**Title**: SEP-1 Bundle Compliance and Clinical Outcomes Among Patients with Sepsis: A Systematic Review

**Anticipated Start Date:** October 18, 2023

**Revised Anticipated Completion Date:** November 14, 2024

**Stage of Review at time of initial submission:** Preliminary searches complete

**Stage of Review at time of this protocol update:** Review complete, submitted for publication

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**Funding Sources/Sponsors** – None

**Collaborators:** None

**Conflicts of Interest** - None

**Review Question:** Is there any moderate or high-level evidence to suggest that SEP-1 bundle compliance *or* SEP-1 implementation was associated with an improvement in sepsis mortality.

**Data Sources:** Pubmed, Web of Science, Embase, CINAHL, Cochrane from 1 Jan 2015 to 13 November 2023 with no language restrictions

**Search Strategy (**Will upload as separate document)
Prepared in collaboration with a UCSF librarian who is part of the research team.

Example below:

**PubMed:**
("sepsis" OR "Sepsis"[Mesh] OR "severe sepsis" OR "septic shock" OR "Shock, Septic"[Mesh]) AND ("early goal-directed therapy" OR "EGDT" OR "serial lactate" OR "30 cc/kg" OR "serial lactate" OR "30 ml/kg" OR "Sepsis Bundle" OR "SEP-1" OR "SEP-1 bundle" OR "surviving sepsis" OR "Patient Care Bundles"[Mesh] OR "patient care bundles")

**Condition or domain being studied:**

Sepsis remains a focal point of public health research and intervention, because of its exceptionally high prevalence and mortality. Large, prospective studies and meta-analyses from various global regions have demonstrated a mortality between 18-35%.[1-4] In 2015, the Centers for Medicare and Medicaid Services (CMS) implemented the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1).[5] The SEP-1 bundle was comprised of three core components for all patients (measuring the lactate level, obtaining blood cultures prior to administration of antibiotics and administration of antibiotics) in all patients, as well as additional components for patients with signs of shock (hypotension or initial lactate levels ≥4mmol/L).[6] In 2018, CMS updated SEP-1 to recommend a 30cc/kg IVF bolus among patients with severe sepsis who were hypotensive at anytime. SEP-1 is accompanied by a litany of administrative tasks and documentation requirements that can take as long as 3 hours for clinicians to satisfy.[7] Because of its cumbersome documentation requirements, the SEP-1 has been heavily scrutinized, and legitimate questions remain as to whether this administrative burden is justified by improvement in clinical outcomes. For many patients with sepsis, their care will begin in the emergency department (ED), and decisions have momentum, often dictating how continuity of care once patients are admitted and there is some evidence that some components of the SEP-1 bundle may do harm, particularly when prescribed generically across large populations.[7] Finally, CMS has announced that it plans to include SEP-1 as a pay-for-performance measure by incorporating it into the Hospital Value-Based Purchasing Program. Hence, assessing the clinical impact of complying with the SEP-1 bundle in the ED is of utmost clinical, administrative and economic importance.

**OBJECTIVES**

1. To assess whether SEP-1 bundle compliance is associated with an improvement in mortality
2. To assess whether SEP-1 bundle implementation is associated with an improvement in mortality

**Participants/Population:**
We will include adults (at least 18 years old) requiring early management (within 6 hours of presentation) of sepsis, severe sepsis or septic shock. The definitions of sepsis, severe sepsis and septic shock for each study will be recorded. Each study must include at least one intervention and one control group, and outcome of interest (see below). The control group will be those that do not receive the intervention or those that receive usual care.

**Intervention or Exposure:**

**- Compliance Aim:** Completion of entire SEP-1 Bundle
- **Implementation Aim**: Post-SEP-1 bundle implementation period

| **3-Hour Bundle** |
|---|
| **1.** Lactate drawn<br>**2.** Blood cultures drawn before antibiotics administered<br>**3.** Broad spectrum antibiotics administered<br>**4.** 30ml/kg IV fluid bolus (if hypotensive or lactate ≥ 4mmol/L) |
| **6-Hour Bundle** |
| 1. **R**epeat lactate (if initial lactate ≥ 2mmol/L)<br>**If septic shock present:**<br>2. Vasopressors (if still hypotensive after 30ml/kg intravenous fluids)<br>3. Volume status and tissue perfusion reassessment (physical exam, cardiac ultrasound, passive leg raise, etc.) |

**Comparator**
- Compliance Aim: Incomplete SEP-1 Bundle
- Implementation Aim: Pre-SEP-1 bundle implementation period

**Types of Studies:** Randomized control trials, cohort studies, case-control studies, quasi-experimental studies (before and after), time-series studies

**Context:** Studies related to sepsis in hospital emergency departments, inpatient wards or intensive care units

**Inclusion criteria:**
- Studies of adults ≥18 years with sepsis
- The following study designs: randomized control trials, cohort studies, case-control studies, quasi-experimental studies (before and after), time series studies

**Exclusion criteria:**
- Studies of adults <18 years with hospital acquired sepsis or those who are already admitted to an inpatient service
- The following study designs: case series, case reports, expert opinion

**Main Outcome:** Hospital survival (or 30-day or 60-day or 90-day or ICU survival, prioritized in that order).

**Measures of Effect for Main Outcome:**

The primary outcome was mortality. There was considerable heterogeneity with regards to which mortality outcome was reported (i.e. in-hospital mortality, 28-day mortality etc.), which measure of association was reported (i.e. odds ratio, risk ratio), and whether the measure of association

was unadjusted or adjusted. Thus, we present the outcome and measure of associations reported by each study, without standardization. When unadjusted differences in mortality were the only measure of association reported, we manually calculated the corresponding 95% confidence interval, to help define the precision of the estimate of effect.

**Additional Outcomes:** We did not systematically assess additional outcomes

**Measures of Effect for Additional Outcomes:** mean difference (95% CI)

**Selection of Studies**

- **Citation Management Process:** I will download citations from each database and upload into Covidence a systematic review management software. This will allow me to easily remove duplicates.
- **Study Selection Process:** Once duplicates are removed, I will use the inclusion/exclusion criteria as above, modeled after the PICO framework, to select studies. I will use two reviewers working independently. Each reviewer will receive titles, abstracts and keywords of remaining records and provide provisional "yes" or no" for inclusion. Reviewers will then meet to compare results and discuss results that are discordant and come to a consensus about which ones to include. A third "tie-breaker" individual will be use when consensus is not possible. Then reviewers will review full text articles independently using the inclusion/exclusion criteria, and provide a "yes" or "no". Reviewers will meet about which articles to include, as above. All studies that are excluded will have a reason listed by each reviewer. This whole process can be expeditiously performed and tracked with active record keeping, in Covidence.

**Data Standardization:**

I will use the following data standardization

- Intervention: Those who received the complete SEP-1 bundle (yes/no)
- Outcomes:
    - Death at 30 days
    - Hospital length of stay (days)

**Data Extraction**

Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) will be used to manage the systematic review. A standardized form will be made for data abstraction. I will extract data related to the following categories and key words: the name of the first author; publication year; country; study design; sample size; study period; mean age of study population; male percentage; sepsis definition; infection site (pulmonary, urinary tract, or soft tissue); severity of illness (e.g. APACHE, SAP scores); comorbid illnesses (e.g. diabetes, COPD, cancer, immunodeficiency) and lifestyle factors (e.g. drug, ethanol use); study setting (i.e. emergency department, intensive care unit or hospital ward); inclusion of the performance measure interventions either individually or in a bundle; type of control group not receiving the intervention; time from presentation of sepsis to when the interventions were performed; survival; length of hospitalization; development of organ injury and costs of care. When the report has only one outcome, we will contact the authors for other outcome data.

## Risk of Bias (Quality) Assessment

Two, paired, independent reviewers will assess publications selected for potential risk of bias. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

To assess risk-of-bias in observational studies, we will use the Newcastle-Ottawa Scale. This tool uses an 8-point criteria list that assesses issues with participant selection, comparability of participants, and assessment of exposure or outcome.

To assess risk-of-bias in RCTs, we will use the Revised Cochrane risk-of-bias tool for randomized trials (RoB-2). This tool gives an overall risk assessment (low, high, some concerns), after considering risk of bias arising from randomization, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result.

## Strategy for Data Synthesis and Analysis

We will rate overall certainty of evidence for each outcome of interest using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria, which incorporates risk-of-bias, imprecision, inconsistency, indirectness and publication bias.

In addition to using GRADE, we also used the National Quality Forum's (NQF) system for evaluating process measures.

For imprecision, we will rate down when the 95% CI of the pooled point estimate crosses the threshold of no effect, or, if when the pooled point estimate is close to the null, the corresponding 95% CI spans more than 0.5% (binary outcome: mortality) or more than one day (continuous outcome: hospital LOS).

We will group studies by study design (randomized controlled trial vs. observational study). For each group, the study characteristics (including their specific study design, study details and a description of the number and characteristics of the study participants included) will be presented in summary tables. We will perform separate subgroup analyses for each study design, bundle/intervention if sufficient numbers of studies are available. Otherwise, an attempt will be made to model the effect of each intervention if we can reasonably assume their effects are additive. Odds ratios [OR] of mortality will be analyzed using random-effects models. Heterogeneity among studies will be assessed statistically using the standard Q statistic and I-squared values. Subgroup analyses based on different study designs and/or patient characteristics (e.g. age, severity of illness, co-morbidities, etc.) and/or quality of study evidence, will be performed if appropriate. Publication bias will be assessed by funnel plot and Egger's regression. All analyses will be performed using Stata 17.0.

## Analysis of subgroups or subsets

We will conduct subgroup analyses based on study designs and/or patient characteristics (e.g. severity of illness, co-morbidities, etc.), if appropriate. We will also consider subgroup analyses by quality of evidence (very low, low, moderate, high).

**Dealing with Missing Data:**

I will search for other reports from the same study or group to see if it has been previously published in both the regular databases and the grey literature. If not, we will contact the authors for the information needed.

**DECLARATION OF INTERESTS**: The authors have no conflicts of interest to disclose

**APPENDICES**: none

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