Does the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) Improve Survival in Septic Adults?

TAKE-HOME MESSAGE

No high- or moderate-level evidence shows that the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) hemodynamic interventions improve survival in sepsis.

METHODS

DATA SOURCES

The authors searched PubMed, EMBASE, Scopus, Web of Science, and ClinicalTrials.gov without language restrictions from inception to November 28, 2017. They also searched the references of analyzed studies and other review articles.

STUDY SELECTION

Investigators included randomized trials and observation studies of patients aged 16 years or older with sepsis, severe sepsis, and septic shock that compared mortality rates in patients receiving versus not receiving one or more of the following SEP-1 interventions: serial lactate measurements, a crystalloid infusion of 30 mL/kg, or assessment of volume status and tissue perfusion. Studies of central venous pressure and $ScvO_2$ measurements were excluded, as were those that did not include a usual care control group. Nonrandomized observational studies were included only if they had a before-after or a concurrent control design.

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Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Pepper DJ, Jaswal D, Sun J, et al. Evidence underpinning the US government–mandated hemodynamic interventions for sepsis: a systematic review. *Ann Intern Med.* 2018;168:558-568.**

Results

Summary of included studies.

What Studies Involved	No. of Studies	Intervention		Control	
		Survivors	Total	Survivors	Total
Serial lactate measurements	5	393	512	395	648
Fluid infusion of 30 mL/kg	7	3,607	4,411	8,676	11,251
Serial lactate measurements and fluid infusion of 30 mL/kg	4	6,208	7,099	5,632	6,752
Assessing fluid responsiveness	3	99	109	102	111
Assessing SEP-1	1	94	110	35	48

After screening of 56,563 references, 18 reports representing 20 studies met inclusion criteria and compared survival in septic patients receiving one or more of the SEP-1 interventions versus a control group. Meta-analysis was not performed because of the large heterogeneity between included studies.

DATA EXTRACTION AND ANALYSIS

Two authors extracted data with a standardized tool, with a third author checking the extracted data for accuracy. Data extracted included time from admission to intervention, proportion of patients receiving the intervention, measured level (if the intervention was a measurement), amount administered (if the intervention was a treatment), and bundle composition and administration. For each study, the authors examined the appropriateness and timeliness of antibiotic administrations between control and intervention groups and whether adjunctive aids were administered. The primary outcome was mortality, reported as the relative risk or odds ratio of death. Authors assessed risk of bias with the Cochrane Risk of Bias Tool[1] and the Newcastle-Ottawa Scale.[2] All components of either tool had to be graded low risk of bias for the study to be rated low risk overall.

Of the 16 studies that investigated serial lactate measurements, a fluid infusion of 30 mL/kg, or both, all reported improved survival, with the results of 10 of them reaching statistical significance. In the studies that provided data on antibiotic administration, antibiotics were administered more quickly in all cases, but timing and significance of choice of antibiotics were not stated in the systematic review. Only one observational study assessed the SEP-1 bundle in its entirety and found no improvement in survival. Serial lactate measurements from 2 randomized controlled trials and 7 observational studies were associated with improved odds of survival but were of low quality because of bias. Fluid infusion of 30 mL/kg from 11 observational studies was also associated with improved survival. None of the 3 randomized controlled trials investigating fluid responsiveness (a stroke volume increase of 15% after administration of 500 mL of crystalloid fluids) showed improved survival and the risk of bias was not analyzed in these studies because there was no evidence of increase in survival. All remaining studies had significant confounders, creating a high risk of bias. Per guidelines published by the Centers for Medicare & Medicaid Services (CMS), all included articles are considered to have low-level evidence.

Commentary

Despite many advances in health care, sepsis remains a major contributor to morbidity and mortality in the United States. The CMS sepsis bundle was the first national quality initiative requiring coordination between multiple providers and an overall team-based approach to sepsis management.[3,4] Although this policy is motivated by a laudable goal, no high- or moderate-level evidence has been produced supporting this initiative, triggering this systematic review. After review of available studies using CMS's grading criteria, only low-level evidence was found to support a survival benefit when certain elements of SEP-1 were implemented. These articles were noted to be at high risk of bias and lack appropriate controls.

There are multiple challenges and concerns when protocols for sepsis care are implemented, including the ambiguous definition of sepsis, unknown safety profiles of interventions, and limited structure on how to incorporate clinical judgment. Sepsis is a complex disease state with significant biological and clinical heterogeneity between patients. During the past several decades, the definition of sepsis, severe sepsis, and septic shock has been heavily debated, and having one definition for sepsis can lead to misclassification of disease processes.[3,5] Even if sepsis is correctly identified, the unknown safety index of CMS's mandated interventions poses another problem with SEP-1. CMS's time-sensitive protocol can result in clinicians' administering unwarranted treatments, with potential negative ramifications. We know that early antibiotics decrease mortality in patients with sepsis, but unnecessary antibiotics can be harmful; for example, leading to increased rates of *Clostridium difficile*.[6] Because the standard fluid bolus of 30 mL/kg in this bundle is not adjusted on comorbidities, this volume can cause harm to patients with congestive heart failure, chronic kidney disease, and chronic liver disease.[3,5] Clinicians should be able to titrate the resuscitation by patient and allow for deviation in the setting of well-documented clinical judgment. A one-size-fits-all approach for diagnosis and treatment places constraints on clinicians and forces them to do what may not be considered best practice instead of instituting their clinical judgment.[4]

Logistically, SEP-1 is a complicated measurement tool associated with a high reporting burden. It requires manual chart abstraction, with

each case taking an average of 1 to 2 hours for review. This requirement promotes a focus on high-quality documentation rather than high-quality care.[4] Although CMS's initiative was aimed to decrease the morbidity and mortality associated with sepsis, no high- or moderate-level evidence exists that demonstrates that the measures accomplish that objective. Bundled care may have a place in the management of septic patients, but CMS's SEP-1 should be a clinical tool that is used as an adjunct to clinical judgment.[7]

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