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Use of the Sepsis Bundle in Hospital-Onset and Community-Onset Sepsis and Effects of Lack of Insurance in Community-Onset Sepsis

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Use of the Sepsis Bundle in Hospital-Onset and Community-Onset Sepsis and Effects of Lack of Insurance in Community-Onset Sepsis

A dissertation submitted in partial satisfaction of the

Requirements for the degree of Doctor of Philosophy

in Health Policy and Management

by

Jonathan Baghdadi

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ABSTRACT OF THE DISSERTATION

Use of the Sepsis Bundle in
Hospital-Onset and Community-Onset Sepsis
and Effects of Lack of Insurance
in Community-Onset Sepsis

by

Jonathan Baghdadi
Doctor of Philosophy in Health Policy and Management
University of California, Los Angeles, 2019
Professors Robert Brook, Co-Chair
Professor Jack Needleman, Co-Chair

Problem: Hospital-onset sepsis is understudied and was not considered in the development and implementation of Centers for Medicare and Medicaid Services (CMMS) core quality measure related to sepsis, SEP-1.

Methods: Samples of patients with sepsis were identified by diagnosis codes from the electronic health records of 4 university hospitals and publicly available administrative data from the California Department of Public Health. Multilevel models with random effects were used to

evaluate for an association between risk factors and outcomes of interest. Endogenous treatment effects models were used to estimate treatment effects from observational data.

Findings: Providers are about 3-times less likely to deliver SEP-1-adherent care for patients with hospital-onset sepsis than patients with community-onset sepsis. The care bundle outlined in SEP-1 was not associated with a treatment benefit (reduced mortality, decreased requirement for vasopressors) in the total sample of eligible patients, in the cohort with community-onset sepsis, or in the cohort with hospital-onset sepsis. However, multiple components of the bundle appeared to improve outcomes in patients with community-onset sepsis. Only the use of antibiotics was associated with reduced mortality in patients with hospital-onset sepsis.

Meaning: Hospital-onset and community-onset sepsis are distinct clinical entities—they are managed differently by providers and respond differently to SEP-1-adherent care. Low levels of adherence to the SEP-1 core quality measure for patients with hospital-onset sepsis may not represent a quality gap. Rather, consideration should be given to excluding patients with hospital-onset sepsis from the core quality measure.

The dissertation of Jonathan Baghdadi is approved.

Mitchell Wong

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2019

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CHAPTER 1. INTRODUCTION

Overview

Sepsis is among the most common reasons for hospitalization in the US and is the leading cause of death in non-cardiac intensive care units.[1-3] In the following dissertation, three studies are described that examine factors related to timeliness and effectiveness of care in sepsis. Studies 1 and 2 pertain to in-hospital care, while Study 3 addresses pre-hospital factors.

Goals & Objectives

This dissertation originated in a conversation with my clinical mentor, Dr. Daniel Uslan, about the upcoming rollout of the Centers for Medicare & Medicaid Services (CMS) core measure for early sepsis care—the SEP-1 sepsis bundle. The premise was that an earlier core measure related to community-acquired pneumonia had led to antibiotic overuse and needed to be withdrawn. We were concerned that SEP-1 may likewise lead to unintended consequences. In particular, the new core measure's "one size fits all" approach appeared misguided. We drew a distinction between patients with hospital-onset sepsis and those with community-onset sepsis. We suspected that hospital-onset sepsis would require a different approach than what was required by SEP-1.

The first goal of this dissertation was to identify patients with hospital-onset sepsis as a subgroup of interest. Hospital-onset of sepsis is commonly one of the exclusion criteria in the clinical trials evaluating care bundles and protocols in early sepsis management. Thus, the foundational literature upon which SEP-1 is based almost completely omits patients with hospital-onset sepsis, except for a few observational studies. Given the lack of evidence, the impact of SEP-1 in this population could not be predicted. Supporters of SEP-1 had either

assumed that patients with hospital-onset sepsis were the same as those with community-onset or had not considered hospital-onset sepsis at all.

The second goal was to evaluate the effectiveness of SEP-1-adherent care in hospital-onset sepsis. We started from a position of very little evidence. Therefore, the first step was to find out what providers were actually doing for patients with hospital-onset sepsis. The second step was to determine what they should be doing. Our objectives were (1) to compare SEP-1 adherence in hospital-onset v. community-onset sepsis and (2) to estimate the treatment effect of SEP-1-adherent care in hospital-onset v. community-onset. Our hypotheses were that (1) SEP-1 adherence would be lower in hospital-onset sepsis, and that though (2) SEP-1 adherence would be associated with reduced mortality overall, (3) it would be associated with a smaller mortality reduction in hospital-onset. A smaller mortality reduction was expected because hospital inpatients may possess risk factors for mortality that are either not modifiable, such as terminal illness, or not addressed by SEP-1, such as invasive fungal infection.

State of the Literature

The basis for the modern sepsis bundle is early goal-directed therapy (EGDT). In a nutshell, EGDT is a form of intense fluid resuscitation based on hemodynamic parameters. In 2014 and 2015, three large multicenter trials found lack of benefit from EGDT.[4-6] Based on the new evidence, the 2016 revision of the Surviving Sepsis Campaign guidelines removed the recommendation for EGDT, and SEP-1 does not include EGDT.

Though it may no longer be clinically relevant, EGDT remains important because it defines the state of the literature on sepsis bundles. Because EGDT requires a central line and close monitoring, studies on implementation of sepsis bundles prior to 2015 tend to fixate on

barriers posed by EGDT, rather than the rest of the bundle. The literature on the current version of the sepsis bundle begins in 2015, which is when the plan for this dissertation was being developed.

How the Literature Changed

After 2015, the literature has developed in five important ways. First, clinicians and researchers began reporting their experience with the SEP-1 bundle in practice, including one multicenter observational study that found no association between SEP-1 adherence and mortality.[7] Second, investigators have looked backwards, re-examining the evidence underlying SEP-1 and finding it questionable.[8] Third, the definition of sepsis changed.[2] There is no longer a clinical entity known as "severe sepsis" (except in the CMS manual for SEP-1). Fourth, the CDC Epicenters program re-examined trends in the epidemiology of sepsis and found that recent increases in the number of sepsis diagnoses do not correlate with increases in objective clinical markers of infection.[9] Rather, apparent changes in the incidence of sepsis appear related to new policies in medical billing and coding.[10] Fifth, investigators have begun approaching the heterogeneity of sepsis in more intelligent ways.[11]

By raising questions about the diagnosis of sepsis and the value of the SEP-1 bundle, these developments have—to an extent—undermined this dissertation. SEP-1 is now recognized as having flaws, and many providers feel empowered to question it. However, the research we performed remains relevant. We, like others in this area, intend to introduce evidence to maximize the potential benefit from use of the SEP-1 sepsis bundle in the real world. Unfortunately, ours is just one voice among many.

Review of the Literature

Definition of Sepsis

Historically, "sepsis" and "septicemia" were non-specific, interchangeable terms used to indicate overwhelming infection.[12] In 1991, a consensus definition was drafted which differentiated sepsis from bacteremia and other non-septic infectious syndromes by the development of a systemic inflammatory response.[13, 14] In sepsis, immune homeostasis is disrupted such that both over-activation and relative suppression of different immune pathways can cause harm.[15, 16] Dysregulation of the host response to infection is considered a driving force behind sepsis-related morbidity and mortality, which may involve cardiovascular collapse and multiple organ system failure.[17] In 2016, the definition of sepsis was updated to improve its specificity and emphasize organ dysfunction as a core feature. Per the new definition, known as "Sepsis-3," sepsis is now defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[2]

Epidemiology of Sepsis

Between 894,000 and 3.1 million inpatients are diagnosed with sepsis every year.[18] Meanwhile, estimates using objective clinical markers of severe infection estimate that the incidence of sepsis is 1.7 million cases per year.[9, 19] Sepsis is also a leading cause of death in the hospital, with attributable mortality estimated to be about 15-25%. Sepsis has been estimated to contribute to up to 1 in 3 in-hospital deaths.[3, 20]

Trends in the Diagnosis of Sepsis

In recent years, the probability that an individual with a systemic inflammatory response to suspected infection is diagnosed as having sepsis has increased.[21] Researchers have noted that this apparent increase in the incidence of sepsis coincided with the introduction of sepsis-specific diagnosis codes in the 2003 update of *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and the overhaul of Medicare diagnosis-related groups in 2007 linking reimbursement to severity of illness.[10, 22] Meanwhile, epidemiologic studies monitoring cases of sepsis using clinical indicators of disseminated or severe infection have not detected a change in the incidence over the same time span.[9, 19] Thus, the apparent rise in the incidence of sepsis over the last decade[23, 24] is likely attributable to increased diagnosis rather than a change in the true incidence of illness.

Hospital-Onset Sepsis

The definition of "hospital-onset" sepsis varies by study. However, across studies, 10-20% of sepsis cases develop in the hospital.[19, 25-27] Mortality among patients with hospital-onset sepsis is 1.5-2x higher than when sepsis develops in the community.[9, 10, 26] The cause of this increased mortality is not known but is likely related to a confluence of factors, including differences in baseline health, differences between hospital-acquired and community-acquired infections (such as likelihood of being associated with a drug-resistant pathogen or indwelling device), and—possibly—differences in care. In part, questions about higher mortality in hospital-onset sepsis remain unanswered because studies describing sepsis in the hospital tend to focus on patients with community-onset sepsis or to not specify in which setting sepsis arose.[28-32]

However, it does appear that death from hospital-onset sepsis is no more or less preventable than death from community-onset sepsis.[33]

The SEP-1 Sepsis Bundle

Sepsis bundles are protocols for early sepsis care that combine diagnosis and treatment. The progenitor of the modern sepsis bundle was introduced in 2004 by the Surviving Sepsis Campaign (SSC), a collaboration between the Society of Critical Care Medicine and the European Society of Intensive Care Medicine.[34] The SSC bundle has since been revised twice.[35, 36] Notably, the most recent set of SSC guidelines was not endorsed by the Infectious Disease Society of America (IDSA).[37] As the primary justification for this decision, the IDSA raised concerns regarding the guidelines' aggressive approach to all patients with *suspected* sepsis, when fewer than 60% of patients in this category admitted to the ICU will subsequently be determined to have either probable or definite infection.[38]

In October 2015, the Centers for Medicare and Medicaid Services (CMS) adopted The Early Management Bundle for Severe Sepsis / Septic Shock (National Quality Forum #0500), also known as SEP-1, as a performance measure.[39] CMS performance measures represent an effort to improve transparency and allow consumers to evaluate better the quality of medical care provided across hospitals. CMS collects data on its performance measures and publishes the results on Hospital Compare (http://www.hospitalcompare.hhs.gov/), a website that is free and open to the public. Facility-level performance measure data are also available from the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) via Quality Check (http://www.qualitycheck.org). As part of its Value-Based Purchasing program, CMS uses

certain performance measures to adjust hospital reimbursement.[40] To date, however, SEP-1 has been only been used for public reporting.

Seven components comprise SEP-1. Within 3 hours of presentation of sepsis, providers are expected to (1) obtain blood cultures before antibiotics, (2) administer broad spectrum antibiotics, (3) check a serum lactate, and (4) administer intravenous fluids if the lactate is elevated or blood pressure is low. Within 6 hours of onset of sepsis, providers must (5) repeat the serum lactate if the initial was abnormal, (6) assess tissue perfusion (including follow-up blood pressure measurement to evaluate for persistent hypotension) and consider additional intravenous fluids, and (7) start vasopressors for persistent hypotension after fluids.[39] CMS considers SEP-1 an all-or-nothing entity requiring all eligible components be performed within the appropriate time frame.

Studies evaluating the relationship between sepsis bundles and mortality are mixed. Some investigators performing retrospective analyses have found an association between adherent care and reduced mortality,[25] and others have not.[7] Most notably, in 2013, New York state mandated hospitals to follow evidence-based protocols for the identification and management of patients with sepsis. Though local tailoring of protocols was allowed, all hospitals were required to incorporate 3- and 6-hour bundles. In a retrospective evaluation of the impact of the policy, the block of 3-hour components, when taken together, were found to reduce risk of in-hospital death such that every hour of delay increased mortality by an odds ratio of 1.04.[41] When each component was evaluated independently, lactate measurement, blood cultures, and antibiotics were all associated with reductions in mortality, while administration of intravenous fluids was not.

Most of the remaining evidence supporting sepsis bundles derives from quality improvement projects. These studies are likely biased by changes in the population of individuals being diagnosed with sepsis over the last decade. However, two prospective international initiatives stand out as worth discussing.

First, in 2005, the SSC led a program intended to improve the quality of sepsis care at >100 medical centers across Europe and the Americas.[42] In an evaluation of the program, investigators found that participating sites with high levels of adherence (defined as adherence ≥ 15%, the median for the study) reported lower sepsis mortality than low-adherence sites (mortality of 29% vs 39%).[43] All components of the sepsis bundle showed an association with reduced mortality, though use of intravenous fluids was evaluated jointly with vasopressors. This study is remarkable because nearly half (48%) of the patients included developed sepsis while admitted to the ward or ICU. Unfortunately, no specific analysis was performed to evaluate the effectiveness of the SSC sepsis bundle in patients with hospital-onset sepsis.

The second major initiative—the International Multicentre Prevalence Study on Sepsis (IMPreSS)—collected data from 618 hospitals in 62 countries.[44] The IMPreSS investigators evaluated the 3- and 6-hour components of the sepsis bundle as blocks and found that both were associated with reductions in mortality (20% vs. 31% for the early components, 22% vs. 32% for the late components).[44] IMPreSS did not report the associations between individual bundle components and mortality. Though IMPreSS included patients with hospital-onset sepsis, no specific analyses were reported in this subgroup.

The evidence supporting use of sepsis bundles from other quality improvement projects is summarized in a systematic review.[45] Out of 50 studies identified, 48 included mortality as an outcome. On average, published quality improvement projects tend to show an association with

reduced mortality. However, the authors of the review note that their findings suggest publication bias.

Sepsis Bundles in Hospital-Onset Sepsis

Previous iterations of the SSC guidelines explicitly assert that the greatest potential for benefit can be realized when they are applied "in the non-ICU setting and across the spectrum of acute care," including the inpatient wards, the peri-operative areas, the emergency department, and other areas in addition to the ICU.[35] However, no randomized controlled trial cited in the guidelines included ward inpatients (though 11% of the patients included in cited meta-analyses received their care on the wards).[46] It is unknown what proportion of these patients had hospital-onset sepsis and what proportion received their initial sepsis care in the emergency department.

Individual Bundle Components

Out of the 6 components of SEP-1, only early antibiotics and vasopressors for persistent hypotension are recommended based on at least moderate quality evidence in the SSC guidelines.[36] In particular, observational data support an association between early antibiotics and reduced mortality in sepsis such that mortality is expected to increase for every hour that antibiotics are delayed.[7, 47-52]

Administration of intravenous crystalloid is the most problematic component of the bundle. Retrospective studies have shown an association between early administration of intravenous fluids and reduced mortality from sepsis.[53-55] Prospective studies, on the other hand, have both failed to show a benefit from fluid challenge[51, 56] and noted an association

between positive fluid balance and increased sepsis mortality.[57-59] Unfortunately, this latter finding—that patients who receive larger volumes of fluid are more likely to die from sepsis—is difficult to interpret given likely confounding from the relationship between the decision to administer additional fluids and severity of illness. For instance, in a multicenter European cohort of intensive care unit patients with sepsis shock, the patients that received larger volumes of intravenous fluid were found, on average, to have a higher initial serum lactate.[56] Further, calculation of fluid balance depends both on the volume of fluids administered and on urine output. In one of the prospective studies that identified positive fluid balance as a correlate of sepsis mortality, the group of patients with positive fluid balance had lower overall urine output, a marker of more severe illness.[57]

The Simplified Severe Sepsis Protocol 2, a randomized controlled trial based in the emergency department of a 1500-bed hospital in Zambia, partially addresses concerns about selection bias in the observational studies demonstrating an association between positive fluid balance and sepsis mortality.[59] This trial, which was nonblinded, randomized patients to receive either 4L of intravenous crystalloid based on a structured protocol or usual care. The usual care group received less intravenous fluid overall (median 2.0 vs. median 3.5L for the protocol group), and only 48% of the usual care group received a fluid bolus. In-hospital mortality was significantly higher in the protocol group than the usual care group (48% vs. 33%), corroborating the finding from observational data that overuse of intravenous fluids may be harmful in sepsis. However, it may not be appropriate to generalize the findings from this trial to the US. In the US, sepsis is predominantly an illness afflicting the elderly,[60] while the average age of the Zambian sample was only 37. Further, 89% of the Zambian sample were HIV-positive, and 24% were receiving treatment for tuberculosis. Given the central role of the

immune system in the pathophysiology of sepsis and the impact secondary infection can have on sepsis mortality,[61] these differences make the Zambian sample essentially noncomparable to the population of individuals with sepsis in the US.

Meta-analysis of data from clinical trials supports a mortality benefit from use of serum lactate as a guide of tissue perfusion in sepsis.[62] Elevated initial serum lactate also has prognostic value in the setting of sepsis.[63, 64] However, critics of SEP-1 have noted that the cut-off used to denote abnormal ($2 \geq$ mmol/L) differs from the value typically used in the literature ($4 \geq$ mmol/L).[52]

Earlier initiation of vasopressors has been associated with reduced mortality in the setting of septic shock, and every hour in which vasopressors are delayed results in a 5% increase in mortality.[65] Mean arterial pressure has been identified as a stronger predictor of mortality in septic shock than serum lactate.[66] The only potential criticism of the inclusion of vasopressors in SEP-1 is that recommending initiation of vasopressors within 6 hours may not be soon enough.[52]

Adherence to the Sepsis Bundle

Adherence to SEP-1 varies widely by hospital.[67] At UCLA Health, adherence typically ranges from 10% to 30%. Other major medical centers have reported similar performance.[7] Adherence to individual bundle components is less frequently reported but likely ranges from 50 to 65% for the 3-hour components and from 60 to 80% for the 6-hour components.[44]

Studies exploring the reasons for non-adherence have examined factors related to the physician, the patient, and the health care system. Five years after the first SSC guidelines were published, a survey was administered to a random sample of physicians affiliated with the

American Medical Association to determine whether physician specialty—internal medicine, emergency medicine, or critical care medicine—influenced guideline implementation.[68] The survey results suggest that priorities in early sepsis care differ by specialty. For instance, intensivist respondents were more likely to "almost always" check a serum lactate, establish central venous access, and closely monitor serum glucose, while emergency medicine physicians were most likely to administer antibiotics within 4 hours, though all three specialty types reported "almost always" administering antibiotics within one hour of onset of sepsis at the same rate. Curiously, 5% of respondents reported commonly cooling septic patients to 34°C, a practice that is "unconventional" and theoretically harmful.

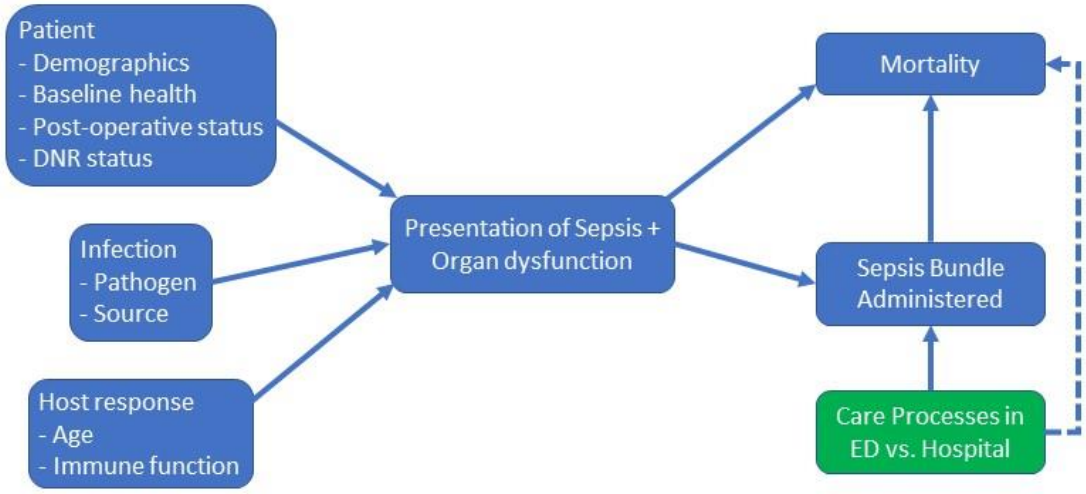
At Samsung Medical Center in Seoul, Korea, a prospective sepsis registry based in the emergency department was used to examine factors associated with sepsis bundle adherence.[69] Patients were split into groups based on whether the sepsis bundle was administered with high fidelity or low fidelity. On multivariable analysis, the only provider-level factor associated with higher likelihood of adherence was more experience (nurses with 3 or more years of clinical experience, senior residents or board-certified physicians versus junior residents). Patient-level factors associated with bundle adherence were fever and hypotension. System-level variables, such as presentation during night or weekend shift and emergency department occupancy rate, were not significantly related to adherence. However, somewhat paradoxically, a subsequent publication based on the same registry found emergency department occupancy rate to be a significant predictor of bundle adherence.[70] In that follow-up study, emergency department occupancy percentage was evaluated as a proxy for crowding, which is a known risk factor for treatment delays.[71]

Prior to the 2016 update, the SSC guidelines recommended protocolized resuscitation of patients with sepsis-induced hypoperfusion based on hemodynamic targets including central venous pressure, mean arterial pressure, urine output, and/or mixed or central venous oxygen saturation.[34, 35] This practice, called "early goal-directed therapy," has since been proven to have no impact on sepsis mortality and has been removed from the guidelines.[72] However, because early goal-directed therapy required central venous access and close monitoring of urine output, many studies examining barriers to early sepsis care from the last decade fixate on barriers associated with early goal-directed therapy.[73-76] Nonetheless, these studies have some applicability to the sepsis bundle in its current form. For instance, in a telephone survey of physicians and nurses from emergency departments across the US, lack of awareness of sepsis and the challenge of recognizing septic patients were raised as common barriers to sepsis care.[73] Per one provider from that survey, "Sepsis is harder to identify than myocardial infarction or cerebrovascular accident," which is probably still true.

Another proposed barrier to adherence is poor coordination between services, such as lack of coordination between physicians in the emergency department and the ICU.[74, 76] Though coordination between services has not been formally studied, one quality improvement project targeting sepsis found that after the intervention, septic patients spent longer in the emergency department prior to ICU admission.[77] The authors attribute this delay to the additional procedures that emergency physicians were expected to perform prior to admission in order to initiate appropriate sepsis care (i.e., early goal-directed therapy). However, delaying admission to facilitate placement of a central line that could have occurred just as easily (and perhaps more safely) in the ICU suggests problems related to coordination during the handoff process.

A third potential barrier is providers' disagreement with guidelines. The lack of evidence supporting individual components of SEP-1,[8] the burden of reporting for SEP-1,[78] and the poor interrater reliability of SEP-1[79] have led many to question the validity of SEP-1 as a performance measure.

Conceptual Model



The model shown above was adapted from PIRO (predisposition, infection, response, and organ dysfunction), a system for staging sepsis.[80] PIRO has been used as the basis for prognostic models intended to estimate risk of sepsis mortality.[81-83] For instance, PIRO was used as the conceptual framework for a study modeling mortality among individuals presenting with suspected infection in the emergency department at Harvard hospitals.[82] PIRO has also been used to model likelihood of sepsis mortality in the ICU.[81] When predicting mortality among patients with sepsis, PIRO has been found to be superior to the Sequential Organ Failure Assessment (SOFA), the system of staging organ dysfunction from sepsis currently employed in the Surviving Sepsis Campaign guidelines.[83] For this project, PIRO has been selected over SOFA because it presents a more comprehensive framework.

In the figure above, PIRO has been adapted to represent the analyses contained in this dissertation. Factors related to the host, the infection, and the immune response contribute to the presentation of sepsis and organ dysfunction. These factors are treated as confounders that can influence both whether the sepsis bundle is administered and the clinical outcome. The effect of processes and systems of care delivery in the emergency department and in the hospital on the clinical outcome are mediated by likelihood of administering the sepsis bundle. Indirect effects of care processes on mortality are represented by the dashed line.

CHAPTER 2

Title: Adherence to the SEP-1 Sepsis Bundle in Hospital-Onset v. Community-Onset Sepsis: A Multicenter Retrospective Cohort Study

Running Title: Guideline Adherence in Hospital-Onset Sepsis

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ABSTRACT

Background: Sepsis is the leading cause of in-hospital death. The SEP-1 sepsis bundle is a protocol for early sepsis care that requires providers to diagnose and treat sepsis quickly. Limited evidence suggests that adherence to the sepsis bundle is lower in patients with hospital-onset sepsis.

Objective: To compare sepsis bundle adherence in hospital-onset vs. community-onset sepsis.

Design: Retrospective cohort study using multivariable analysis of clinical data

Participants: 4,658 inpatients age 18 or older were identified by diagnosis codes consistent with sepsis or disseminated infection.

Setting: 4 university hospitals in California between 2014 and 2016.

Main Outcomes and Measures: The primary outcome was adherence to key components of the sepsis bundle defined by the Centers for Medicare and Medicaid Services in their core measure, SEP-1. Covariates included clinical characteristics related to the patient, infection, and pathogen.

Key Results: Compared with community-onset, patients with hospital-onset sepsis were less likely to receive SEP-1 adherent care (relative risk 0.33, 95% confidence interval 0.29 – 0.38, $p < 0.001$). With the exception of vasopressors (RR 1.11, $p = 0.002$), each component of SEP-1 evaluated—blood cultures (RR 0.76, $p < 0.001$), serum lactate (RR 0.51, $p < 0001$), broad-spectrum antibiotics (RR 0.62, $p < 0.001$), intravenous fluids (0.47, $p < 0.001$), and follow-up lactate (RR 0.71, $p < 0.001$)—was less likely to be performed within the recommended time frame in hospital-onset sepsis. Within the hospital, patients with hospital-onset sepsis arising on the ward were less likely to receive SEP-1-adherent care than were patients whose sepsis arose in the intensive care unit (RR 0.68, $p = 0.004$).

Conclusions: Inpatients with hospital-onset sepsis receive different management than individuals with community-onset sepsis. It remains to be determined whether system-level factors, provider-level factors, or factors related to measurement explain the observed variation in care or whether variation in care affects outcomes.

Introduction

Sepsis is a leading cause of death in the hospital.[1, 3] Though the definition varies, 10-20% of cases can be considered "hospital-onset", meaning the signs and symptoms of sepsis developed after hospital admission.[19, 26, 27] Hospital-onset is associated with a mortality rate that is twice as high as community-onset.[10, 19, 84] It is unknown whether patients with hospital-onset sepsis receive the same quality of care as do patients with community-onset.

Protocols for early sepsis care, called "sepsis bundles," have been demonstrated to reduce mortality in community-onset sepsis when implemented in the emergency department (ED).[41, 46] Though sepsis bundles do not have the same basis in evidence in hospital-onset sepsis,[7, 46, 85] the Centers for Medicare and Medicaid Services (CMS) and professional societies recommend their use for all patients with sepsis and organ dysfunction, including those of hospital-onset.[35, 39, 86]

Overall adherence to the CMS sepsis bundle, known as SEP-1, is only 30-50%.[7, 44, 67, 87] We hypothesize that adherence may be lower in hospital-onset sepsis. Inpatient providers may be more likely to attribute signs of sepsis to other causes, such as postoperative fever, to remain anchored on admitting diagnoses, or to decide that a standardized care protocol is not appropriate for their patient. We sought to determine whether adherence to SEP-1 differs between community- and hospital-onset sepsis, and, by extension, whether the highest risk patients with sepsis are as likely to receive the standard of care.

Materials and Methods

Data Source

We obtained clinical data from the electronic health records of four University of California hospitals offering diverse clinical services. All data were collected during routine clinical care. The UCLA IRB provided approval.

Definitions

We defined "sepsis" as suspected infection with organ dysfunction, including syndromes previously called severe sepsis and septic shock, based on Sepsis-3.[2] Other definitions were based on the CMS core measure SEP-1 (National Quality Forum #0500).[86] "Time zero" of sepsis was determined without chart review using an automated algorithm (Appendices 1-2).

Community-onset and hospital-onset were defined by time zero in the ED and on an inpatient unit, respectively.

Variables

The primary outcome was adherence to the SEP-1 sepsis bundle, an all-or-nothing measure requiring 4 components within 3 hours of time zero and 2 components within 6 hours of time zero. The 3-hour components include (1) blood cultures prior to antibiotics, (2) broad-spectrum antibiotics, (3) a serum lactate, and, if the lactate is elevated or the blood pressure low, (4) intravenous crystalloid. Within 1 hour of the fluid bolus completing, the patient's blood pressure must be checked twice to evaluate for persistent hypotension. The 6-hour components are (5) a repeat lactate if initially abnormal and (6) vasopressors for persistent hypotension after intravenous fluids. Re-assessment of tissue perfusion within 6 hours of time zero, a seventh component, was excluded due to inherent flexibility and the lack of a pertinent field in the electronic health record. Rechecking the blood pressure was excluded due to inconsistent charting of fluid infusion rates. Secondary outcomes included each individual bundle component and the 3-hour components as a block (the 3-hour bundle).

Covariates included year of admission, age, gender, baseline health, pathogen, source of infection, immunosuppression, postoperative status and hospital (see Appendix 3 for details of variable construction). Baseline health was represented by count of conditions from the Elixhauser Comorbidity Index.[88, 89] Categories for source of infection were pneumonia, urinary tract infection, skin and/or soft tissue infection, and bloodstream infection (excluding possible skin contaminants, see Appendix 1).

Study Design

We conducted a retrospective study comparing adherence to the SEP-1 bundle between cohorts with community-onset and hospital-onset sepsis.

Inclusion and Exclusion Criteria

All encounters for individuals age 18 or older between 10/01/2014 and 10/01/2016 associated with a diagnosis of sepsis or disseminated infection were eligible (Appendix 4). Individual patients were able to contribute multiple encounters. Exclusion criteria were from

SEP-1: hospitalization >120 days or <6 hours, admission by acute care transfer, or receipt of intravenous antibiotics for ≥24 hours at time zero.

For encounters prior to October 1, 2015, the set of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) diagnosis codes used to identify sepsis encounters was based on methodology employed by Martin et. al[90] that has since been validated and replicated.[91-93] For hospitalizations beginning October 2015, ICD-10-CM diagnosis codes provided by CMS in SEP-1 were paired with diagnosis codes for organ dysfunction in a process analogous to the Martin methodology (Appendix 4).

Statistical Analysis

Multilevel mixed-effects Poisson regression with robust error variance was used to evaluate the relative risk of adherence since relative risk is the parameter of interest.[94] Fixed and random effects were incorporated to account for clustering by and within hospital units. Survival analysis, including Kaplan-Meier curves and Cox proportional hazards modeling, evaluated the association between hospital-onset of sepsis and time to 3-hour bundle components. Analyses were performed using Stata/IC version 14.1.

Results

4,658 patient encounters were analyzed (Fig. 1). Characteristics of the sample are described in Table 1 (see Supplemental Table 4 for differences by hospital). The average age was 63, 44% were female, and the median number of Elixhauser comorbidities was 5. 1,437 individuals (30.9%) received the SEP-1 bundle within the recommended time frame. Patients with hospital-onset were younger (average age 60.9 v. 64.4 years), more immunosuppressed (37.6% v. 26.4%), and more often postoperative (15.9% vs. 2.5%). Community-onset sepsis was more commonly associated with bacteremia (33.2% vs. 22.0%) or MRSA (10.8% v. 8.7%).

Multivariable regression demonstrated factors associated with timely administration of SEP-1 (Table 2). Patients with hospital-onset sepsis were less likely to receive SEP-1-adherent care (39.9% probability for community-onset, 13.0% for hospital-onset; RR 0.33, $p < 0.001$). SEP-1 non-adherence was also associated with postoperative status (RR 0.59, $p < 0.001$) and increased number of Elixhauser comorbidities (RR 0.98 for each additional comorbidity, $p < 0.001$). Presence of fever (RR 1.37, $p < 0.001$) or bacteremia (RR 1.20, $p < 0.001$) were

associated with SEP-1 adherence. These associations held when excluding the SEP-1 requirement for intravenous fluids. On stratified analyses, hospital-onset was a significant predictor of non-adherence at all four hospitals and regardless of admitting provider specialty (Supplemental Tables 5 and 6).

Adherence to SEP-1 differed across inpatient areas (Table 3). Compared with the ward, patients with sepsis arising in the intensive care unit (ICU) were more likely to receive the complete SEP-1 bundle (RR 1.48, $p = 0.004$) and more likely to have a serum lactate checked (RR 1.42, $p < 0.001$). When indicated, patients in the ICU were less likely to receive intravenous fluids (RR 0.69, $p = 0.013$) but more likely to be started on vasopressors (RR 1.66, $p < 0.001$). Patients with sepsis arising in the perioperative area were less likely than those on the ward to have timely blood cultures (RR 0.75, $p = 0.002$).

Time-to-event analysis was performed for the 3-hour bundle components (Figs. 2A-2E). The median time from onset of sepsis to completion of the 3-hour bundle was 3.0 hours (95% confidence interval, 2.5 – 3.7) in community-onset and 79.6 hours (95% confidence interval, 67.5 – 96.8) in hospital-onset. Median time to serum lactate (0.0 hours in community-onset, 5.9 hours in hospital-onset) and intravenous fluids (1.8 hours in community-onset, 19.3 hours in hospital-onset) were significantly longer in hospital-onset ($p < 0.001$ by log-rank test comparing survival curves). On the other hand, median time of blood cultures and broad-spectrum antibiotics coincided with or preceded time zero in both community-onset and hospital-onset. Cox proportional hazards models identified that patients with hospital-onset sepsis were less likely to have timely blood cultures (HR 0.66, $p < 0.001$), serum lactate (0.47, $p < 0.001$), broad-spectrum antibiotics (HR 0.65, $p < 0.001$), intravenous fluids (HR 0.60, $p < 0.001$), or the 3-hour bundle (HR 0.43, $p < 0.001$).

Discussion

The SEP-1 bundle, which is embodied in professional society guidelines and has been adopted by CMS as a core measure, recommends that all patients with sepsis be managed the same way. However, in this multicenter cohort study, providers appeared to approach hospital-onset and community-onset sepsis differently. In our sample, only 12.7% of patients with patients with hospital-onset sepsis received SEP-1-adherent care, compared with 45.9% of patients with community-onset sepsis. Given that the attributable mortality is higher in hospital-

onset sepsis than community-onset, less frequent guideline adherence in this population requires further exploration.

EDs are designed to triage and deliver rapid care for conditions in which every minute counts, such as myocardial infarction or stroke. Thus, it is perhaps unsurprising that SEP-1 adherence was higher in the ED than in the hospital, a monitored setting. Independent of patient characteristics, patients with hospital-onset sepsis were 3-times less likely (risk ratio 0.31, risk difference 0.31) to receive guideline-adherent care. This association was observed at every study site and has been reported by others (though notably, only delayed antibiotics have been associated with increased mortality in hospital-onset sepsis),[7] suggesting a relationship that is systematic to inpatient care.

The hospital is a complex system,[95, 96] and differences in systems of care delivery between the ED and inpatient areas likely contribute to the observed variation in sepsis management. The relevant factors are structural (patient-to-staff ratios, colocation of providers and patients), functional (rounding schedules, team size, frequency of communication), and related to hospital policy (where vasopressors can be administered, whether "code sepsis" can be called). Though similar, even the ICU and ED differ in ways that may affect their ability to mount a rapid response, such as the presence of an attending overnight or whether an elevator ride is required when traveling to the computed tomography scanner. Each area has evolved to match the expected length of stay: hours in the ED versus days in the inpatient areas. The timescale in the ED is a better fit for SEP-1.

Provider-level differences between the ED and inpatient areas likely also contribute to the observed variation in sepsis care. Context affects clinical reasoning,[97, 98] and the additional information available to inpatient providers may make them more susceptible to cognitive biases such as anchoring. To illustrate this point, consider the steps required for early sepsis care. Emergency providers assess an undifferentiated patient and, if sepsis is recognized, respond accordingly. For inpatient providers, onset of sepsis is more likely to represent a change. The inpatient provider must make an assessment, filter new information, and integrate it with what is already known. If sepsis is recognized, the physician must pivot from the admitting diagnosis to enact a new plan of care. The question is not whether providers can respond, but whether they are as likely to respond within 3 hours. Communication is critical, and delays may be amplified if coordination is required among multiple providers, such as consultants or trainees.[99]

Alternatively, because more information about the patient is available in hospital-onset sepsis, inpatient providers may feel more confident observing while withholding components of SEP-1. To determine whether providers were selecting among bundle components, we evaluated reconfigured bundles that omitted intravenous fluids and serum lactate (Table 2). Regardless of bundle configuration, individuals with hospital-onset sepsis were less likely to receive timely care. Thus, low SEP-1 adherence in hospital-onset sepsis appears unrelated to providers' doubts regarding the hemodynamic components.[8] However, providers may have other reasons for withholding treatment bundles in hospital-onset sepsis, such as terminal illness.[100]

Finally, lower adherence to SEP-1 in hospital-onset sepsis may be related to less precision when identifying time zero in this population. Based on review of a limited subsample of patient charts (see Appendix 2), we suspect that time zero can be ascertained more precisely in community-onset sepsis, when there are fewer laboratory values and vital signs obtained before sepsis manifests, than in hospital-onset sepsis, when days may pass before labs, vital signs, and clinical documentation meet the criteria. If estimation of time zero has higher variance in hospital-onset than in community-onset sepsis (as may occur if labs are being checked less frequently in the hospital than in the ED), then more hospital-onset cases may be misclassified as non-adherent or meeting the measure's exclusion criteria. Moreover, if the confidence intervals surrounding time zero in hospital-onset sepsis exceed 3 hours, then whether bundle components were performed within 3 hours cannot be determined at all. The precision of time zero measurement in hospital-onset sepsis must be characterized to determine the validity of SEP-1 in this population.

Beyond issues related to measurement, our findings illustrate issues with SEP-1 as a performance measure. SEP-1 adherence varies dramatically based on patient-level characteristics. If the intended purpose of SEP-1 is hospital comparison, adjustment will be needed to account for hospital-level differences in the patient populations served. Otherwise, facilities that cater to groups in whom the likelihood of adherence is low, such as postoperative patients, will be systematically underrated.

It remains to be determined if better adherence to SEP-1 would improve outcomes from hospital-onset sepsis. In a previous study, adherence was not found to be associated with a mortality benefit.[7] However, sepsis is a heterogeneous syndrome,[101, 102] and subtypes of sepsis may respond differently to treatment.[11] In our sample, fever was a strong predictor of

SEP-1 adherence, even in patients in whom fever may be considered an unreliable indicator of infection, such as those who were postoperative (RR 2.11, 95% CI 1.13 - 3.91) or immunosuppressed (RR 1.47, 95% CI 1.26 - 1.72). Future research into the impact of sepsis bundles should consider their effectiveness in the subgroups who are most likely to receive them, such as patients with fever, compared with patients who are more likely to present with atypical signs and symptoms of infection.

Limitations

We did not examine outcomes such as mortality, morbidity or length of stay. Instead, the primary outcome was adherence to SEP-1, the current standard of care.[36] We acknowledge that the quality of evidence supporting SEP-1 in hospital-onset sepsis is poor, that SEP-1 encourages liberal antibiotic use, and that a proportion of sepsis mortality may not be preventable.[8, 33] As the consensus regarding optimal management of sepsis evolves, measures that better reflect quality may emerge. Further, we caution that implementation of SEP-1 must be balanced against hospital policies and procedures for antimicrobial stewardship. Future studies evaluating the clinical impact of SEP-1 should incorporate antibiotic use as a balancing measure.

Our sample may not generalize to patients with sepsis in other hospitals and regions. Because our method of patient identification depended on diagnosis codes, we were unable to capture individuals in whom sepsis and organ dysfunction were never diagnosed or documented/coded in the electronic health record. This methodology has been validated in the sepsis literature and mirrors the method used with SEP-1. However, because of limitations of the sample, our conclusions should only apply to the individuals covered by SEP-1, rather than the broader population with sepsis.

Temporal trends in the incidence of sepsis suggest that coding practices have changed.[10, 19] Consequently, our results may be susceptible to bias from local interventions to change coding over time. Comparability between the community-onset and hospital-onset cohorts may be affected by differences in coding between the emergency and inpatient areas (i.e., coding in the inpatient area depends on problem lists generated by house staff without training in medical billing). Confounding may occur if entry of a diagnosis code is linked to treatment (i.e., ED staff only code “sepsis” if the sepsis protocol was initiated). Though, to our knowledge, neither of these practices is occurring.

We determined adherence using laboratory, vital sign, and medication data extracted from the electronic health record, rather than manual chart review. As a consequence, we likely ascertained adherence incorrectly in cases with an administrative contraindication (i.e., physician documented patient refusal) or when determination of time zero might hinge on documentation (i.e., labs and vitals meet the criteria but provider documents "this is not sepsis"). Given that chart review for SEP-1 is known to be an imperfect process with poor interobserver reliability, use of non-standard methodology was considered acceptable to allow evaluation of a larger sample.[78, 79, 103] The omission of re-evaluation of tissue perfusion, one of the seven components of SEP-1, from this analysis may bias estimates of overall SEP-1 adherence but should not affect the relationships between predictors and timely administration of core bundle components, such as serum lactate or antibiotics.

To isolate and examine inpatient processes of care, we defined sepsis arising after arrival on an inpatient unit as "hospital-onset." This definition differs from other studies, which have defined hospital-onset by time zero >48 hours after admission or by whether the diagnosis of sepsis was "present on admission".[7, 27, 103] Though differences in the definition of "hospital-onset" may affect the comparability of our study to others, a sensitivity analysis in which hospital-onset was defined by time zero >48 hours after admission did not change our findings (Supplemental Table 7).

During the study period, the study sites had uncoordinated quality initiatives related to sepsis, including campaigns for sepsis awareness and nurse-initiated sepsis screening, that involved both the EDs and inpatient areas. Nurse-driven sepsis screening has been associated with higher levels of adherence to guidelines, particularly in the ED.[104, 105] However, discussion with partners at the study sites suggests that implementation of sepsis screening was inconsistent. Thus, the impact of these initiatives is not straightforward. If nurse-initiated sepsis screening facilitated SEP-1 bundle adherence, we suspect it was most likely in the ICU, where patient-to-nurse ratios are low, or in the ED, where evidence supports nurse-initiated screening.

Conclusions

Though CMS applies the SEP-1 core measure uniformly to all patients with sepsis, providers appear to manage patients with hospital-onset and community-onset sepsis differently. While lower rates of adherence to SEP-1 in hospital-onset sepsis may represent a quality gap,

there are alternative reasons for the observed differences in care, including potential measurement error. Further, it remains to be determined how adherence to the SEP-1 bundle affects outcomes from hospital-onset sepsis. Consistent and adequate sepsis care will not be possible until the unique challenges related to hospital-onset sepsis, including issues in measurement of time zero, are better understood. Then, consideration should be given to whether systems of care delivery and protocols for early sepsis care can be redesigned to better suit this high-risk patient population.

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Conflicts of Interest:

There are no conflicts of interest to disclose.

Table 1. Characteristics of Patients with Community-Onset v. Hospital-Onset Sepsis

	Community-Onset (n = 2952)	**Hospital-Onset (n = 1706)**	**p-value***
Age – **mean (sd)**	64.4 (17.9)	60.9 (17.8)	< 0.001†
Female – **n (%)**	1307 (44.3)	755 (44.3)	0.99
ECI – **median (IQR)**	5 (3 – 7)	5 (3 – 7)	0.11‡
Immunosuppressed – **n (%)**	780 (26.4)	641 (37.6)	< 0.001
Postoperative – **n (%)**	73 (2.47)	271 (15.9)	< 0.001
Infection site			
Pneumonia – n (%)	1410 (47.8)	813 (47.7)	0.94
UTI – n (%)	1055 (35.7)	555 (32.5)	0.027
SSTI – n (%)	327 (11.1)	195 (11.4)	0.71
BSI – n (%)	979 (33.2)	375 (22.0)	< 0.001
Multiple – n (%)	1069 (36.2)	481 (28.2)	< 0.001
Pathogen			
MSSA – n (%)	183 (6.20)	115 (6.74)	0.47
MRSA – n (%)	318 (10.8)	149 (8.73)	0.026
MDR Gram-negative – n (%)	151 (5.12)	100 (5.86)	0.28
VRE – n (%)	58 (1.96)	40 (2.34)	0.38
Organ Dysfunction at Time 0			
Low blood pressure – n (%)	1398 (47.4)	965 (56.6)	< 0.001
Respiratory failure – n (%)	250 (8.47)	225 (13.2)	< 0.001
Elevated creatinine – n (%)	359 (12.2)	186 (10.9)	0.20
Elevated bilirubin – n (%)	189 (6.40)	143 (8.38)	0.011
Thrombocytopenia – n (%)	300 (10.2)	200 (11.7)	0.097
Coagulopathy – n (%)	276 (9.35)	248 (14.5)	< 0.001
Elevated serum lactate – n (%)	694 (23.5)	118 (6.92)	< 0.001
Multiple – n (%)	368 (12.5)	264 (15.5)	0.003
Outcome			
LOS – median (IQR)	8 (4.3 – 15.5)	15.5 (8 – 27.5)	< 0.001‡
Mortality – n (%)	553 (18.7)	368 (21.6)	0.019

Legend: ECI, Elixhauser Comorbidity Index; UTI, urinary tract infection; SSTI, skin/soft tissue infection; BSI, bloodstream infection; MSSA, Methicillin-sensitive Staphylococcus Aureus, MRSA, Methicillin-resistant Staphylococcus Aureus, MDR, multi-drug resistant; VRE, Vancomycin-resistant enterococci, LOS, overall length of stay for admission; * All p-values from Chi-square test of proportions unless otherwise specified; † Student's t test; ‡ Rank sum test

Table 2. Association between Sepsis Bundle and Patient Factors in Terms of Relative Risk

	Sepsis Bundle	**Sepsis Bundle without IV Fluids**	**Blood Cultures and Antibiotics Only**
Age (in 10-year increments)	1.02 (p = 0.10)	**1.03 (p = 0.003)**	1.00 (p = 0.22)
Female	1.00 (p = 0.95)	0.99 (p = 0.85)	1.01 (p = 0.72)
ECI	**0.98 (p < 0.001)**	**0.98 (p = 0.002)**	1.00 (p = 0.27)
Immunosuppressed	0.97 (p = 0.55)	1.03 (p = 0.39)	1.04 (p = 0.11)
Postoperative	**0.59 (p < 0.001)**	**0.66 (p < 0.001)**	**0.63 (p < 0.001)**
Fever	**1.37 (p < 0.001)**	**1.34 (p < 0.001)**	**1.31 (p < 0.001)**
Hospital-Onset of Sepsis	**0.33 (p < 0.001)**	**0.37 (p < 0.001)**	**0.61 (p < 0.001)**
Infection site			
Pneumonia	1.04 (p = 0.38)	1.03 (p = 0.44)	**1.06 (p = 0.002)**
UTI	0.99 (p = 0.74)	0.98 (p = 0.49)	0.99 (p = 0.73)
SSTI	1.10 (p = 0.13)	**1.14 (p = 0.007)**	1.06 (p = 0.060)
BSI	**1.22 (p < 0.001)**	**1.15 (p < 0.001)**	**1.11 (p < 0.001)**
Pathogen			
MSSA	0.97 (p = 0.71)	0.97 (p = 0.57)	**0.93 (p = 0.048)**
MRSA	1.05 (p = 0.45)	1.06 (p = 0.23)	1.05 (p = 0.074)
MDR Gram-Negative	1.00 (p = 0.96)	1.01 (p = 0.93)	1.08 (p = 0.052)
VRE	0.98 (p = 0.87)	0.94 (p = 0.63)	1.02 (p = 0.78)

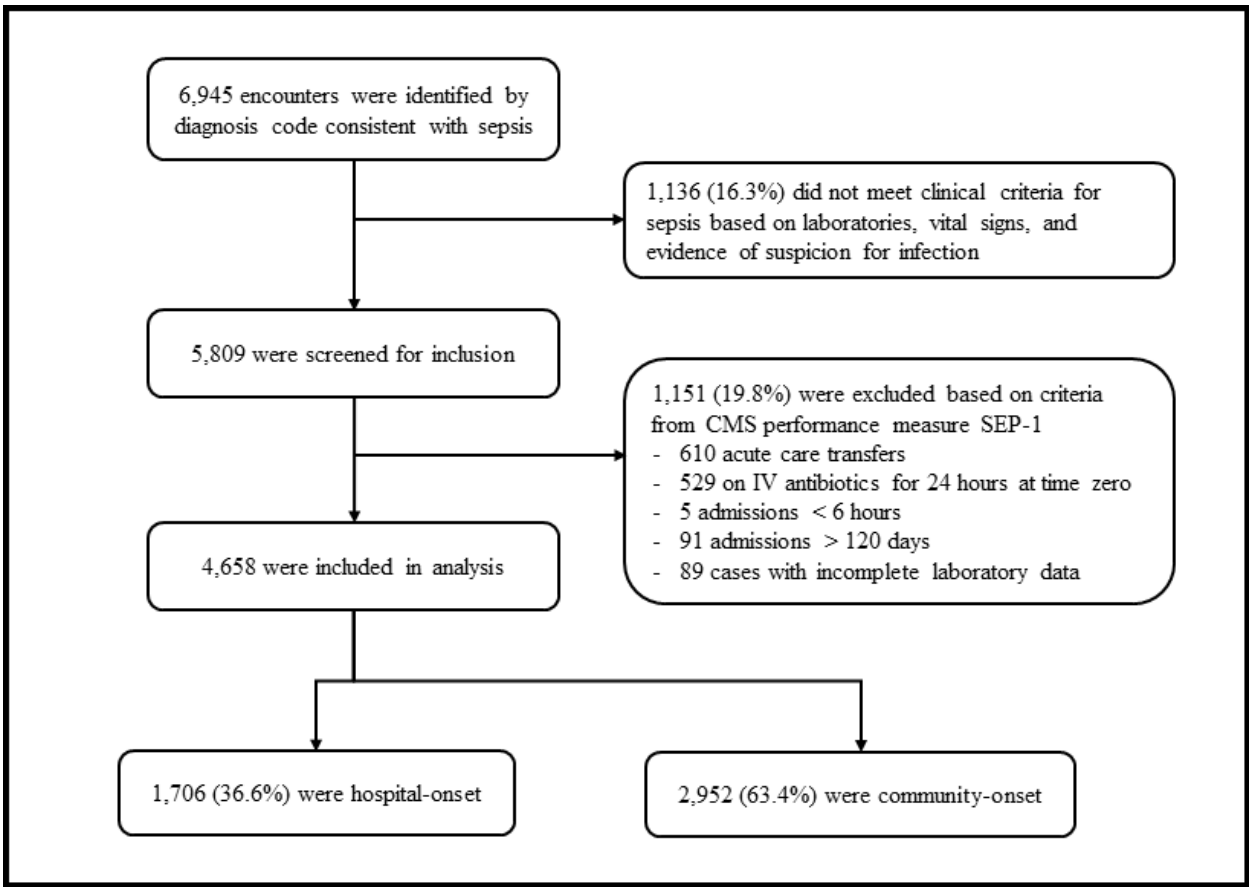
Legend: ECI, Elixhauser Comorbidity Index; UTI, urinary tract infection; SSTI, skin/soft tissue infection; BSI, bloodstream infection; MSSA, Methicillin-sensitive Staphylococcus Aureus, MRSA, Methicillin-resistant Staphylococcus Aureus, MDR, multi-drug resistant; VRE, Vancomycin-resistant enterococci.

Table 3. Relative Risk of SEP-1 Sepsis Bundle Components in Hospital-Onset Compared to Community-Onset Sepsis

	Hospital-Onset	**ICU-Onset†**	**Ward-Onset†**	**Perioperative †**
Blood Cultures	0.76 ($p < 0.001$)	0.78 ($p < 0.001$)	0.77 ($p < 0.001$)	0.58 ($p < 0.001$)
Serum Lactate	0.51 ($p < 0.001$)	0.61 ($p < 0.001$)	0.43 ($p < 0.001$)	0.39 ($p < 0.001$)
Broad Antibiotics	0.62 ($p < 0.001$)	0.66 ($p < 0.001$)	0.60 ($p < 0.001$)	0.49 ($p < 0.001$)
IV Fluids*	0.47 ($p < 0.001$)	0.41 ($p < 0.001$)	0.59 ($p < 0.001$)	0.44 ($p = 0.001$)
Follow-up Lactate*	0.71 ($p < 0.001$)	0.76 ($p = 0.005$)	0.66 ($p < 0.001$)	0.77 ($p = 0.22$)
Vasopressors*	1.11 ($p = 0.002$)	1.26 ($p < 0.001$)	0.76 ($p = 0.001$)	0.95 ($p = 0.65$)
3-Hour Block	0.31 ($p < 0.001$)	0.35 ($p < 0.001$)	0.29 ($p < 0.001$)	0.23 ($p < 0.001$)
6-Hour Block*	0.97 ($p = 0.39$)	1.17 ($p < 0.001$)	0.66 ($p < 0.001$)	0.83 ($p = 0.17$)
Complete Bundle	0.33 ($p < 0.001$)	0.41 ($p < 0.001$)	0.28 ($p < 0.001$)	0.21 ($p < 0.001$)

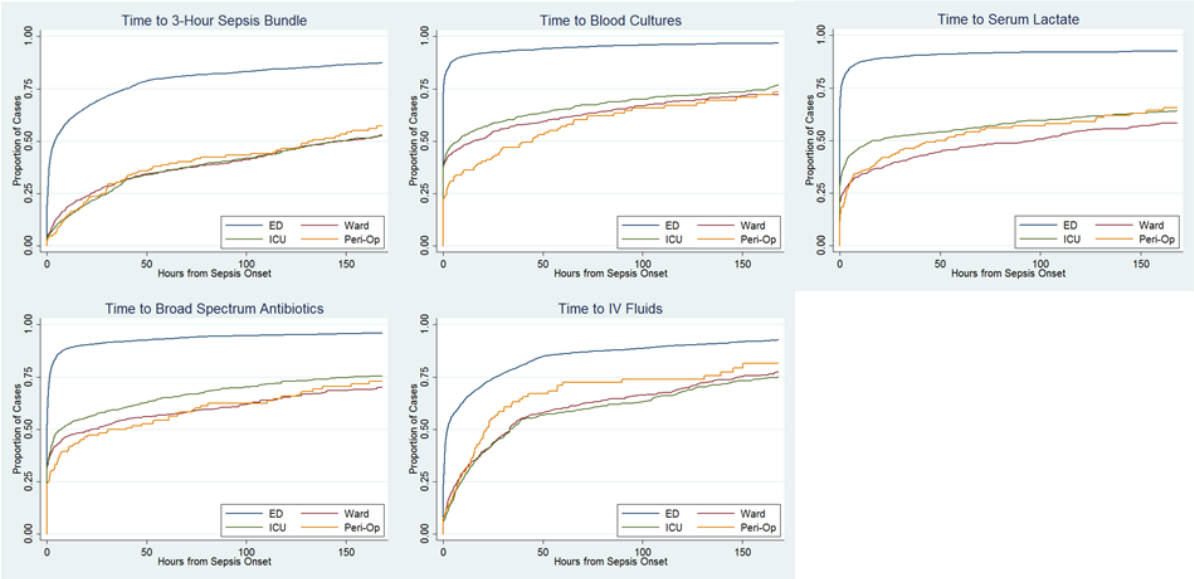
Legend: *If required. †Relative to the Emergency Department. ICU, intensive care unit.

Figure 1. Patient Flow Diagram



Legend: CMS, The Centers for Medicare & Medicaid Services. SEP-1, Early Management Bundle, Severe Sepsis / Septic Shock.

Figures 2 Parts A-E. Time to 3-Hour Sepsis Bundle and Components



Legend: Curves have been truncated at 7 days. ED, emergency department. ICU, intensive care unit. Peri-op, perioperative area. IV, intravenous.

Appendix 1. Determination of Time Zero

Per the Specifications Manual for National Hospital Inpatient Quality Measures Version 5.2 (https://www.jointcommission.org/specifications_manual_for_national_hospital_inpatient_quality_measures.aspx), time zero of sepsis requires 2 signs of a systemic inflammatory response and 1 sign of organ dysfunction in the setting of suspected or confirmed infection. We determined time zero without chart review using an automated algorithm that identified the first moment in time within a given encounter when a patient's laboratory values and vital signs met these criteria.

To proxy for provider suspicion of infection, time zero was required to occur within 48 hours of an order for an antibiotic, antifungal, or clinical culture (described below). Clinical documentation was not used in the determination of time zero, both because of challenges associated with natural language processing and because the time stamps associated with a given note (i.e., when a noted is opened, when a note is signed) were considered unreliable indicators of when infection was first suspected. A 48-hour window was used to account for situations in which an abnormal value on daily morning labs (i.e., new leukocytosis) did not arouse suspicion for infection until found to be persistent the following day.

Definitions of Clinical Cultures, Bloodstream Infection

For determination of time zero, placement of an order for an antibiotic, antifungal agent, or "clinical culture" were used as a proxy for suspicion of infection.

Supplemental Table 1A. Tests Included as "Clinical Cultures"

Bacterial, fungal, or acid-fast bacilli cultures from any site
Specific bacterial tests based on polymerase chain reaction, including tests for *Bordetella pertussis*, *Mycobacterium tuberculosis*, *Chlamydophila pneumonia*, and multiplex enteric pathogen panel
Specific antigen testing for *Cryptococcus*, *Legionella pneumophila*, *Streptococcus pneumoniae*, and Rotavirus
Cultures or smears for specific organisms, including Pneumocystis, Nocardia, Legionella, and Malaria
Specific viral tests based on polymerase chain reaction, including influenza, enterovirus, norovirus, and the multiplex respiratory virus panel (excluding CMV); Herpesviridae (including CMV, HSV, VZV and EBV) were excluded
Notable exclusions included surveillance cultures for Methicillin-resistant *Staphylococcus aureus*, Vancomycin-resistant enterococci, and Carbapenem-resistant Enterobacteriaceae; Other exclusions included tests for sexually transmitted diseases, HIV, parasites, *H. pylori*, *C. difficile*, hepatitis, non-specific fungal markers (galactomannan, B-D glucan), serological tests (IgM, IgG), viral culture, Gram stains without a culture

Blood cultures were considered positive with growth of any organism except the following potential skin contaminants:

- Coagulase negative Staphylococci
- *Bacillus* species, not anthracis
- *Corynebacterium* species or "diphtheroids"
- *Aerococcus* species
- *Micrococcus* species
- *Propionibacterium* species

However, if a single potential skin contaminant was isolated from two separate blood cultures within 1 week of onset of sepsis, blood cultures were considered positive.

Appendix 2. Validation of Automated Algorithm for Determination of Time Zero

Time zero from the automated algorithm was compared to the "time of presentation date" recorded by trained chart abstracters for CMS reporting from the study period. The automated algorithm and chart abstracters agreed on the date of onset of sepsis in 91 of 108 cases (84%). In community-onset sepsis, the automated algorithm and chart abstracters agreed in 86 of 91 cases (94.5%). In hospital-onset sepsis, the automated algorithm and chart abstracters agreed in 10 of 17 cases (58.8%).

Cases of hospital-onset sepsis in which the automated algorithm and chart abstracters disagreed on time zero were reviewed. There were 5 cases in which the time of presentation date recorded by the chart abstracter did not match clinical documentation, 1 case in which the automated algorithm did not match clinical documentation, and 1 case in which neither matched clinical documentation.

An additional 30 charts from patients with hospital-onset included in the analysis were reviewed to evaluate determination of time zero by the automated algorithm. In all 30 cases, time zero as determined by the automated algorithm represented a moment of clinical instability. In 25 cases (83%), provider notes either concurrent with or immediately following time zero reported suspected infection. In two cases, the automated algorithm captured a non-septic episode in which a patient was intubated for severe neurologic injury and had respiratory cultures sent at time of intubation.

Supplemental Table 1B. Cases of Disagreement with Time Zero from Automated Algorithm and Trained Chart Abstracters

Time of presentation date from chart abstracter does not match clinical documentation	#1. The patient was admitted with stroke. Chart abstracter (CA) recorded sepsis from hospital day 3 (HD3). At that time, the patient was agitated and hypertensive, but provider note reports "no evidence of infection". Automated algorithm (AA) identified time zero on HD4 in setting of new leukocytosis and new requirement of Bi-PAP. The following morning, provider note first reports work-up and management for sepsis. #2. The patient was admitted with small bowel obstruction. Admitting H+P was started on HD1 but signed on HD2 and reports severe sepsis based on labs which resulted on HD2. CA recorded sepsis presentation from HD1. AA identified time zero on HD2. #3. The patient presented with altered mental status and respiratory failure. She failed Bi-PAP and required intubation on HD2. Provider note does not mention sepsis until HD2. CA recorded sepsis presentation from HD1. AA identified time zero on HD2. #4. The patient presented with pneumonia. On HD2, Bi-PAP was initiated for respiratory failure. Admission H+P reports "no signs of sepsis." Progress note from HD2 first adds sepsis to the problem list. CA recorded sepsis presentation as HD1. AA identified time zero on HD2. #5. The patient presented with hyperglycemia and lower extremity cellulitis. He required intubation and developed shock on HD1. Provider notes do not mention septic shock until HD2. CA recorded time of presentation as HD2, AA identified time zero on HD1.
Automated Algorithm does not match clinical documentation	#1. The patient presented with syncope. Admission H+P reports severe sepsis. CA recorded sepsis from HD1. AA identified time zero associated with an aspiration event and subsequent febrile neutropenia on HD11.
Neither matches clinical documentation	#1. The patient presented with hypoglycemia and was already on oral antibiotics for pneumonia from a previous admission. CA recorded sepsis from HD1. AA identified time zero on HD10 associated with a fever and neutropenia attributed to chemotherapy. Blood cultures were obtained, but antibiotics were not changed from oral therapy for pneumonia. Broad-spectrum antibiotics were initiated for hypotension on HD17. The diagnosis of sepsis is not mentioned until hospital day 29, when the patient developed a bowel perforation.

Appendix 3. Covariates

Covariates included year of admission, patient age, gender, baseline health, pathogen, source of infection, immunosuppression, and hospital.

Baseline health was represented by count of conditions present from the Elixhauser Comorbidity Index, a set of chronic illnesses that are known to influence in-hospital mortality.[88, 89]

Presence of pneumonia, urinary tract infection, and skin and/or soft tissue infection were determined by diagnosis codes for the encounter. Sets of diagnosis codes were developed and validated using the Healthcare Utilization Project's Clinical Classification Software (https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp#download) as a guide. A category was not created for abdominal infections because the Clinical Classification Software does not distinguish between infectious and non-infectious etiologies for multiple intra-abdominal processes, including "diverticulosis and diverticulitis," "biliary tract disease," and "hepatitis". Categories of infection were not mutually exclusive—a patient was allowed to carry a diagnosis of urinary tract infection, pneumonia, and skin or soft tissue infection concurrently.

Presence of bloodstream infection was defined by a positive blood culture within 1 week of sepsis (including both bacterial and fungal pathogens but excluding possible skin contaminants, see Appendix 1).

Immunosuppression was determined by receipt of chemotherapy, corticosteroid, or other immunosuppressive medication. HIV status was not considered when determining whether an individual was immunosuppressed.

The postoperative period included days 1-90 after a major diagnostic or therapeutic procedure as defined by the Healthcare Cost and Utilization Project's procedure classes (https://www.hcup-us.ahrq.gov/toolssoftware/procedure/procedure.jsp).

Relevant pathogens were identified by positive culture within 1 week of sepsis, including cultures both preceding and following time zero. Multi-drug resistant Gram-negatives were defined by resistance to at least 3 classes of antibiotics with potential efficacy.

Appendix 4. Diagnosis Codes Used For Inclusion Criteria

Supplemental Table 2. Patient Identification ICD-9-CM Search Criteria[90]

<table>
<tr><th>Sepsis Codes Requiring Organ Dysfunction</th><th>Organ Dysfunction Codes</th></tr>
<tr><td>• Septicemia (038.0, 038.10, 038.11, 038.12, 038.19, 038.2, 038.3, 038.40, 038.41, 038.42, 038.43, 038.44, 038.49, 038.8, 038.9)
• SIRS (995.90)
• Sepsis (995.91)
• Bacteremia (790.7)
• Other fungal infection (117.9)
• Systemic candidiasis (112.5)
• Candidal endocarditis (112.81)
• Acute and subacute bacterial endocarditis (421.0)
• Acute endocarditis (421.9)
• Salmonella septicemia (003.1)
• Septicemic plague (020.2)
• Anthrax septicemia (022.3)
• Meningococcal septicemia (036.2)
• Waterhouse-Friderichsen syndrome (036.3)
• Herpetic septicemia (054.5)
• Gonococcemia (098.89)
• Sepsis due to indwelling urinary catheter (996.64)
• Infection due to central venous catheter (999.31, 999.32)</td><td>Diagnoses
• Respiratory (518.51, 518.81, 518.82, 518.84, 786.09, 799.1)
• Cardiovascular (458.0, 458.21, 458.29, 458.8, 458.9, 785.50, 785.51, 785.59, 796.3)
• Renal (584.5, 584.6, 584.7, 584.8, 584.9)
• Hepatic (570, 572.2, 573.4)
• Hematologic (286.6, 286.7, 286.9, 287.49, 287.5)
• Metabolic (276.2)
• Neurologic (293.0, 293.1, 293.9, 348.30, 348.31, 348.39, 357.82, 359.81, 780.09)

Procedures
• Respiratory (93.90, 96.70, 96.71, 96.72, 31.1, 33.21, 33.22, 33.23, 33.24, 33.27, 31.29)
• Cardiovascular (00.17, 88.72, 89.62, 89.64)
• Renal (39.95)
• Hematologic (99.04, 99.05, 99.06, 99.07)
• Neurologic (89.14)</td></tr>
<tr><td colspan="2">Sepsis Codes Sufficient without Concurrent Organ Dysfunction</td></tr>
<tr><td colspan="2">• Severe sepsis (995.92)
• Septic shock (785.52)</td></tr>
</table>

Supplemental Table 2 is drawn from:

Martin GS, Mannino DM, Eaton S, et al., The epidemiology of sepsis in the United States from 1979 through 2000. New England Journal of Medicine, 2003. 348(16): p. 1546-1554.

Supplemental Table 3. Patient Identification ICD-10-CM Search Criteria

Sepsis Codes Requiring Organ Dysfunction	Organ Dysfunction Codes
• Sepsis: A02.1, A03.9, A04.7, A20.7, A21.7, A22.7, A23.9, A24.1, A26.7, A28.0, A28.2, A32.7, A39.2, A39.3, A39.4, A40.0, A40.1, A40.3, A40.8, A40.9, A41.01, A41.02, A41.1, A41.2, A41.3, A41.4, A41.50, A41.51, A41.52, A41.53, A41.59, A41.81, A41.89, A41.9, A42.7, A54.86, B00.7, B37.7, B95.4, B95.61, B95.620, J18.9, J44.0, N39.0	• Respiratory (J80, J96.00, J96.01, J96.02, J96.90, J96.91, J96.92, R09.2) • Cardiovascular (R57.0, R57.1, R57.8, R57.9, I95.1, I95.9) • Renal (N17.0, N17.1, N17.2, N17.8, N17.9) • Hepatic (K72.0, K72.9, K76.3) • Neurological (F05, F05.9, G93.1, G93.40, G93.41) • Hematologic (D69.5, D69.6, D65) • Procedures (0BH13EZ, 0BH17EZ, 0BH18EZ)
Sepsis Codes Sufficient without Concurrent Organ Dysfunction	
• Severe sepsis without septic shock (R65.20) • Severe sepsis with septic shock (R65.21)	

Appendix 5. Sensitivity Analyses

Supplemental Table 4. Patient Characteristics by Hospital

	Hospital 1	Hospital 2	Hospital 3	Hospital 4
Sample size – n	1576	1346	1033	703
Age – mean (sd)	61.1 (18.0)	70.5 (17.2)	58.1 (16.5)	60.9 (16.9)
Female – n (%)	677 (43.0)	632 (47.0	463 (44.8)	290 (41.3)
ECI – median (IQR)	5 (3 – 7)	5 (3 – 7)	5 (3 – 8)	5 (3 – 7)
Immunosuppressed – n (%)	503 (31.9)	171 (12.7)	419 (40.6)	328 (46.7)
Postoperative – n (%)	183 (11.6)	66 (4.9)	42 (4.1)	53 (7.5)
Hospital-onset – n (%)	571 (36.2%)	380 (28.2%)	477 (46.2%)	278 (39.5%)
Infection site				
Pneumonia – n (%)	729 (46.3)	694 (51.6)	474 (45.9)	326 (46.4)
UTI – n (%)	526 (33.4)	546 (40.6)	338 (32.7)	200 (28.5)
SSTI – n (%)	171 (10.9)	146 (10.9)	139 (13.5)	66 (9.4)
BSI – n (%)	419 (26.6)	360 (26.8)	361 (35.0)	214 (30.4)
Pathogen				
MSSA – n (%)	105 (6.7)	67 (5.0)	83 (8.0)	43 (6.1)
MRSA – n (%)	129 (8.2)	152 (11.3)	132 (12.8)	54 (7.7)
MDR Gram-negative – n (%)	23 (1.5)	39 (2.9)	127 (12.3)	62 (8.8)
VRE – n (%)	30 (1.9)	23 (1.7)	31 (3.0)	14 (2.0)
Organ Dysfunction at Time 0				
Low blood pressure	669 (42.5)	599 (44.5)	682 (66.0)	413 (58.8)
Elevated creatinine	206 (13.1)	109 (8.1)	148 (14.3)	82 (11.7)
Elevated bilirubin	100 (6.4)	63 (4.7)	108 (10.5)	61 (8.7)
Thrombocytopenia	155 (9.8)	115 (8.5)	130 (12.6)	100 (14.2)
Coagulopathy	148 (9.4)	72 (5.4)	179 (17.3)	125 (17.8)
Elevated serum lactate	404 (25.6)	374 (27.8)	22 (2.1)	12 (1.7)
Multiple	256 (16.2)	144 (10.7)	157 (15.2)	75 (10.7)
Outcome				
SEP-1 Adherence – n (%)	435 (27.6)	594 (44.3)	236 (22.9)	172 (24.5)
LOS – median (IQR)	13 (6 – 25)	8 (5 – 15)	10 (5 – 20)	10 (5 – 21)
Mortality – n (%)	319 (20.2)	267 (19.8)	180 (17.4)	155 (22.1)

Legend: ECI, Elixhauser Comorbidity Index; IQR, interquartile range; UTI, urinary tract infection; SSTI, skin/soft tissue infection; BSI, bloodstream infection; MSSA, Methicillin-sensitive *Staphylococcus Aureus*; MRSA, Methicillin-resistant *Staphylococcus Aureus*; MDR, multi-drug resistant; VRE, Vancomycin-resistant enterococci; SEP-1, Early Management Bundle, Severe Sepsis / Septic Shock; LOS, overall length of stay for admission

Supplemental Table 5. Association between SEP-1 Bundle and Patient Factors at Each Study Hospital, Expressed in Terms of Relative Risk

	Hospital 1 (n = 1576)	Hospital 2 (n = 1346)	Hospital 3 (n = 1033)	Hospital 4 (n = 703)	All but Hospital 2 (n = 3312)
Age in years	1.00 (p = 0.19)	1.00 (p = 0.38)	1.00 (p = 0.65)	1.00 (p = 0.19)	1.00 (p = 0.14)
Female	0.97 (p = 0.70)	1.00 (p = 0.96)	1.05 (p = 0.61)	1.01 (p = 0.94)	1.01 (p = 0.84)
ECI	0.98 (p = 0.21)	**0.95 (p < 0.001)**	0.99 (p = 0.61)	0.99 (p = 0.72)	0.99 (p = 0.25)
Immunosuppressed	1.06 (p = 0.54)	1.03 (p = 0.77)	0.92 (p = 0.41)	0.94 (p = 0.64)	0.94 (p = 0.33)
Postoperative	**0.63 (p = 0.040)**	0.68 (p = 0.083)	0.41 (p = 0.13)	0.63 (p = 0.33)	**0.55 (p = 0.002)**
Fever	**1.64 (p < 0.001)**	**1.17 (p = 0.016)**	**1.58 (p < 0.001)**	**1.65 (p < 0.001)**	**1.56 (p < 0.001)**
Hospital-Onset	**0.27 (p < 0.001)**	**0.33 (p < 0.001)**	**0.40 (p < 0.001)**	**0.30 (p < 0.001)**	**0.33 (p < 0.001)**
Infection site					
Pneumonia	1.05 (p = 0.53)	0.98 (p = 0.71)	1.04 (p = 0.72)	1.03 (p = 0.84)	1.07 (p = 0.27)
UTI	0.91 (p = 0.27)	1.05 (p = 0.55)	1.05 (p = 0.68)	0.98 (p = 0.86)	0.94 (p = 0.31)
SSTI	1.13 (p = 0.31)	1.11 (p = 0.24)	1.03 (p = 0.84)	1.26 (p = 0.21)	1.14 (p = 0.13)
BSI	**1.25 (p = 0.007)**	**1.15 (p = 0.037)**	1.19 (p = 0.077)	1.07 (p = 0.60)	**1.23 (p = 0.001)**
Pathogen					
MSSA	0.88 (p = 0.36)	0.99 (p = 0.96)	1.05 (p = 0.72)	0.60 (p = 0.064)	0.93 (p = 0.47)
MRSA	1.18 (p = 0.18)	0.91 (p = 0.34)	1.18 (p = 0.24)	0.68 (p = 0.20)	1.12 (p = 0.22)
MDR Gram-Negative	1.40 (p = 0.12)	1.15 (p = 0.36)	0.94 (p = 0.71)	0.74 (p = 0.18)	0.95 (p = 0.67)
VRE	1.19 (p = 0.50)	1.07 (p = 0.77)	0.97 (p = 0.90)	0.25 (p = 0.19)	0.98 (p = 0.89)

Legend: ECI, Elixhauser Comorbidity Index; UTI, urinary tract infection; SSTI, skin/soft tissue infection; BSI, bloodstream infection; MSSA, Methicillin-sensitive Staphylococcus Aureus, MRSA, Methicillin-resistant Staphylococcus Aureus, MDR, multi-drug resistant; VRE, Vancomycin-resistant enterococci

Supplemental Table 6. Association between SEP-1 Bundle and Patient Factors by Admitting Specialty, Expressed in Terms of Relative Risk

	Non-Surgical Service (n = 4111)	Surgical Service (n = 550)	Hospitalist* (n = 702)	Internal Medicine* (n = 1085)
Age	1.00 (p = 0.13)	1.01 (p = 0.27)	1.00 (p = 0.63)	1.00 (p = 0.39)
Female	1.01 (p = 0.86)	0.93 (p = 0.73)	1.20 (p = 0.063)	0.95 (p = 0.48)
ECI	**0.98 (p < 0.001)**	0.96 (p = 0.27)	0.98 (p = 0.21)	**0.96 (p = 0.006)**
Immunosuppressed	0.98 (p = 0.65)	0.73 (p = 0.24)	0.84 (p = 0.12)	1.04 (p = 0.64)
Postoperative	**0.70 (p = 0.025)**	**0.38 (p = 0.012)**	1.01 (p = 0.97)	0.70 (p = 0.17)
Fever	**1.32 (p < 0.001)**	**4.05 (p < 0.001)**	**1.55 (p < 0.001)**	**1.30 (p = 0.001)**
Hospital-Onset	**0.35 (p < 0.001)**	**0.37 (p < 0.001)**	**0.36 (p < 0.001)**	**0.33 (p < 0.001)**
Infection site				
Pneumonia	1.04 (p = 0.37)	1.02 (p = 0.94)	**1.30 (p = 0.015)**	0.98 (p = 0.84)
UTI	1.00 (p = 0.92)	0.80 (p = 0.34)	1.07 (p = 0.57)	1.09 (p = 0.25)
SSTI	1.11 (p = 0.11)	0.87 (p = 0.68)	**1.45 (p = 0.005)**	1.01 (p = 0.93)
BSI	**1.21 (p < 0.001)**	1.43 (p = 0.18)	1.23 (p = 0.064)	1.05 (p = 0.53)
Pathogen				
MSSA	0.99 (p = 0.87)	0.67 (p = 0.30)	0.71 (p = 0.12)	0.94 (p = 0.71)
MRSA	1.02 (p = 0.73)	1.12 (p = 0.72)	0.92 (p = 0.66)	1.13 (p = 0.27)
MDR Gram-Negative	1.00 (p = 0.99)	0.91 (p = 0.95)	0.88 (p = 0.52)	0.97 (p = 0.88)
VRE	0.95 (p = 0.73)	1.39 (p = 0.50)	0.54 (p = 0.14)	1.07 (p = 0.81)

Legend: ECI, Elixhauser Comorbidity Index; UTI, urinary tract infection; SSTI, skin/soft tissue infection; BSI, bloodstream infection; MSSA, Methicillin-sensitive Staphylococcus Aureus, MRSA, Methicillin-resistant Staphylococcus Aureus, MDR, multi-drug resistant; VRE, Vancomycin-resistant enterococci

Supplemental Table 7. Association between SEP-1 Bundle and Patient Factors Based on Time Zero > 48 Hours After Admission, Expressed in Terms of Relative Risk

	Relative Risk
Age	**1.03 (p = 0.012)**
Female	1.01 (p = 0.80)
ECI	**0.98 (p = 0.001)**
Immunosuppressed	0.95 (p = 0.29)
Postoperative	**0.50 (p < 0.001)**
Fever	**1.47 (p < 0.001)**
Time Zero > 48 Hours After Admission	**0.30 (p < 0.001)**
Infection Site	
Pneumonia	1.08 (p = 0.075)
UTI	0.99 (p = 0.85)
SSTI	1.05 (p = 0.43)
BSI	**1.27 (p < 0.001)**
Pathogen	
MSSA	0.93 (p = 0.35)
MRSA	1.07 (p = 0.27)
MDR Gram-Negative	0.98 (p = 0.90)
VRE	1.03 (p = 0.80)

Legend: ECI, Elixhauser Comorbidity Index; UTI, urinary tract infection; SSTI, skin/soft tissue infection; BSI, bloodstream infection; MSSA, Methicillin-sensitive Staphylococcus Aureus, MRSA, Methicillin-resistant Staphylococcus Aureus, MDR, multi-drug resistant; VRE, Vancomycin-resistant enterococci

CHAPTER 3

Title: Effect of the SEP-1 Sepsis Bundle on Mortality in Hospital-Onset v. Community-Onset Sepsis: A Retrospective Cohort Study

Running Title: SEP-1 and Mortality in Hospital-Onset Sepsis

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Appendices: 1

Title: Effect of the SEP-1 Sepsis Bundle on Mortality in Hospital-Onset v. Community-Onset Sepsis: A Retrospective Cohort Study

Abstract

SEP-1 is a care bundle for the early sepsis management. Published evidence regarding an effect of SEP-1 on mortality is mixed and largely excludes patients with hospital-onset sepsis.

Methods Retrospective cohort study using clinical data from 4 hospitals. The purpose was to estimate the treatment effect of the SEP-1 sepsis bundle and four bundle components—blood cultures, serum lactate, broad-spectrum antibiotics, and intravenous fluids—in cohorts with hospital-onset and community-onset sepsis. The primary outcome was in-hospital mortality, and days on vasopressors (vasopressor days) was the secondary outcome. To control for nonrandom treatment assignment, each cohort was reweighted using propensity scores and Mahalanobis distance between variables to balance patients who did and did not receive treatment on observable covariates.

Results 6,404 sepsis-related patient encounters met the inclusion criteria, including 4,144 patients with community-onset sepsis and 2,260 patients with hospital-onset sepsis. In the community-onset cohort, checking a serum lactate within 3 hours of time zero of sepsis was the only bundle component associated with reduced mortality (7.23% reduction, 95% CI -14.2% to -0.25%). However, three of the four bundle components were associated with fewer days on vasopressors, including blood cultures (-0.94 days, 95% CI -1.70 to -0.19), serum lactate (-0.67 days, 95% CI -1.19 to -0.14), and antibiotics (-0.48 days, 95% CI -0.83 to -0.14). In the hospital-onset cohort, broad-spectrum antibiotics were the only bundle component associated with any treatment effect (mortality reduced by 4.96%, 95% CI -9.80% to -0.12%). The SEP-1 bundle was not associated with a treatment benefit in either cohort or in the total sample.

Conclusions Multiple SEP-1 bundle components were associated with treatment benefit in the cohort with community-onset sepsis, but only antibiotics provided benefit in the cohort with hospital-onset sepsis. The SEP-1 care bundle was not associated with treatment benefit in any cohort or the total sample.

Introduction

Most patients with sepsis exhibit the signs and symptoms of a dysregulated host response to infection at time of admission to the hospital (i.e., community-onset sepsis).[19, 26, 27] Only 10-20% of cases are hospital-onset, meaning the signs and symptoms develop after admission. Individuals with sepsis vary dramatically in their risk of mortality.[11, 101, 102] On average, in-hospital mortality is more frequent in hospital-onset sepsis than in community-onset.[10, 19, 25, 84]

Protocols that combine multiple interventions for early sepsis care, or sepsis bundles, have mainly been studied in community-onset sepsis.[8, 46, 106] In hospital-onset sepsis, the effectiveness of sepsis bundles remains unproven. Nonetheless, the Early Management Bundle for Severe Sepsis / Septic Shock (National Quality Forum #0500), abbreviated as SEP-1, has been adopted as a core measure and is recommended for all patients with sepsis, including cases of hospital-onset.[36, 107] The purpose of this study was to compare the impact of the SEP-1 sepsis bundle on mortality and organ dysfunction in patients with community-onset and hospital-onset sepsis, and, by extension, to determine whether SEP-1 is a valid quality metric in patients with hospital-onset sepsis.

Materials and Methods

Data Source

We obtained clinical data from the electronic health records of four University of California hospitals offering diverse clinical services, including solid and liquid organ transplantation and subspecialty surgery. All data were collected as part of routine clinical care. The UCLA IRB approved the protocol for this study.

Definitions

We defined "sepsis" as suspected infection with organ dysfunction, including syndromes previously called severe sepsis and septic shock, based on Sepsis-3.[2] Other definitions were based on the CMS core measure SEP-1 (National Quality Forum #0500).[86]

"Time zero" of sepsis requires 2 signs of a systemic inflammatory response and 1 sign of organ dysfunction in the setting of suspected or confirmed infection. We determined time zero using an automated algorithm that identified the first instance in a given encounter when a

patient's laboratory values and vital signs met these criteria, rather than with chart review. To proxy for provider suspicion of infection, time zero was required to occur within 48 hours of an order for an antibiotic, antifungal, or clinical culture. A 48-hour window for provider suspicion was chosen to capture situations in which morning labs show a new abnormality, such as leukocytosis, that does not a provoke a response until found to be persistent the following day. 2-day window periods have been employed for similar purposes in other electronic measures attempting to identify episodes of sepsis, such as the "adult sepsis event".[108, 109] Hospital-onset sepsis was defined by occurrence of time zero after arrival on an inpatient unit.

Variables

The primary outcome was in-hospital mortality expressed as an absolute risk difference comparing those who did and did not receive the sepsis bundle. Negative values represented mortality reduction, or increased likelihood of survival, with treatment.

The secondary outcome was requirement of blood pressure support with a vasopressor in the 10 days following time zero, expressed as vasopressor days. Vasopressor days are a marker of organ dysfunction that may reflect improved sepsis physiology in the absence of a mortality difference.[110] When counting vasopressor days, death was given equal weight to vasopressor administration; thus, patients who expired within the 10-day window were counted as being on vasopressors from time of death until the end of day 10. This method of accounting for deaths is typical, if not universal, when counting organ support-free days.[110, 111] Vasopressor days were used, rather than vasopressor-free days,[111] so that the sign matched the primary outcome (i.e., lower mortality and fewer vasopressor days represent a treatment benefit). A 10-day window was chosen to limit bias from lack of post-discharge follow-up. Because our data set provided medication administration times rather than calendar dates, vasopressor days were calculated based on the number of hours in which vasopressors were administered.

Treatments evaluated included the complete SEP-1 bundle and four of its core components: (1) blood cultures, (2) broad-spectrum antibiotics, (3) serum lactate, and, if the blood pressure is low or lactate elevated, (4) intravenous crystalloid. Each of these core components is required within 3 hours of onset of sepsis. Additionally, the complete SEP-1 bundle requires a re-assessment of tissue perfusion (including an evaluation for persistent hypotension after fluids), a follow-up serum lactate if initially elevated, and initiation of

vasopressors for persistent hypotension. Among these additional components, the re-assessment of tissue perfusion was excluded from our evaluation due to inconsistencies in charting among the study sites and lack of a relevant structured field in the electronic health record.

Covariates included year of admission, patient age, gender, baseline health, source of infection, immunosuppression, postoperative status, features of sepsis such as fever and shock, and admitting hospital. Baseline health was represented by count of conditions present from the Elixhauser Comorbidity Index, a set of chronic illnesses that are known to influence in-hospital mortality.[88, 89] Source of infection was determined by diagnosis codes for pneumonia, urinary tract infection, or skin and/or soft tissue infection that were marked "present on admission." Immunosuppression was determined by receipt of chemotherapy, corticosteroid, or other immunosuppressive medication. The postoperative period included days 1-90 after a major diagnostic or therapeutic procedure as defined by the Healthcare Cost and Utilization Project's procedure classes (https://www.hcup-us.ahrq.gov/toolssoftware/procedure/procedure.jsp). Septic shock was defined per the CMS manual by either persistent hypotension after intravenous fluids or an elevated lactate ≥ 4 mmol/L. New bacteremia was defined by a positive blood culture in the 7 days following onset of sepsis in absence of a previous positive culture (including both bacterial and fungal pathogens but excluding possible skin contaminants).

Study Design

Retrospective observational study estimating the treatment effect of the SEP-1 bundle and core components in eligible cohorts with community-onset and hospital-onset sepsis.

Inclusion and Exclusion Criteria

For this study, we included all hospital admissions with a diagnosis consistent with sepsis or disseminated infection that occurred at one of the 4 study hospitals between 10/01/2014 and 10/01/2017. Individual patients were allowed to contribute multiple encounters. Exclusion criteria were as specified by SEP-1: hospitalization >120 days or <6 hours, admission by transfer from other acute care facility, or receipt of intravenous antibiotics for 24 hours or longer at time zero of sepsis. We also excluded patients younger than age 18.

For encounters prior to October 1, 2015, the set of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) diagnosis codes used to identify

sepsis encounters was based on methodology employed by Martin et. al[90] that has since been validated and replicated in the sepsis literature.[91-93] For hospitalizations after October 1, 2015, the ICD-10-CM diagnosis codes provided by CMS for use with SEP-1 were paired with diagnosis codes for organ dysfunction in a process analogous to the Martin methodology.

Statistical Analysis

The average treatment effect on the treated attributable to the SEP-1 bundle was estimated by comparing outcomes between patients who did and did not receive SEP-1. To address non-random treatment assignment, we used "doubly robust" endogenous treatment effects models. First, we generated weights using propensity scores and Mahalanobis distance between key variables to balance the samples of treated and untreated patients on observable characteristics (Stata command *kmatch*). We then performed regression adjustment incorporating the propensity score on the re-weighted sample (Stata command *teffects ra*).

Propensity scores were estimated separately for the complete SEP-1 bundle and each component in cohorts with community-onset sepsis, hospital-onset sepsis, and the total sample. We evaluated the models using balance diagnostics, including comparison of standardized differences of the means.[112-114] We estimated 95% confidence intervals (CI) for outcomes using bootstrapping methods. We used Stata/IC version 14.1 for all analyses. All analyses were prespecified.

Results

Characteristics of the Total Sample

6,404 sepsis-related patient encounters met the inclusion and exclusion criteria. Of these, 2,260 (35%) patients had hospital-onset sepsis and 4,144 (65%) had community-onset. The average age was 66 years, and 45% were female. 1,475 (23%) patients were immunosuppressed. 1,786 (28%) were diagnosed with pneumonia present on admission. 1,722 (27%) cases of sepsis were associated with fever, and 2,436 (38%) met the criteria for septic shock. After onset of sepsis, 928 (14%) patients were found on blood culture to have new bacteremia. 1,928 (30%) patients received SEP-1-adherent care. Inpatient mortality occurred in 1,216 (19%) encounters.

Characteristics of the Cohort with Community-Onset Sepsis

In the cohort with community-onset sepsis, patients who received SEP-1 differed significantly from those who did not (Table 1). Patients with community-onset sepsis who received SEP-1, compared with those who did not receive SEP-1, were slightly older (mean age 66 vs. 65), had fewer comorbidities (4.9 v. 5.2 Elixhauser conditions), were less frequently postoperative (1.8% v. 2.9%), and more often had pneumonia present on admission (35% v. 30%). Regarding signs and symptoms in this cohort, patients in this cohort who received SEP-1 were more frequently febrile (38% v. 27%) and less often developed shock (26% v. 47%) than those who did not receive SEP-1. Mortality from community-onset sepsis was 18%.

Many of the differences observed between those who did and did not receive SEP-1 in the cohort with community-onset sepsis were independently associated with mortality, including number of Elixhauser comorbidities, presence of pneumonia, development of septic shock, and presence of fever (Supplemental Table 1). After being reweighted, patients with community-onset sepsis who did and did not receive the SEP-1 bundle were similar in their observable characteristics (Table 1).

Characteristics of the Cohort with Hospital-Onset Sepsis

Significant differences were identified within the cohort of patients with hospital-onset sepsis between those who received SEP-1 and those who did not (Table 2). Patients with hospital-onset who received SEP-1, compared with those who did not receive SEP-1, developed sepsis earlier in their hospital course (51 v. 74 hours after arrival), were less frequently postoperative (10% v. 18%), more often had pneumonia present on admission (27% v. 20%), more frequently had skin and/or soft tissue infection present on admission, (8.4 v. 5.3%), and were less frequently immunosuppressed (23 v. 31%). Regarding signs and symptoms in this cohort, patients who received SEP-1 were more frequently febrile (33% v. 18%) than those who did not receive SEP-1. Mortality from hospital-onset sepsis was 20%.

Among patients with hospital-onset sepsis, frequency of fever was the only difference between those who did and did not receive SEP-1 that was associated with mortality (Supplementary Table 1). After being reweighted, patients with hospital-onset sepsis who did and did not receive the SEP-1 bundle were similar in their observable characteristics (Table 2).

Treatment Effects in the Cohort with Community-Onset Sepsis

In the reweighted cohort with community-onset sepsis, the complete SEP-1 bundle was not associated with a treatment benefit (Table 3). However, three of the four bundle components evaluated were associated with improved outcomes. Measurement of serum lactate was associated with a 7.23 percentage-point reduction in risk of mortality (95% confidence interval -14.2% to -0.25%) and 0.67 fewer vasopressor days (equivalent to 16 hours on vasopressors, 95% confidence interval -1.19 to -0.14). Obtaining blood cultures (-0.94, 95% confidence interval -1.70 to -0.19) and starting broad-spectrum antibiotics (-0.48, 95% confidence interval -0.83 to -0.13) were both associated with fewer vasopressor days.

Treatment Effects in the Cohort with Hospital-Onset Sepsis

In the reweighted cohort, broad-spectrum antibiotics reduced mortality by 4.96 percentage points (-4.96% risk difference, 95% confidence interval -9.80% to -0.12%), on average (Table 3). Blood cultures, serum lactate, intravenous fluids, and the SEP-1 bundle were not associated with treatment benefit in terms of mortality or vasopressor days.

Treatment Effects in the Total Sample and Other Cohorts

Estimates of treatment effects associated with SEP-1 and the four components in the reweighted total sample and other reweighted cohorts are listed in Supplemental Tables 4, 6 and 7. In the reweighted total sample, broad-spectrum antibiotics were associated with a 3.19 percentage-point reduction in mortality (-6.37% to -0.01%). The SEP-1 bundle was not associated with a treatment benefit in the reweighted total sample or any other reweighted cohort; rather, SEP-1 was associated with increased vasopressor use in multiple cohorts.

Discussion

Sepsis is a leading cause of death in the hospital.[19] In this retrospective analysis of observational data from 4 medical centers, we found that SEP-1, the protocol for early sepsis management that is currently recommended by professional societies in critical care and has been adopted by CMS as a core measure, was not associated with a reduction in mortality or decreased requirement for vasopressor support among eligible patients. Our work adds to the

growing body of literature suggesting that SEP-1 may not impact outcomes, particularly in hospital-onset sepsis.[7, 33]

Sepsis is widely recognized as a heterogeneous condition.[11] Classically, this heterogeneity is understood as comprising different types of patients, pathogens, infections, immune responses, and dysfunctional organ systems.[82] In this study, we added a new layer: patients with sepsis differ in their level of risk and likelihood of response to therapy based on the context in which sepsis arises. We identified significant differences in the performance of SEP-1 and its components based on where a patient was located when sepsis presented. To our knowledge, this study is the first to estimate the impact of the SEP-1 care bundle in a large cohort of patients with hospital-onset sepsis.

It should be noted that we defined "hospital-onset" by whether time zero occurred after admission to an inpatient unit, rather than with a time cut-off (i.e., 48 hours after admission) or based on whether a diagnosis code was marked "present on admission." We chose this definition to isolate differences in systems and processes for care delivery between the emergency department and inpatient areas. Though SEP-1 is complicated, it is by no means comprehensive. It is not the act of checking a serum lactate within 3 hours of time zero that is expected to influence the outcome, but rather what is done in response to the serum lactate. We suspect that the impact of checking a serum lactate within 3 hours of time zero (and the rest of the SEP-1 bundle) differs in the inpatient and emergency settings because of what happens in response.

The SEP-1 bundle appears to correlate better with sepsis outcomes in community-onset sepsis than in hospital-onset sepsis. In the community-onset cohort, multiple bundle components were associated with treatment benefit; in the hospital-onset cohort, only broad-spectrum antibiotics within 3 hours of time zero were. Thus, we suspect that protocolized care may only facilitate effective management of sepsis in the emergency department—a setting in which checking a serum lactate may guide triage and in which blood cultures are not routine. In the inpatient setting, it may be more appropriate to individualize care. Though rapid recognition of sepsis and initiation of antibiotics should be emphasized, the decision to initiate empiric broad-spectrum antibiotics for sepsis must be weighed against competing interests, including the need for antibiotic stewardship and patient-centered care. We suspect that more patients with hospital-onset sepsis may have underlying terminal illness—a context in which protocolized care may be less appropriate.

SEP-1 is an all-or-nothing measure. For the purpose of reporting to CMS, a case of sepsis in which a repeat serum lactate was indicated but not performed is coded identically to one in which broad-spectrum antibiotics were not administered: both are considered a failure to meet the requirements of the quality measure. Our analysis suggests that this approach is misguided. In the total sample of patients included in this study, broad-spectrum antibiotics within 3 hours of time zero were the only bundle component (of the 4 evaluated) that appeared to influence mortality. Further, antibiotics were associated with treatment benefit in both the community-onset and hospital-onset cohorts. To improve SEP-1 as a measure of quality, antibiotics should be prioritized.

There are several potential reasons why the SEP-1 bundle may not be associated with treatment benefit, either in the total sample or the cohorts with community-onset or hospital-onset sepsis. One such reason is heterogeneity of treatment effects.[115] If SEP-1 only benefits certain high risk patients, studies that include low risk patients in large numbers may fail to detect that treatment benefit. To investigate this possibility, we evaluated SEP-1 in high-risk cohorts, including patients with septic shock (Supplemental Table 5). Because SEP-1 was not effective in any cohort, heterogeneity of treatment effects would not seem to explain why we were unable to detect a benefit from SEP-1.

Another potential reason for lack of benefit from SEP-1 is that sepsis mortality is inevitable—i.e., patients who die from sepsis were going to die no matter what care was provided. An investigation from the Centers for Disease Control and Prevention Epicenters Program found that the majority of sepsis deaths are likely unpreventable, even with better care.[33] Based on our results, this explanation is plausible. We estimated that broad-spectrum antibiotics were associated with an average mortality reduction of 3.19%, corresponding to a number needed to treat of 32. Extrapolated to the 2,201 patients who did not receive SEP-1-adherent antibiotics, there may have been 70 preventable deaths—only 6% of the 1,216 deaths observed. And yet, we observed an effect on mortality from broad-spectrum antibiotics. So, lack of preventable deaths does not explain why we were unable to detect a treatment effect from SEP-1.

We suspect that the reason why SEP-1 did not demonstrate a treatment effect is because the bundle is too complicated. In our analysis, individual bundle components were associated with treatment benefit, but the complete bundle was not. The multiple components of SEP-1—

both those evaluated as "core components" in this study and those not evaluated, such as follow-up lactate or re-assessment of tissue perfusion—contribute random noise that obscures any potential signal. It would likely be easier to demonstrate a benefit from SEP-1, and less burdensome for medical centers to implement,[78] if the bundle were simplified.

Limitations

We performed a retrospective analysis using propensity scores. One major limitation is that, historically, observational studies employing propensity scores to balance routinely collected data may estimate treatment effects inaccurately.[116] The statistical models employed in this study require treatment assignment to be based exclusively on observable characteristics. Though we collected a substantial amount of clinical data, we were nonetheless likely unable to control for confounding from unobservable variables related to severity of illness, likelihood of treatment, and mortality. If, for instance, patients in our sample who were more severely ill were more likely to receive treatment with SEP-1, our results would likely be biased towards the null. Prospective studies are needed before the treatment effect associated with SEP-1, or lack thereof, can be truly known.

We were also limited by our use of mortality, a relatively insensitive outcome. Vasopressor days have been proposed as an alternative to mortality when studying septic shock.[110, 111] However, vasopressor days may not be an ideal outcome for the evaluation of the SEP-1 bundle, because bundle-adherent care requires initiation of vasopressors for persistent hypotension. Thus, increased vasopressor days among patients who receive SEP-1 may be a sign of adherent care, rather than increased organ dysfunction (at least in the period immediately following time zero). Other signs of organ dysfunction, such as days requiring mechanical ventilation or renal replacement therapy, are likely preferable but present their own challenges. Ventilator use was not consistently documented in the vital sign flowsheets at two of the hospitals participating in this study, and no study site included a structured field in the electronic health record to represent administration of renal replacement therapy.

Post-discharge follow-up data were not available. To account for this in the study design, we shortened the time window in which we evaluated patients for vasopressors from 4 weeks, which is commonly used, to 10 days.[111] Nonetheless, our estimates of vasopressor days may be biased by patients who were discharged and then expired out of the hospital within 10 days of

time zero. In these cases, we likely underestimated the number of vasopressor days and overestimated the potential benefit from treatment.

We did not perform chart review. Administration of SEP-1 components was determined using structured data from the electronic health record. Thus, we were unable to account for cases with an "administrative contraindication" to treatment—for instance, patient refusal of care. Patient preference is unobservable and thus cannot be expected to have been balanced by our matching procedures. However, this limitation should not interfere with interpretation of our results, since we explicitly set out to estimate the average effect of treatment, rather than the intention to treat.

Our results may not be generalizable. Our sample was identified using diagnosis codes and therefore did not capture individuals in whom sepsis was missed or whose diagnosis was never coded. Because we identified patients this way, our results may be sensitive to specific coding practices at the participating hospitals and may be susceptible to bias from changes in coding practices over time.[10, 19]

Finally, we performed multiple comparisons without statistical correction. Thus, the analyses whose results are reported in Supplemental Tables 5 and 6 should be considered exploratory. Treatment effects were compared between cohorts qualitatively, rather than using interaction terms.

Conclusions

As specified in the CMS manual, SEP-1 is a process measure that applies to patients with both community-onset and hospital-onset sepsis. However, we found that patients with community-onset and hospital-onset sepsis respond differently to SEP-1-adherent care. Though multiple components of SEP-1 were associated with improved outcomes among patients with community-onset sepsis, only the use of antibiotics was associated with benefit among patients with hospital-onset sepsis (and in the total sample). Based on this evidence, consideration should be given to excluding patients with hospital-onset sepsis from SEP-1. Hospital-onset sepsis and community-onset sepsis are distinct clinical entities; quality measures should reflect that distinction.

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Figures and Tables

Table 1. Characteristics of Cohort with Community-Onset Sepsis Before and After Being Reweighted

	Raw Cohort n = 4,144			Reweighted* Cohort n = 3568		
	Treated	**Untreated**	**p**	**Treated**	**Untreated**	**p**
Time Zero of Sepsis (Hours**)	2.07	3.17	**< 0.001**	1.74	1.73	0.94
Age	66.2	64.5	**0.004**	67.2	67.4	0.73
Female **(%)**	44.0	45.9	0.21	44.3	45.2	0.58
Elixhauser Comorbidities	4.90	5.24	**< 0.001**	4.71	4.73	0.80
Postoperative **(%)**	1.81	2.89	**0.028**	0.33	0.33	1.00
Pneumonia POA† **(%)**	35.2	29.7	**< 0.001**	34.0	34.0	1.00
Urinary tract infection POA **(%)**	26.3	24.9	0.33	26.8	28.2	0.36
Skin / soft tissue infection POA **(%)**	7.92	6.59	0.10	7.61	7.13	0.59
New Bacteremia‡ **(%)**	15.5	16.7	0.32	16.0	16.8	0.54
Immunosuppressed **(%)**	18.6	19.8	0.31	15.9	15.9	1.00
Fever **(%)**	37.5	26.8	**< 0.001**	35.9	35.9	1.00
Septic Shock **(%)**	26.4	46.5	**< 0.001**	26.7	26.7	1.00
Hospital 1 **(%)**	9.85	10.6	**0.44**	8.80	8.80	1.00
Hospital 2 **(%)**	11.7	14.6	**0.007**	11.0	11.0	1.00
Hospital 3 **(%)**	33.5	41.4	**< 0.001**	33.6	33.6	1.00
Hospital 4 **(%)**	45.0	33.4	**< 0.001**	46.6	46.6	1.00

Legend: POA, present on admission. * In reweighted cohort, treated and untreated patients have been balanced on observable characteristics using propensity scores and Mahalanobis distance between covariates. ** Hours from arrival. † Source of infection present on admission was determined by diagnosis codes. ‡ New bacteremia was defined by positive blood culture after time zero of sepsis in a patient who did not have a positive blood culture in the preceding week. Possible skin contaminants were excluded.

Table 2. Characteristics of Cohort with Hospital-Onset Sepsis Before and After Being Reweighted

	Raw Cohort n = 2,260			Reweighted Cohort* n = 1859		
	Treated	**Untreated**	**p**	**Treated**	**Untreated**	**p**
Time Zero of Sepsis (Hours**)	50.6	73.8	**0.008**	39.4	42.7	0.52
Age	62.2	61.8	0.75	62.7	62.9	0.92
Female **(%)**	42.0	44.5	0.43	42.6	42.4	0.96
Elixhauser Comorbidities	4.98	5.02	0.86	4.86	4.89	0.89
Postoperative **(%)**	10.2	18.3	**0.001**	9.70	9.54	0.94
Pneumonia POA† **(%)**	26.6	19.6	**0.007**	25.7	25.7	1.00
Urinary tract infection POA **(%)**	19.7	16.3	0.16	21.1	20.2	0.76
Skin / soft tissue infection POA **(%)**	8.39	5.31	**0.039**	7.59	8.13	0.78
New Bacteremia‡ **(%)**	9.12	11.7	0.20	9.28	10.6	0.53
Immunosuppressed **(%)**	23.4	30.8	**0.012**	24.5	24.3	0.94
Fever **(%)**	32.8	17.5	**< 0.001**	29.1	29.1	1.00
Septic Shock **(%)**	33.9	37.9	0.20	33.3	33.3	1.00
Hospital 1 **(%)**	9.85	12.8	0.17	8.02	8.02	1.00
Hospital 2 **(%)**	24.5	20.7	**0.15**	25.3	27.1	0.57
Hospital 3 **(%)**	28.1	41.1	**< 0.001**	30.0	28.2	0.57
Hospital 4 **(%)**	37.6	25.4	**< 0.001**	36.7	36.7	1.00

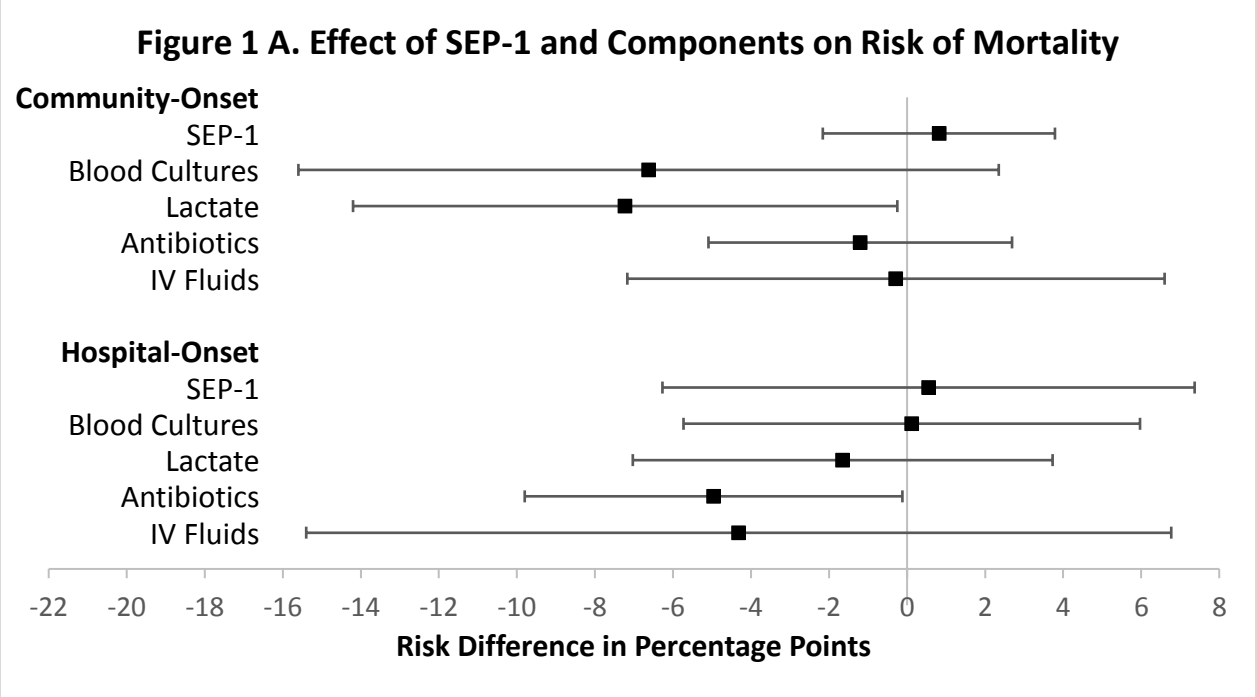
Legend: POA, present on admission. * In reweighted cohort, treated and untreated patients have been balanced on observable characteristics using propensity scores and Mahalanobis distance between covariates. ** Hours from arrival. † Source of infection present on admission was determined by diagnosis codes. ‡ New bacteremia was defined by positive blood culture after time zero of sepsis in a patient who did not have a positive blood culture in the preceding week. Possible skin contaminants were excluded.

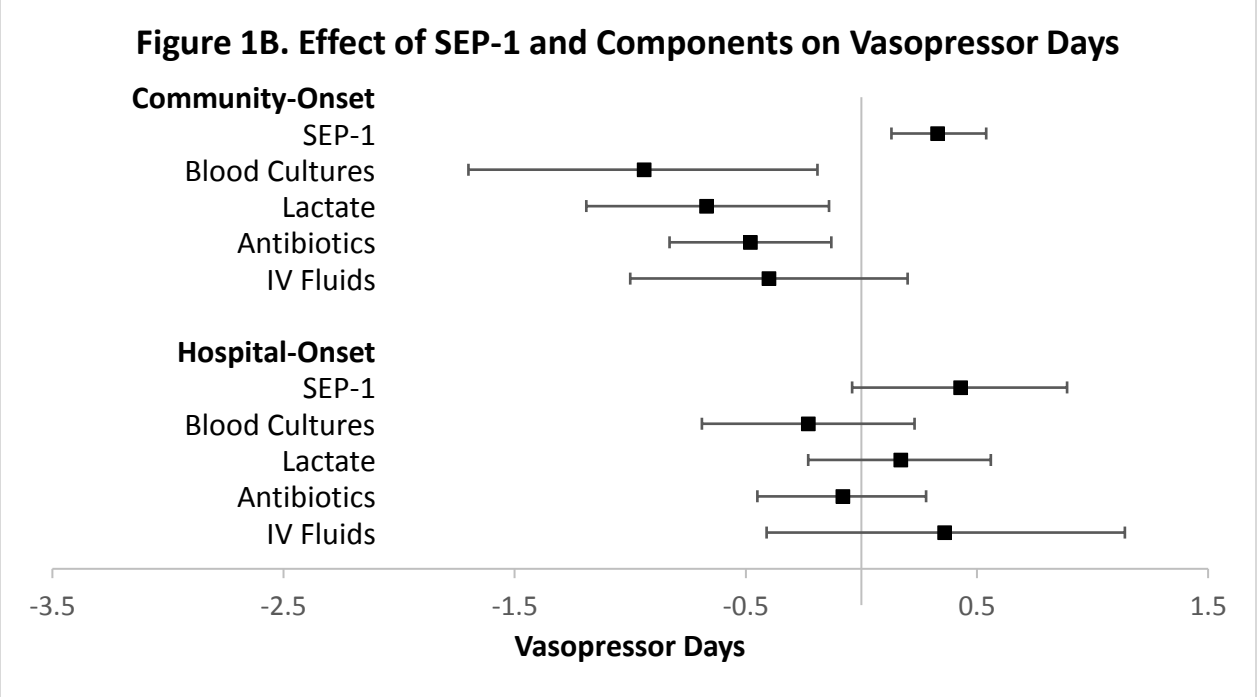
Table 3. Treatment Effects of the SEP-1 Sepsis Bundle and Components in Reweighted Cohorts with Community-Onset & Hospital-Onset Sepsis

	Community-Onset Sepsis		**Hospital-Onset Sepsis**	
	Mortality Risk Difference*	95% CI	Mortality Risk Difference*	95% CI
SEP-1 Bundle	+0.82%	(-2.16, 3.79)	+0.55%	(-6.27, 7.37)
Blood cultures	-6.62%	(-15.6, 2.35)	+0.12%	(-5.73, 5.97)
Serum Lactate	**-7.23%**	**(-14.2, -0.25)**	-1.65%	(-7.03, 3.73)
Antibiotics	-1.20%	(-5.09, 2.69)	**-4.96%**	**(-9.80, -0.12)**
Intravenous Crystalloid	-0.29%	(-7.17, 6.60)	-4.32%	(-15.4, 6.77)
	Vasopressor Days	95% CI	Vasopressor Days	95% CI
SEP-1 Bundle	**+0.33**	**(0.13, 0.54)**	+0.43	(-0.04, 0.89)
Blood cultures	**-0.94**	**(-1.70, -0.19)**	-0.23	(-0.69, 0.23)
Serum Lactate	**-0.67**	**(-1.19, -0.14)**	+0.17	(-0.23, 0.56)
Antibiotics	**-0.48**	**(-0.83, -0.13)**	-0.08	(-0.45, 0.28)
Intravenous Crystalloid	-0.40	(-1.00, 0.20)	+0.36	(-0.41, 1.14)

Legend: 95% CI, 95% confidence interval. SEP-1 refers to the Early Management Bundle for Severe Sepsis / Septic Shock (National Quality Forum #0500). * Differences in probability of in-hospital mortality and days spent on vasopressors were estimated as the average treatment effect on the treated. Mortality risk difference was expressed in terms of percentage points.

Figures 1A & 1B. Treatment Effects of SEP-1 and Components in Cohorts with Community-Onset and Hospital-Onset Sepsis





Appendix 1.

Supplemental Table 1. Relative Risk of In-Hospital Mortality Associated with Clinical Variables in the Raw Cohorts with Community-Onset and Hospital-Onset Sepsis

	Community-Onset Sepsis n = 4144		Hospital-Onset Sepsis n = 2260	
	Relative Risk	p-value	Relative Risk	p-value
Age in years	**1.01**	**< 0.001**	**1.09**	**0.001**
ECI	**1.06**	**< 0.001**	**1.07**	**< 0.001**
Female	1.04	0.55	1.08	0.33
Postoperative	1.18	0.40	1.02	0.89
Pneumonia POA	**1.41**	**< 0.001**	1.19	0.074
UTI POA	**0.65**	**< 0.001**	**0.69**	**0.004**
SSTI POA	0.85	0.25	0.89	0.53
New Bacteremia	1.02	0.79	1.30	**0.022**
Immunosuppressed	**1.23**	**0.009**	**1.26**	**0.011**
Fever	**0.47**	**< 0.001**	**0.64**	**0.001**
Septic Shock	**1.77**	**< 0.001**	**1.28**	**0.003**

Supplemental Table 2. Characteristics of the Total Sample Before and After Being Reweighted

	Raw Total Sample			Reweighted Total Sample		
	Treated	**Untreated**	**p-value**	**Treated**	**Untreated**	**p-value**
Time Zero of Sepsis (Hours*)	8.97	34.3	**< 0.001**	6.77	8.94	**0.005**
Age	65.6	63.3	**< 0.001**	65.7	66.1	0.96
Female (%)	44.5	45.3	0.23	43.7	44.7	0.46
Elixhauser Comorbidities	4.91	5.14	**0.006**	4.87	4.87	0.28
Postoperative (%)	3.01	9.67	**< 0.001**	2.22	2.22	1.00
Pneumonia POA† (%)	34.0	25.3	**< 0.001**	34.2	34.2	1.00
Urinary tract infection (%)	25.4	21.2	**< 0.001**	25.5	26.2	0.58
Skin / soft tissue infection (%)	7.99	6.03	**= 0.004**	8.00	6.73	0.084
New Bacteremia‡ (%)	14.6	14.5	0.91	14.6	15.9	0.20
Immunosuppressed (%)	19.2	24.7	**< 0.001**	18.8	18.8	1.00
Fever (%)	36.8	22.7	**< 0.001**	36.0	36.0	1.00
Septic Shock (%)	27.5	42.7	**< 0.001**	27.3	27.3	1.00
Hospital 1 (%)	9.85	11.6	**0.047**	9.76	9.76	1.00
Hospital 2 (%)	13.5	17.3	**< 0.001**	13.5	13.5	1.00
Hospital 3 (%)	32.7	41.3	**< 0.001**	32.7	32.7	1.00
Hospital 4 (%)	44.0	29.8	**< 0.001**	44.0	44.0	1.00

Legend: POA, present on admission. * Hours from admission. † Pneumonia POA was determined by diagnosis codes. ‡ New bacteremia was defined by positive blood culture after time zero of sepsis in a patient who did not have a positive blood culture in the preceding week. Possible skin contaminants were excluded.

Supplemental Table 3. Relative Risk of In-Hospital Mortality Associated with Clinical Variables in the Raw Total Sample

	Relative Risk	95% Confidence Interval	p-value
SEP-1 Sepsis Bundle	0.99	(0.88, 1.12)	0.88
Hospital-Onset of Sepsis	1.05	(0.94, 1.17)	0.381
Age in years*	**1.01**	**(1.01, 1.01)**	**< 0.001**
Female	1.06	(0.96, 1.17)	0.28
Elixhauser Comorbidities*	**1.07**	**(1.05, 1.08)**	**< 0.001**
Postoperative	1.35	(0.88, 1.30)	0.48
Pneumonia POA	**1.35**	**(1.21, 1.50)**	**< 0.001**
Urinary Tract infection POA	**0.67**	**(0.58, 0.77)**	**< 0.001**
Skin / soft tissue infection POA	0.85	(0.68, 1.06)	0.16
New Bacteremia	1.12	(0.98, 1.28)	0.10
Immunosuppressed	**1.25**	**(1.11, 1.40)**	**< 0.001**
Fever	**0.51**	**(0.44, 0.59)**	**< 0.001**
Septic Shock	**1.55**	**(1.40, 1.72)**	**< 0.001**

Legend: POA, present on admission. * Relative risk is reported for incremental increase in 1 year of age or 1 additional Elixhauser comorbidity.

Supplemental Table 4. Treatment Effect of the SEP-1 Sepsis Bundle and Components on Mortality and Vasopressor Days in the Reweighted Total Sample

Treatment	Mortality Difference*	95% CI	Vasopressor Days	95% CI
SEP-1 Bundle	+1.08	(-1.29, 3.46)	**+0.43**	**(0.26, 0.60)**
Blood cultures	-4.28	(-9.51, 0.94)	-0.40	(-0.80, 0.01)
Serum Lactate	-3.32	(-7.51, 0.87)	**-0.37**	**(-0.70, -0.04)**
Broad-spectrum antibiotics	**-3.19**	**(-6.37, -0.01)**	**-0.42**	**(-0.68, -0.15)**
Intravenous Crystalloid	-0.60	(-6.11, 4.92)	-0.24	(-0.72, 0.24)

Legend: 95% CI, 95% confidence interval. SEP-1 refers to the Early Management Bundle for Severe Sepsis / Septic Shock (National Quality Forum #0500). * Differences in probability of in-hospital death and days spent on vasopressors were estimated as the average treatment effect on the treated.

Supplemental Table 5. Results from Endogenous Treatment Effects Models Compared with Unweighted / Unbalanced Regression

Treatment		ATET	NATE
SEP-1	MD	+1.08	-0.23
	VD	+0.43	-0.60
Blood Cultures	MD	-4.28	+0.97
	VD	-0.40	-0.28
Serum Lactate	MD	-3.32	+1.26
	VD	-0.37	+0.28
Antibiotics	MD	-3.19	-1.03
	VD	-0.42	-0.27
IV Fluids	MD	-0.60	+2.64
	VD	-0.24	-010

Legend: ATET, average treatment effect on the treated. NATE, naïve (i.e., unweighted / unbalanced) treatment effect. MD, Mortality difference calculated as the average difference in probabilities between the treated and untreated (unit is percentage points); VD, vasopressor days;

Supplemental Table 6. Treatment Effect of the Complete SEP-1 Bundle in Different Cohorts†

Subgroup	Mortality Difference*	Vasopressor Days
Age ≥ 65	+0.43% (-3.01, 3.87)	**+0.44 (0.22, 0.66)**
Age < 65	**+3.19% (0.15, 6.23)**	**+0.54 (0.28, 0.81)**
Pneumonia POA	-1.71% (-7.14, 3.71)	+0.60 (0.27, 0.93)
No Pneumonia POA	+1.62% (-1.01, 4.04)	+0.40 (0.21, 0.60)
Immunosuppressed	**+5.94% (0.27, 11.6)**	**+1.00 (0.59, 1.41)**
Not Immunosuppressed	-0.21% (-2.83, 2.41)	**+0.32 (0.14, 0.51)**
New Bacteremia	+2.47% (-3.64, 8.59)	+0.36 (-0.25, 0.97)
No New Bacteremia	+0.95% (-1.70, 3.59)	**+0.47 (0.29, 0.64)**
Fever	+2.11% (-0.88, 5.10)	**+0.33 (0.07, 0.59)**
Afebrile	+0.72% (-2.63, 4.07)	**+0.45 (0.23, 0.67)**
Septic Shock	+1.13% (-4.14, 6.39)	+0.38 (-0.07, 0.83)
Sepsis without Shock	-0.80% (-3.50, 1.90)	-0.05 (-0.21, 0.11)

Legend: SEP-1 refers to the Early Management Bundle for Severe Sepsis / Septic Shock (National Quality Forum #0500). * Difference in probability of in-hospital death was estimated as the average treatment effect on the treated and is expressed in percentage points. † Dedicated propensity and outcomes models were run within the subgroup of interest. Subgroup analyses excluded all encounters from outside the subgroup.

Supplemental Table 7. Treatment Effects of SEP-1 Bundle Components in Different Cohorts*

		Blood Cultures	Lactate	Antibiotics	IV Fluids†
Age ≥ 65 n = 3376	MD	**-9.99 (-19.8, -0.20)**	-4.08 (-10.5, 2.38)	-4.27 (-9.04, 0.51)	-0.37 (-12.4, 4.91)
	VD	-0.53 (-1.21, 0.15)	-0.48 (-0.99, 0.03)	**-0.45 (-0.83, -0.07)**	-0.20 (-0.90, 0.51)
Age < 65 n = 3028	MD	-2.68 (-8.54, 3.18)	-0.86 (-5.29, 3.57)	1.24 (-2.76, 5.24)	5.66 (-0.75, 12.1)
	VD	-0.40 (-0.93, 0.14)	-0.26 (-0.66, 0.15)	-0.20 (-0.55, 0.15)	-0.10 (-0.79, 0.58)
Pneumonia POA n = 2260	MD	-9.54 (-24.2, 5.09)	-3.05 (-11.4, 5.29)	-3.81 (-11.4, 3.79)	0.78 (-17. 0, 18.6)
	VD	-0.06 (-0.93, 0.80)	-0.11 (-0.76, 0.54)	-0.19 (-0.74, 0.37)	-0.18 (-1.81, 1.46)
No Pneumonia POA n = 2260	MD	-3.76 (-8.87, 1.36)	-3.34 (-7.91, 1.22)	-1.97 (-5.27, 1.32)	-2.66 (-8.93, 3.60)
	VD	**-0.54 (-1.00, -0.08)**	**-0.47 (-0.85, -0.09)**	**-0.47 (-0.77, -0.16)**	-0.35 (-0.90, 0.21)
Immunosuppressed n = 1475	MD	-3.76 (-14.6, 7.13)	-3.54 (-13.8, 6.69)	-0.39 (-9.07, 8.29)	14.5 (-0.31, 29.3)
	VD	-0.36 (-1.10, 0.38)	-0.24 (-1.00, 0.52)	**-0.87 (-1.56, -0.18)**	0.31 (-1.49, 2.11)
Non-immunosuppressed n = 4929	MD	-4.70 (-10.9, 1.48)	-3.74 (-8.47, 0.97)	**-3.57 (-7.10, -0.03)**	-1.98 (-8.22, 4.25)
	VD	**-0.48 (-0.96, -0.01)**	**-0.40 (-0.78, -0.02)**	**-0.35 (-0.65, -0.05)**	-0.43 (-0.97, 0.11)
New Bacteremia n = 928	MD	-13.7 (-31.2, 3.86)	-2.58 (-15.4, 10.2)	-4.44 (-13.0, 4.12)	-4.83 (-25.7, 16.1)
	VD	**-1.98 (-3.34, -0.62)**	-0.74 (-1.80, 0.31)	**-1.38 (-2.19, -0.58)**	0.11 (-1.69, 1.90)
No New Bacteremia n = 5476	MD	-1.95 (-7.08, 3.18)	-2.36 (-6.93, 2.21)	-2.28 (-5.72, 1.16)	1.43 (-3.20, 6.07)
	VD	-0.19 (-0.58, 0.21)	-0.12 (-0.47, 0.23)	-0.21 (-0.49, 0.07)	-1.18 (-0.41, 0.38)
Fever n = 1722	MD	-0.05 (-13.7, 13.6)	-5.04 (-13.9, 3.82)	-1.57 (-7.58, 4.44)	3.39 (-4.32, 1.11)
	VD	0.53 (-0.65, 1.72)	0.07 (-0.54, 0.69)	-0.15 (-0.62, 0.32)	0.34 (-0.65, 1.33)
Afebrile n = 4682	MD	-5.54 (-11.6, 0.49)	-4.39 (-9.63, 0.85)	-3.56 (-7.48, 0.36)	061 (-6.85, 8.07)
	VD	**-0.70 (-1.16, -0.24)**	**-0.48 (-0.87, -0.09)**	**-0.50 (-0.82, -0.17)**	-0.36 (-1.03, 0.31)
Septic Shock n = 2436	MD	-4.12 (-12.7, 4.45)	-8.97 (-18.4, 0.51)	-4.70 (-11.4, 2.02)	-6.13 (-14.6, 2.30)
	VD	-0.55 (-1.44, 0.33)	-0.43 (-1.12, 0.24)	-0.51 (-1.06, 0.03)	-0.60 (-1.32, 0.12)
Sepsis without Shock n = 3968	MD	-4.96 (-10.9, 1.00)	-3.70 (-7.75, 0.34)	-2.20 (-5.49, 1.10)	2.96 (-5.70, 11.6)
	VD	-0.32 (-0.69, 0.05)	-0.21 (-0.52, 0.10)	-0.11 (-0.31, 0.08)	0.19 (-0.40, 0.78)

Legend: MD, Mortality difference calculated as the average difference in probabilities between the treated and untreated (unit is percentage points); VD, vasopressor days; 95% CI, 95% confidence interval. POA, present on admission. * Dedicated propensity and outcomes models were run within the subgroup of interest. Subgroup analyses excluded all encounters from outside the subgroup. † Only measured among individuals in whom intravenous fluids were indicated based on SEP-1 guidance

CHAPTER 4

Lack of Insurance as a Barrier to Care in Sepsis: A Retrospective Cohort Study

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ABSTRACT

Nationally-representative data suggest an association between lack of insurance and in-hospital death from sepsis.[117] It remains to be determined whether this association is attributable to differences in baseline health, care-seeking behaviors, hospital care, or other factors.

Purpose To determine whether organ dysfunction present on admission for community-onset sepsis mediates the association between lack of insurance and mortality in sepsis.

Materials and Methods Retrospective cohort study using public discharge data from the California Office of Statewide Health Planning and Development. Inpatients age 18-64 with community-onset sepsis at California hospitals in 2010 were identified by diagnosis codes.

Results Controlling for demographics, comorbidities, infection source, and hospital characteristics, lack of insurance was associated with an adjusted odds ratio (OR) of 1.26 (absolute risk difference 4.75%, $p<0.001$) for organ dysfunction present on admission for community-onset sepsis. Lack of insurance predicted in-hospital mortality (adjusted OR 1.15, $p<0.001$). Organ dysfunction present on admission was the only significant mediator, explaining 22.3% ($p<0.001$) of the effect of lack of insurance.

Conclusions The association between lack of insurance and organ dysfunction on admission in community-onset sepsis suggests that lack of insurance may impede timely care for patients with community-onset infections.

INTRODUCTION

Sepsis, defined as a dysregulated host response to infection, is among the most common reasons for hospitalization in the US and is the leading cause of death in non-cardiac intensive care units.[1-3] Though nationally-representative data suggest that lack of insurance is associated with increased risk of in-hospital death from sepsis with organ dysfunction,[117] it is unclear whether this disparity in mortality is attributable to differences in baseline health, care-seeking behaviors, in-hospital care, or other as-yet unidentified factors.

Health insurance has been linked to multiple health-related outcomes, including improved self-reported health status and reduced mortality.[118-120] One of the mechanisms by which insurance improves health is by facilitating earlier presentation and recognition of illness. For instance, in patients with cancer, lack of insurance has been associated with advanced stage at time of diagnosis and a corresponding reduction in survival.[121, 122] In the setting of acute illness, uninsured individuals may face both financial and nonfinancial barriers to care, such as lack of transportation.[123] In sepsis, every hour of delay between diagnosis and initiation of treatment increases the risk of death.[41] We hypothesized that lack of insurance increases risk of death from sepsis by acting as a barrier to timely care.

The definition of sepsis has recently changed, such that it is no longer possible to have sepsis without organ dysfunction.[2] However, when the patients from our retrospective cohort received their treatment, it was possible to be coded as having sepsis prior to the onset of organ dysfunction. Sepsis progressed to "severe sepsis" if organ dysfunction developed. Patients who were coded as having sepsis that was "present on admission," but whose organ dysfunction developed after admission, are ascertained to have been admitted to the hospital earlier in the course of their illness than individuals who had both sepsis and organ dysfunction present on admission. The purpose of this study was to exploit these distinctions to test our hypothesis.

MATERIALS AND METHODS

Data Source

The primary source of patient-level information was the California Office of Statewide Health Planning and Development (OSHPD) Patient Discharge Data public use file. OSHPD compiles comprehensive data on inpatient admissions to licensed hospitals in California with one record for each discharge. The OSHPD data is collected via the Medical Information Reporting

for California (MIRCal) System. For hospital-level data, the OSHPD patient discharge data file was linked to OSHPD financial disclosure reports.

Study Design

The design was an observational, retrospective cohort study evaluating whether lack of insurance predicts organ dysfunction at time of admission to hospital with community-onset sepsis.

Inclusion and Exclusion Criteria

We included patients age 18-64 who were admitted from home to a nonfederal hospital in California for acute care in 2010 and assigned International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) diagnosis codes consistent with sepsis, septic shock, or disseminated infection (see supplementary Table 1).[90, 91, 93, 124] To meet the inclusion criteria, diagnosis codes needed to indicate "severe sepsis", "septic shock", or both sepsis and organ dysfunction. The subcategories of organ dysfunction were respiratory, cardiovascular, renal, hepatic, hematologic, or neurologic.

Only patients whose diagnosis of sepsis, severe sepsis, or septic shock was present on admission, indicating community-onset sepsis, were included in the sample. Patients age 65 or older were excluded based on Medicare eligibility. We chose 2010 as the most recent year of publicly available data from OSHPD in which key covariates, including age, gender, race and ethnicity were included. After applying our inclusion and exclusion criteria, patients from 313 California hospitals were identified.

Variables

The proximate outcome was a binary variable indicating that at least one diagnosis code consistent with organ dysfunction was marked as present on admission. The set of diagnoses used (see Appendix 1) was based on methodology first employed by Martin et. al[90] that has since been validated and replicated in the sepsis literature.[91-93] These diagnoses were chosen to represent acute illness, rather than chronic comorbidity or baseline health. Organ dysfunction present on admission was also calculated as a count outcome based on the number of subcategories of organ dysfunction (i.e., respiratory, cardiovascular) identified as present on admission. The distal outcome was in-hospital mortality.

Patient-level covariates included age, race, Hispanic ethnicity, baseline health, code status, and source of infection, including pneumonia, skin and/or soft tissue infection, or urinary

tract infection. Baseline health was represented using a count variable indicating the sum of medical diagnoses present from the Elixhauser Comorbidity Index, a set of clinical conditions representing chronic illness that are known to influence in-hospital mortality.[88, 89] Categories for source of infection were defined by ICD-9 codes using the Healthcare Cost and Utilization Project's Clinical Classification Software (https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp). Hospital-level covariates included type of ownership, bed count, percentage of admissions by acute care transfer, percentage of indigent patients, and number of major surgeries performed annually. Percentage of patients classified as indigent was determined based on the proportion of patients listed as self-pay, indigent, or "other," indicating absence of either public or private insurance.

Statistical Analysis

Multivariable logistic regression was used to assess the relationship between predictor and outcomes after controlling for covariates. During the process of model specification, fixed effects and random effects models were fit to account for clustering by hospitals. Models were compared based on likelihood ratio tests, AIC values and Hausman-Wu test as appropriate. Absolute risk difference and relative risk were calculated based on predictive margins from multivariate logistic regression with fixed effects. To further disentangle the effect of lack of insurance on organ dysfunction, negative binomial regression was performed using number of dysfunctional organ systems present on admission as a count outcome. Standard errors in the negative binomial model were inflated to account for clustering by hospital.

Within-level and cross-level moderation effects were evaluated using interaction terms in multilevel models with random effects. Mediation analysis was performing by decomposing the total effects of lack of insurance on mortality from logistic regression into direct effects and indirect effects attributable to a mediator (using the user-written *khb* command).[125, 126] STATA/IC version 14.1 was used for all analyses.

Missing Data

Six hospitals (1.08% of the total sample) did not provide financial data and were excluded from the reported analysis. In one case, the patient's disposition was marked as "invalid/blank"; this case was excluded from mediation analysis. Of the remaining cases, 29.2% contained missing values in one or more demographic categories. Multiple imputation by chained equations was used to address missing values for covariates. Model specification was

performed using 5 imputations. Final analysis used 30 imputations to approximate the percentage of incomplete cases.[127] The study was conducted using publicly available de-identified data and therefore is exempt from requirements for IRB approval or consent from individuals.

RESULTS

32,561 patients from 312 medical facilities across the state of California were included in the analysis (Fig. 1). Characteristics of the patients and facilities are presented in Tables 1 and 2, respectively. All patients included in the sample developed organ dysfunction; 26,604 (81.7%) had organ dysfunction coded as "present on admission." Significant differences between those who presented with organ dysfunction at time of admission and those who did not were identified. Specifically, patients without organ dysfunction at admission tended to be younger, to be female, to have racial categories other than non-Hispanic White or African American, to be "full code" status, and to have fewer Elixhauser comorbidities. Pneumonia was more common among individuals with organ dysfunction present on admission, while skin and soft tissue infection was less common in this group.

Relationship Between Lack of Insurance and Organ Dysfunction at Admission

On multivariable analysis, lack of insurance was associated with organ dysfunction present on admission with an adjusted odds ratio (OR) of 1.26 ($p < 0.001$) and predicted an increase in absolute risk of organ dysfunction present on admission of 4.75% (relative risk 1.07). Among the other covariates, Elixhauser comorbidity index, "do not resuscitate" status, pneumonia, and urinary tract infection were all associated with increased likelihood of organ dysfunction at admission, while African American race, Hispanic ethnicity, female gender, and skin and soft tissue infections were associated with decreased likelihood of organ dysfunction (see Supplementary Table 2 for full set of coefficients and adjusted ORs). The strongest predictors of organ dysfunction at admission were "do not resuscitate" status (adjusted OR 1.70, $p < 0.001$), pneumonia (adjusted OR 1.30, $p < 0.001$), and lack of insurance (adjusted OR 1.26).

Moderators of the Effect of Lack of Insurance

All covariates were evaluated as potential moderators of the effect of lack of insurance (see supplementary Table 3). Among patient-level covariates, age (adjusted OR 1.01 for the interaction, $p < 0.001$), "do not resuscitate" status (adjusted OR 2.51 for the interaction, $p = 0.004$), pneumonia (adjusted OR 1.60 for the interaction, $p < 0.001$) and urinary tract infection

(adjusted OR 1.25 for the interaction, $p = 0.013$) were moderators that significantly increased the association of lack of insurance with organ dysfunction. Skin and soft tissue infection was likewise significant as a moderator (adjusted OR 0.70, $p = 0.001$) but showed the opposite effect, reducing the magnitude of the association between lack of insurance and organ dysfunction at presentation. Among the hospital-level characteristics tested, teaching status (adjusted OR 1.33, $p = 0.045$), membership in a hospital system (adjusted OR 1.36, $p < 0.001$), and number of licensed beds (adjusted OR 1.0007, $p = 0.017$) were moderators that significantly increased the association between lack of insurance and organ dysfunction present on admission. Type of hospital ownership (i.e., private-for-profit, public) and percent of patients considered indigent did not significantly moderate the association between lack of insurance and organ dysfunction present on admission.

Relationship Between Lack of Insurance and Number of Dysfunctional Organ Systems

The median number of dysfunctional organ systems was 1 (interquartile range 1 – 2). The most common dysfunctional organ systems were renal (dysfunction present in 38.9% of the sample), hematologic (33.7%), and respiratory (30.6%). Among the 26,604 patients (81.7% of the sample) with organ dysfunction present on admission, 53.0% had a single dysfunctional organ system, 26.4% had two dysfunctional organ systems, and 12.5% had three. On negative binomial regression, after controlling for patient- and hospital-level covariates, lack of insurance was significantly associated with increased number of dysfunctional organ systems (incidence rate ratio 1.14, $p < 0.001$). On average, lack of insurance predicted 0.13 additional dysfunctional organ systems present on admission, or about one additional dysfunctional organ system for every eight patients without insurance.

Relationship Between Lack of Insurance, Mediators, and Mortality

Lack of insurance was significantly associated with mortality (adjusted OR 1.15, $p = 0.016$). Organ dysfunction present on admission significantly mediated this relationship, explaining 22.4% of the association between lack of insurance and mortality ($p < 0.001$). No other variables tested, including “do not resuscitate” status and number of comorbidities, were identified as significant mediators.

DISCUSSION

In this retrospective study of observational data from California hospitals, we identified lack of insurance as a significant predictor of organ dysfunction at time of admission for community-onset sepsis. Notably, this association did not vary based on type of hospital ownership (i.e., private-for-profit, public). On average, we found that lack of insurance predicted one additional dysfunctional organ system for every eight patients admitted with community-onset sepsis, controlling for baseline comorbid conditions, patient demographics, and hospital characteristics. These results imply that patients with community-onset sepsis who lack insurance tend to be admitted to the hospital later in the course of their illness, supporting our hypothesis that lack of insurance acts a barrier to timely care.

Additionally, we found an association between lack of insurance and mortality from community-onset sepsis, consistent with previous studies.[117] It is unclear from prior studies whether this disparity in sepsis mortality is due to worse baseline health, more advanced illness at time of admission, or worse outcomes after hospitalization. However, our analysis demonstrates that organ dysfunction present on admission mediates this relationship, explaining about 22% of the effect of lack of insurance. No other factors that we examined were significant mediators. Thus, a large proportion of the association between lack of insurance and sepsis mortality remains unexplained. We suspect this residual may reflect differences in in-hospital care attributable to lack of insurance, though our data lack the granular clinical detail to evaluate this hypothesis.

Our study is subject to several limitations related to the use of administrative data. First, though we used a validated method to identify patients, our cohort likely represented an imperfect sample of the target population of individuals with sepsis. When compared against concrete clinical indicators of disseminated infection, such as positive blood cultures, the sensitivity of the case definition we employed has been estimated to be as high as 77%.[9] However, in recent years, coincident with changes in the structure of federal reimbursements from the Centers for Medicare and Medicaid Services, entering a diagnosis code indicating sepsis has become more common.[10] As a result, the sensitivity of methods employing diagnosis codes to identify cases of sepsis has increased, while the positive predictive value has decreased.[9, 19, 21] Our sample was likely subject to these trends.

Further, our results are sensitive to errors or bias in the "present on admission" coding of organ dysfunction. Though "present on admission" codes have been validated by investigators performing population-level observational studies involving sepsis,[128] we nonetheless acknowledge that coding may be influenced by anticipated reimbursement.[10] In particular, our findings are vulnerable to endogeneity bias arising from differences in patterns of "present on admission" coding by payor. If providers, anticipating reduced reimbursement, are more likely to code conditions as present on admission for patients with insurance than they are for patients without insurance, for whom reimbursement can be expected to be low regardless, the validity of our results may suffer.

Third, in our analysis, we were unable to distinguish between differences in severity of illness at presentation to hospital and at time of admission. Thus, our findings may capture effects from lack of insurance related to both pre-hospital delays in care and factors arising after presentation but before admission. Fourth, to improve the comparability of groups, we excluded patients age 65 or older. Given that sepsis is recognized to be a condition primarily afflicting older individuals, our results may not have direct applicability to a large proportion of individuals who develop sepsis.[60] Finally, our results do not address whether patients would seek care earlier if provided insurance. Uninsured individuals may face other poverty-related barriers including issues with transportation and competing needs, and our data set did not include measures of socioeconomic status with which to account for these factors.

CONCLUSION

In summary, we have demonstrated that lack of insurance is associated with organ dysfunction at time of admission and subsequent mortality in community-onset sepsis. This study provides further evidence that having insurance is associated with better health outcomes. We chose sepsis because it is a common, high stakes condition in which every moment between diagnosis and treatment counts. Future studies are needed to determine if better insurance coverage would lead to better sepsis outcomes including lower mortality.

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Figure 1. Patient Identification and Exclusion Flow Diagram

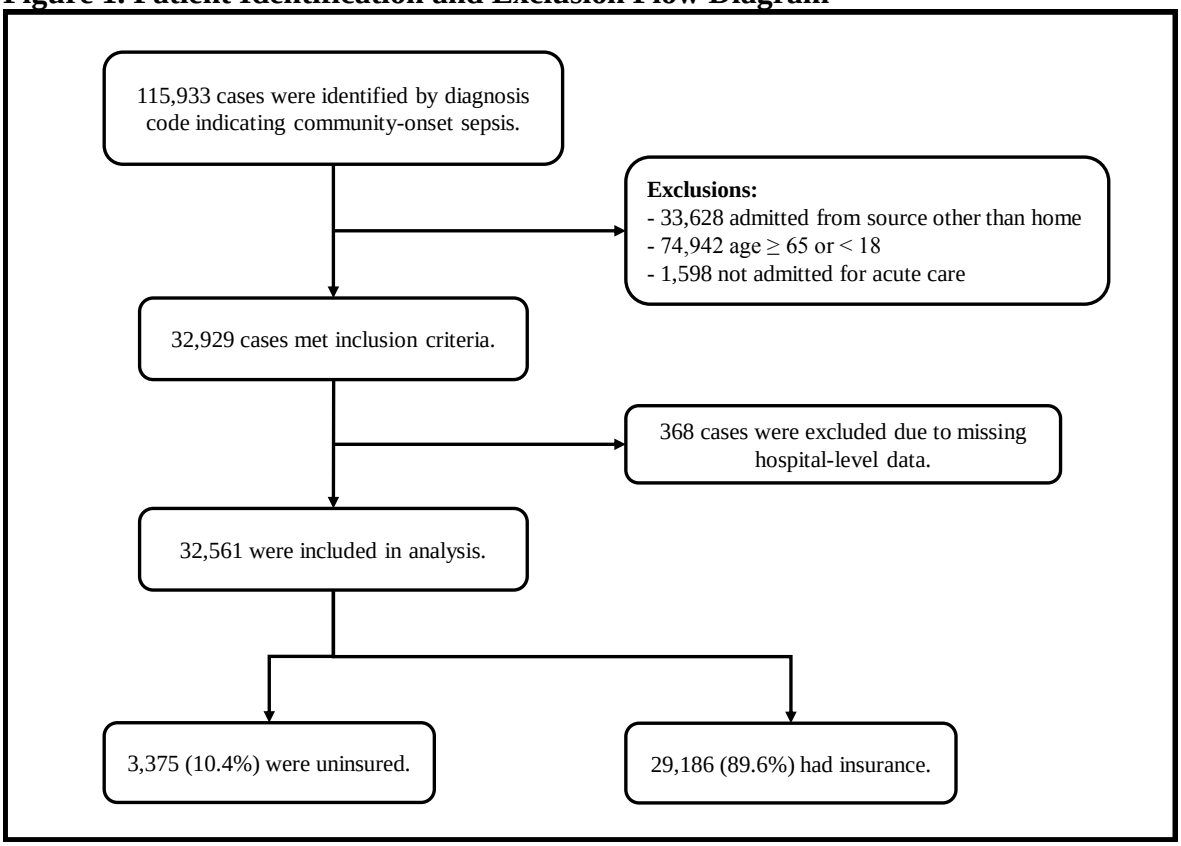

Table 1. Patient Characteristics by Presence or Absence of Organ Dysfunction at Admission

Characteristic	Organ Dysfunction		
	Present on Admission (n = 26,604)	**Not Present on Admission** (n = 5,957)	**p-value***
Age**, mean years (sd)**	50.8 (10.9)	49.4(11.9)	< 0.001†
Female ‡**, n (%)**	11,173 (47.2%)	2,771 (52.4%)	< 0.001
Race ‡**, n (%)**			
Non-Hispanic White	10,945 (54.2%)	2,285 (49.6%)	< 0.001
African American	2,533 (12.0%)	553 (11.6%)	0.52
Asian / Pacific Islander	1,181 (5.58%)	300 (6.31%)	0.051
Other race	2,560 (12.1%)	633 (13.3%)	0.021
Hispanic ethnicity	5,260 (26.2%)	1,385 (30.4%)	< 0.001
Elixhauser comorbidity index**, Median (interquartile range)**	4 (3 – 6)	4 (2 – 5)	< 0.001§
DNR Status**, n (%)**	1,980 (7.44%)	246 (4.13%)	< 0.001
Infection source**, n (%)**			
Pneumonia	8,391 (31.5%)	1,454 (24.4%)	< 0.001
Skin/soft tissue	3,095 (11.6%)	928 (15.6%)	< 0.001
Urinary tract	8,251 (31.0%)	1,828 (30.7%)	0.618
No Insurance**, n (%)**	2,824 (10.6%)	551 (9.3%)	0.002
In-Hospital Death**, n (%)**	4,356 (16.4%)	403 (6.77%)	< 0.001

Table 1 Legend.

Abbreviations: DNR, do not resuscitate

*Chi-square unless otherwise specified

† determined by T test

‡ Percentages reported from among non-missing cases

§ Mann-Whitney U test

Table 2. Hospital Characteristics

Characteristic	Proportion or Hospital Average (n = 312)
Number of Patients**, median (interquartile range)**	78 (32.5 – 150.5)
Type of ownership**, n (%)**	
Public	50 (16.0%)
Private for-profit	67 (21.5%)
Private non-profit	195 (62.5%)
Member of Hospital System**, n (%)**	176 (56.4%)
Teaching Hospital**, n (%)**	23 (7.37%)
Rural location**, n (%)**	47 (15.1%)
Member of Hospital System	177 (56.6%)
Licensed Bed Count**, median (interquartile range)**	213.5 (117 – 358.5)
Percent Admissions by Acute Care Transfer**, mean (sd)**	1.4% (3.7%)
Percent Patients Considered Indigent**, mean (sd)**	26.5% (18.9%)
Major Surgeries Performed Annually**, median (interquartile range)**	2115 (830 - 4562)

Appendix 1.Supplementary Table 1. ICD-9-CM Codes for Septicemia and Organ Dysfunction[93]

Sepsis Codes	Organ Dysfunction Codes
038 Septicemia, 038.0, 038.10, 038.11, 038.12, 038.19, 038.2, 038.3, 038.4, 038.40, 038.41, 038.42, 038.43, 038.44, 038.49, 038.8, 038.9 790.7 Bacteremia 117.9 Disseminated fungal infection – Other & unspecified mycoses 112.5 Systemic candidiasis 112.81 Candidal endocarditis 003.1 Salmonella septicemia 020.2 Septicemic plague 022.3 Anthrax septicemia 036.2 Meningococcal septicemia 036.3 Waterhouse-Friderichsen syndrome 054.5 Herpetic septicemia 421.0 Acute and subacute bacterial endocarditis 421.9 Acute endocarditis, unspecified 098.89 Gonococcemia 995.90 SIRS, unspecified 995.91 Sepsis 995.92 Severe sepsis 996.62 Sepsis due to indwelling catheter 996.64 Sepsis due to indwelling Urinary Catheter 999.31 Unspecified infection due to central venous catheter 999.32 Bloodstream infection due to central venous catheter 785.52 Septic shock	**Respiratory** 518.81 Acute respiratory failure, 518.82 Acute respiratory distress syndrome 518.84 Acute and chronic respiratory failure 518.85 ARDS after shock or trauma 786.09 Respiratory distress not otherwise specified 791.1 Respiratory arrest *Procedures* 93.90 NIMV (BIPAP) 96.7 Other continuous invasive mechanical ventilation 96.71 mechanical ventilation for less than 96 hours 96.72 mechanical ventilation for greater than 96 hours
	Cardiovascular 458.8, 458.9 Hypotension 785.50 Shock NOS 785.51 Cardiogenic shock 785.59 Shock without trauma 796.3 Low blood pressure, nonspecific *Procedures* 00.17 Use of vasopressor agent
	Renal 584.5-584.9 acute renal failure
	Hepatic 570 Acute hepatic failure or necrosis 572.2 Hepatic encephalopathy 573.4 Hepatic infarction
	Hematologic 286.6 Purpura fulminans / defibrination syndrome 286.7 Acquired coagulation factor deficiency 286.9 Coagulopathy 287.49, 287.5 Thrombocytopenia – secondary or unspecified *Procedures* 99.04 Transfusion of packed cells 99.05 Transfusion of platelets 99.06 Transfusion of coagulation factors 99.07 Transfusion of plasma
	Metabolic 276.2 Acidosis – metabolic or lactic
	Neurologic 293.0 Transient organic psychosis 348.1 Anoxic brain injury Acute encephalopathy 348.30, 348.31, 348.39 359.81 Critical illness myopathy 780.01 Coma 780.09 Altered consciousness – unspecific *Procedures* 89.14 EEG

Supplementary Table 2. Association between Predictors and Organ Dysfunction at Admission

Predictor	β	SE	OR	OR 95% CI	p-value
No Insurance	0.229	0.0518	1.26	(1.14, 1.39)	< 0.001
Age	0.00221	0.00137	1.02 (for 10-year increase)	(0.995, 1.005)	0.107
Race					
African American	-0.121	0.0596	0.89	(0.79, 0.995)	0.043
Asian / Pacific Islander	-0.0896	0.0698	0.91	(0.80, 1.05)	0.199
Other race	0.0363	0.0644	1.04	(0.92, 1.18)	0.573
Hispanic Ethnicity	-0.145	0.0511	0.87	0.78, 0.95)	0.005
Female Gender	-0.192	0.0310	0.83	(0.78, 0.88)	< 0.001
Chronic Comorbidity*	0.160	0.00774	1.17	(1.16, 1.19)	< 0.001
DNR Status	0.529	0.0717	1.70	(1.47, 1.95)	< 0.001
Infection Source					
Pneumonia	0.265	0.0345	1.30	(1.22, 1.40)	< 0.001
Urinary tract	0.0962	0.0331	1.10	(1.03, 1.17)	0.004
Skin/soft tissue	-0.387	0.0428	0.68	(0.62, 0.74)	< 0.001

Table 2 Legend

Abbreviations: SE, standard error; OR, odds ratio; DNR, do not resuscitate; CI, confidence interval

*Comorbidity represented as a numerical score indicating number of Elixhauser Index conditions present in hospital diagnoses.

Supplementary Table 3. Interactions between Lack of Insurance and Covariates as Estimated by Separate Multilevel Models*

	β	SE	OR	95% CI	p-value
Patient:					
Age	0.00659	0.00173	1.01	(1.003, 1.01)	< 0.001
Female Gender	-0.0422	0.0763	0.96	(0.83, 1.11)	0.580
Race					
- African American	0.275	0.181	1.32	(0.92, 1.88)	0.129
- Asian / Pacific Islander	0.138	0.238	1.15	(0.72, 1.83)	0.562
- Other	0.196	0.129	1.22	(0.94, 1.57)	0.129
Hispanic Ethnicity	0.00935	0.0969	1.01	(0.83, 1.22)	0.923
Do No Resuscitate status	0.920	0.319	2.51	(1.34, 4.69)	0.004
Number of Elixhauser Index Conditions	0.241	0.0153	1.27	(1.23, 1.31)	< 0.001
Pneumonia	0.470	0.0998	1.60	(1.32, 1.95)	< 0.001
Urinary Tract Infection	0.222	0.0899	1.25	(1.05, 1.49)	0.013
Skin / Soft Tissue Infection	-0.356	0.111	0.70	(0.56, 0.87)	0.001
Hospital:					
Public	0.165	0.133	1.18	(0.91, 1.53)	0.214
Private For-Profit	0.154	0.137	1.17	(0.89, 1.52)	0.261
Teaching	0.283	0.141	1.33	(1.01, 1.75)	0.045
Rural	0.212	0.252	1.24	(0.75, 2.03)	0.400
Member of Hospital System	0.304	0.0820	1.36	(0.14, 0.47)	< 0.001
Number of Licensed Beds	0.000707	0.000297	1.001	(1.000, 1.001)	0.017
Percent Admissions by Acute Care Transfer	-3.47	1.78	0.031	(0.001, 1.008)	0.051
Percent Patients Considered Indigent	0.362	0.249	1.44	(0.88, 2.34)	0.147
Number of Major Surgeries Performed	-0.00003	0.000022	1.000	(1.000, 1.000)	0.175

Table 3 Legend

Abbreviations: SE, standard error; OR, odds ratio; DNR, do not resuscitate; CI, confidence interval

*This table represents the results of a series of multilevel models. Each model included an interaction term between a patient- or hospital-level covariate and lack of insurance**.**

Appendix 2. Mediation Analysis

The Karlson-Holm-Breen method (user written Stata command, *khb*) was used to assess for mediation. This method accounts for "rescaling" effects, or changes in coefficients between nested nonlinear models that are unrelated to confounding or mediation, when variables are added or removed in logistic regression.[125, 129]

The predictor of interest was a binary variable representing lack of insurance. The proposed mediator was a binary variable indicating organ dysfunction present at time of admission to the hospital. The outcome was in-hospital mortality. The full model includes the mediator and the reduced form does not.

Supplemental Table 4. Stata Output from *khb* Command on Multiply Imputed Data Set

	Coefficient	Standard Error	95% Confidence Interval
Reduced Model	0.144	0.0573	(0.0319, 0.257)
Full Model	0.112	0.0573	(-0.0004, 0.224)
Difference	0.0323	0.00592	(0.0206, 0.0439)
Confounding Ratio 1.288		Confounding Percent 22.4%	

The coefficient on lack of insurance in the reduced and full models reflect the total and direct effects of lack of insurance on in-hospital mortality, respectively. The difference between these coefficients is the indirect effect that is mediated by organ dysfunction present on admission.

Supplemental Table 5. Comparison of Mixed Effects Models with and without Mediator

	Full Model (With Mediator)		Reduced Model (No Mediator)	
	Coefficient	95% CI	Coefficient	p-value
Organ dysfunction POA	0.82	(0.71, 0.94)	--	--
Lack of Insurance	0.11	(-0.0004, 0.22)	0.138	(0.026, 0.249)
Age	0.011	(0.008, 0.014)	0.011	(0.008, 0.014)
African American	-0.022	(-0.16, 0.12)	-0.034	(-0.172, 0.104)
Asian / Pacific Islander	-0.019	(-0.16, 0.19)	0.014	(-0.158, 0.187)
Other race	0.025	(-0.13, 0.18)	0.028	(-0.125, 0.181)
Hispanic Ethnicity	0.053	(-0.053, 0.16)	0.041	(-0.065, 0.159)
Female Gender	-0.081	(-0.15, -0.01)	-0.095	(-0.166, -0.0251)
# Elixhauser Comorbidities	0.15	(0.13, 0.17)	0.160	(0.143, 0.176)
DNR Status	2.11	(2.01, 2.21)	2.136	(2.036, 2.237)
Pneumonia	0.29	(0.22, 0.36)	0.313	(0.243, 0.383)
Urinary tract	-0.68	(-0.76, -0.60)	-0.662	(-0.744, -0.581)
Skin/soft tissue	-0.61	(-0.73, -0.49)	-0.639	(-0.758, -0.520)

Legend: POA, present on admission.

Estimates of total and direct effects of lack of insurance on in-hospital mortality from mixed effects models with and without the mediator differ slightly when compared with the estimates produced by the *khb* command. Estimates calculated from these models include differences due to rescaling in addition to mediation effects.

CHAPTER 5. CONCLUSION

In summary, this dissertation reports three studies that examine factors related to timeliness and effectiveness of care in sepsis. Chapter 4 focuses on insurance status as a pre-hospital factor in community-onset sepsis. Chapters 2 and 3 are concerned with in-hospital use of the SEP-1 sepsis bundle for patients with community-onset and hospital-onset sepsis. The work contained in this dissertation has important implications on medical care, policy, and avenues for further research.

Goals, Revisited

1. To identify patients with hospital-onset sepsis as a subgroup of interest.

The first goal of this dissertation was to establish a literature on the use of sepsis bundles in hospital-onset sepsis. By publishing our work, we will have accomplished that. The papers comprising this dissertation are not the first to focus on hospital-onset sepsis, but they are among the first to describe and evaluate the use of a sepsis bundle in this population.

Further, we showed that hospital-onset sepsis is managed differently than community-onset sepsis and responds differently to treatment than does community-onset sepsis. We have thus demonstrated why hospital-onset sepsis should be considered a distinct clinical entity.

2. To evaluate the effectiveness of SEP-1-adherent care in hospital-onset sepsis.

SEP-1 is a process measure that was not, in our analysis, associated with improved outcomes (i.e., mortality). For patients with hospital-onset sepsis, broad-spectrum antibiotics were the only component of SEP-1 which appeared to improve sepsis outcomes. Thus, our work suggests that the care bundle specified in SEP-1 is an ineffective protocol for early management of hospital-onset sepsis. Before this conclusion can be accepted as fact, our findings need to be

replicated in other settings or by studies with prospective designs. However, pending further research, the studies contained in this dissertation raise serious concerns about the application of SEP-1 to all patients with sepsis.

Recommendations

1. Patients with hospital-onset sepsis should be excluded from SEP-1.

We were unable to demonstrate a treatment benefit related to SEP-1 in the total sample of eligible patients. However, in the cohort of patients with community-onset sepsis, multiple SEP-1 components—blood cultures, serum lactate, and antibiotics—were associated with improved sepsis physiology (as represented by decreased vasopressor requirements). In the cohort with hospital-onset sepsis, only the use of antibiotics was associated with a treatment benefit. Taken together, these findings suggest that lower adherence to SEP-1 in hospital-onset sepsis may not represent a quality gap, and that hospital initiatives to improve SEP-1 adherence in hospital-onset sepsis may represent wasted effort. Exclusion of hospital-onset sepsis from SEP-1 would allow providers and medical centers to focus on the population of patients who are most likely to benefit from protocolized early sepsis care—individuals with community-onset sepsis.

2. Measurement of time zero (the moment in which onset of sepsis can be recognized) needs to be validated in hospital-onset sepsis.

When evaluating adherence to SEP-1 among patients with hospital-onset sepsis, it became apparent that identifying time zero is more challenging in this population than in community-onset sepsis. One of the basic assumptions in early sepsis care is that rapid care is better and every hour of delay between onset of sepsis and treatment increases the risk of poor

outcomes. If this is the case, then accurate determination of time zero is a necessary requirement for the evaluation of which treatments are beneficial. The precision and accuracy of current definitions of time zero need to be evaluated in hospital-onset sepsis, and, if found lacking, the definition of time zero in this population should be revised.

3. Inpatient systems of care delivery should be redesigned to facilitate early recognition of sepsis and rapid assessment by a provider with expertise in the management of sepsis.

SEP-1, which standardizes early sepsis management using an elaborate protocol, did not improve outcomes from hospital-onset sepsis. Hospital-onset sepsis can be complex in its pathophysiology, and patients with hospital-onset sepsis may be very different from one another. Rather than standardizing care, we believe that early management of hospital-onset sepsis should be individualized.

Delayed recognition of sepsis has been identified as a potentially preventable cause of sepsis mortality.[33] In particular, patients with septic shock appear to suffer worse outcomes when care is delayed.[130] Acknowledging that sepsis care should be tailored to the individual, early recognition is nonetheless a necessary first step in all cases. In the emergency department, systems of care have been designed for triage and rapid assessment. In the inpatient setting, on the other hand, assessment and triage of patients occur on an ad hoc basis. Rounding schedules may be informed by patients' needs or may be arbitrary.[131] Consideration should be given to redesigning inpatient systems by introducing formal, standardized pathways in which clinical instability due to suspected infection can trigger an organized and coordinated response from providers with expertise in early sepsis management. These pathways may rely on use of real-time data from the electronic health record or simple screeners that can be used by any healthcare

worker. In patients for whom typical signs and symptoms of infection may be unreliable, such as postoperative patients or transplant recipients, the threshold for "suspected infection" may need to be set much lower. Providers with expertise may include hospitalists, intensivists, or infectious diseases providers. Under ideal circumstances, these providers would be designated in advance and present in the medical center at all hours.

Organization of the inpatient response to clinical deterioration events may provide benefits beyond improved care for individual patients. If clinical deterioration events trigger a formal response, they can be logged, tracked, and periodically reviewed. Retrospective review of cases allows for the improvement and maintenance of care processes and is already common practice with other in-hospital complications related to patient safety, such as central-line associated bloodstream infections. By mandating a single approach to all patients with sepsis, SEP-1 may stifle innovation.[132] Instead, medical centers should be provided with a framework within which they can develop locally- and contextually-appropriate strategies to improve the quality of sepsis care.

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