps in sepsis care will inform current and future quality improvement initiatives globally.

3. Methods

A prospective, observational, quality improvement project of the prevalence of patients presenting to intensive care with either severe sepsis or septic shock and compliance with evidence-based practices.

3.1. Inclusion criteria

For the study day (00^{00} to 24^{00}), consecutive patients presenting to either the emergency department (ED) or ICUs (either intermediate care or intensive care) with severe sepsis or septic shock in participating sites will be enrolled. To be eligible patients must have all of the following:

1. Must be admitted or transferred to either the ED or an Intensive Care Unit.
2. Have a high clinical suspicion of an infection
3. Have sepsis as defined by
    a. An infection together with two or more SIRS criteria
4. Evidence of acute organ dysfunction and / or shock

3.2. Exclusion criteria

The following will be excluded:

1. Patients less than 18 years of age
2. Patients in whom the sepsis has been present from before the beginning of the study period
3. Any patients previously included in the study during the same study period

3.3. Centres

This international quality improvement project aims to recruit as many centres as possible.

For this study a network of coordinators will be identified. It will be the task of this group of individuals to enrol sites within their own country, to ensure the necessary regulatory approvals are in place and to coordinate the local communication.

3.4. Ethics/IRB review

Ethics or IRB approval may not be required in all participating nations or sites. Centres will not be permitted to record data unless ethics approval or an equivalent waiver is in place. Each individual site is responsible for appropriate materials for Ethics Board or IRB review. This quality improvement initiative is in effect a large-scale clinical audit.

3.5. Data collection and collation

Data will be collected in the intensive care unit and also in the ED. Any patient will only be included in the study once (therefore if the patient is admitted through the ED to the ITU, only one case report form (CRF) will be completed).

A local site investigator will enter relevant de-identified patient-specific data into an online electronic case report form (eCRF). No identifiable data will be submitted to the online database housed on a secure server in Germany. Data will be published in aggregated form only.

Data will be collected in individual centres on paper case record forms (CRFs) or directly into the web-based electronic case report form. Upon entry into the eCRF, each patient will be assigned a unique study identifier. Local sites will maintain a link between the unique study identifier and the patient for 30 days in order complete outcome follow up. This link kept secure at each site, will not be submitted

or transmitted online, and will be destroyed immediately upon project completion. Access to the data entry system will be protected by username and password. Username and password will be delivered during the registration process for individual local investigators. All electronic data transfer between participating centres and the co-ordinating centre will be username and password protected. Each centre will maintain a project file including a protocol, local investigator delegation log, ethics approval documentation and other documents as appropriate.

De-identified data sent via HTTPS (with SSL) to the server. A specific SSL certificate will be enabled for this quality improvement project. No identifiable patient data will be transmitted. During the registration process, system prompts to investigators name, surname and the CRN. With this data, the system generates a key (HASH) random. The system server is hosted at 1and1 (Germany).

3.6. Dataset

A realistic data set will be fundamental to the success of the investigation. We have identified the key data points whilst not discouraging centres from participating through an excessive burden of data collection. The reliability of data collection will be analysed formally using K-statistics or intra-class correlation coefficients as appropriate.

3.7. Statistical analysis

The data to be collected are all collected as part of routine clinical care. Categorical variables will be described as proportions and will be compared using chi-square or Fisher's exact test. Continuous variable will be described as mean and standard deviation if normally distributed or median and inter-quartile range if not normally distributed. Comparisons of continuous variables will be performed using one-way ANOVA or Mann-Whitney test as appropriate. A logistic regression model will be performed to assess independent association between prognostic factors and outcomes. Significance will be set at $p<0.05$. A single final analysis is planned at the end of the study.

3.8. Sample size analysis

For this prospective study we would aim to enrol as many patients as possible within the 24-hour study period.

3.9. Study timeline

Timeline for the main steps of the study are described below

- June 6th, 2013: Identification of Steering Committee
- June 6th, 2013: Political (ESICM and SCCM) sign off of study
- July 15, 2013: Protocol completion
- July 15th, 2013: Finalization of CRF variables
- July 15, 2013: Commencement of eCRF programming
- August, 2013: Start of centre recruitment
- November 7th, 2013: Study day

3.10. Organisation

The project will be led by a steering committee (TSC) on behalf of the Surviving Sepsis Campaign. The TSC will be responsible for project completion. The duties of this team will include administration of all project tasks, communication between project partners (including funders, steering committee members, national and local co-ordinators, etc), data collation and management. The TSC is responsible for the scientific conduct and consistency of the project. The TSC will ensure communication between the study management team and co-ordinators as necessary.

3.11. National / Local co-ordinators

National / Local co-ordinators will be appointed by the TSC to lead the project within individual nations and to:

- Identify local co-ordinators in participating hospitals
- Assist with translation of project paperwork as required
- Ensure distribution of the project protocol, eCRF and other materials
- Ensure necessary regulatory approvals are in place and are followed prior to the start date
- Ensure good communication with the participating sites in his/her nation
- Ensure that all regulatory paperwork is sent to TSC.

3.12. Local co-ordinators

Local co-ordinators in individual institutions will have the following responsibilities:

- Provide leadership for the project in their institution
- Ensure all relevant regulatory approvals are in place for their institution
- Ensure adequate training of all relevant staff prior to data collection
- Supervise daily data collection and assist with problem solving
- Act as guarantor for the integrity and quality of data collected
- Ensure timely completion of eCRFs
- Communicate with the relevant national coordinator

3.13. Data management and ownership

On behalf of the TSC, the ESICM will act as custodian of the data. The TSC will take responsibility for the content and integrity of any data.

The TSC will retain the right to use all pooled data for scientific and other purposes. Only summary data will be presented publicly.

3.14. Publication plan

Data will be presented and disseminated in a timely manner. The TSC will appoint a writing committee to draft the scientific report(s) of this project. All participating centres will have their efforts recognized by the lead investigator being labelled as a 'collaborator' in the authorship of the paper and thus listed in PubMed.

3.15. Deliverables

The main deliverables will be scientific reports of preliminary findings for general and specialty journals and abstracts for presentation to national and international meetings.

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