# OUTCOMES IN PATIENTS WITH AND WITHOUT ICD-9 DIAGNOSED SEVERE SEPSIS AND SEPTIC SHOCK

By

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OUTCOMES IN PATIENTS WITH AND WITHOUT ICD-9 DIAGNOSED SEVERE SEPSIS AND SEPTIC SHOCK

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## Abstract

**Title:** Outcomes in Patients With and Without ICD-9 Diagnosed Severe Sepsis and Septic Shock

**Purpose:** To evaluate the hypothesis that patients who present to the emergency department with objective findings of severe sepsis or septic shock, but who are not specifically diagnosed, denoted by absence of 995.92 or 785.52, are treated less aggressively and have worse outcomes than similar patients who are specifically diagnosed with severe sepsis or septic shock.

**Design:** Retrospective cohort study

**Setting:** University of Kansas Hospital, academic medical center, emergency department

**Patients:** 6885 patients with severe sepsis or septic shock

**Methods:** Data were extracted from the electronic health record using the query tool HERON, to identify patients with severe sepsis or septic shock admitted through the emergency department, between 11/01/07–09/31/15. Patients aged ≥ 18 years, who had an infection, received an antibiotic ≤ 8 hours after triage, and meet criteria for severe sepsis and/or septic shock were eligible for inclusion. Severe sepsis was defined either by explicit diagnosis, ICD-9 995.92, or clinical criteria, infection + ≥2 sites of organ dysfunction. Septic shock was identified by one of the following: 1) an explicit diagnosis of septic shock, ICD-9 785.52, 2) criteria for severe sepsis and an ICD-9 code of other shock or shock unspecified (785.50 or 785.59), or 3) criteria for severe sepsis and received a vasopressor. We compared treatment rates, based on the Surviving Sepsis Campaign three-hour recommendations, and outcome differences between severe sepsis and septic shock patients who had a diagnosis code of 995.92 or 785.52 to patients who met criteria, but were never diagnosed as denoted by no ICD-9 diagnosis code.

**Main Results:** A total of 6885 eligible patients were identified, with a mean age of 60.4 years ± 16.9 (mean ± standard deviation). Half of patients were male, (51.3%) and 42.5% received an

ICD-9 diagnosis code of 995.92 or 785.52. Septic shock was coded more frequently than severe sepsis (74.1% vs 32.8%). Three-hour bundle protocol completion rates were low for all patients (8.6%), but higher for those with an ICD-9 code than patients without (9.6% vs 7.9%, p=0.02). Average time to first antibiotic administration was also earlier for those with a diagnosis code (3.2 ± 3.1 hours vs 3.93 ± 3.9 hours, p <0.001). Therapeutic components of the 3-hour protocol, administration of an antibiotic and IV fluids if needed, were also found to be administered more often in patients with a diagnosis code (34.8% vs 28.6%, p<0.001).

Within the cohort, 5631 (81.7%) patients had severe sepsis and no shock. Those with an ICD-9 code of 995.92 had higher mortality (6.3% vs 2.3%), higher ICU admission rates (44.7% vs 22.5%), and hospital lengths of stay (9.2 ± 6.9 days vs 6.9 ± 6.7 days), (all p<0.001). Discharge locations were also different. Severe sepsis patients with an ICD-9 diagnosis code were discharged home less (43.6% vs 52.0%, p<0.001), were discharged to hospice more (6.1% vs 4.4%, p<0.001), and were given home health services more often (22.4% vs 19.5%, p=0.01). Readmission rates (30-day) were highest for patients without an ICD-9 code of 995.92 (20.9% vs 25.5%, p<0.001). Among patients with shock (n=1254, 20.5%), there was no significant difference in mortality or post-hospital discharge locations between those with an ICD-9 diagnosis code of 785.52 and those without. Of interest, patients without an ICD-9 code of 785.52 had higher ICU admission rates (90.2% vs 83.8%), longer hospital stays (16.7 ± 14.8 days vs 13.4 ± 12.3 days), and longer ICU stays (7.7 ± 8.2 days vs 5.5 ± 6.2 days), (all p <.001).

**Conclusions**: Patients with severe sepsis and septic shock continue to be underdiagnosed as evidence by ICD-9 codes and undertreated according to international surviving sepsis guidelines. Patients meeting shock criteria are more often diagnosed than those with severe sepsis. Overall, treatment rates were sub-optimal, but patients with an ICD-9 diagnosis had higher total and

therapeutic component rates. Among septic shock patients without a code, secondary outcomes including ICU admission and hospital and ICU length of stays were worse compared to patients with an ICD-9 diagnosis code of 785.52. Patients with severe sepsis and without a diagnosis code had higher 30-day readmission rates. Further investigation is needed to identify factors contributing to ICD-9 code assignments, as well as financial implications of under-coding.

**Disclosures**: The authors have nothing to disclose.

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# Chapter I: Literature Review

## Significance of Severe Sepsis

Severe sepsis is a life-threatening syndrome caused by a systemic immune response to an underlying infection. It is an underestimated principal cause of mortality, and the leading cause of death in non-coronary ICUs [3]. The Centers for Disease Control and Prevention reported severe sepsis as the 11th leading cause of death in 2009; mortality estimates range from 28.6% to 51.0% [4]. Those patients who survive hospitalization, as compared to matched controls without severe sepsis, experience cognitive decline, have decreased quality of life scores, and have higher long term mortality and morbidity [5, 6]. Additionally, the Agency for Healthcare Research and Quality listed sepsis as the most expensive condition treated in U.S. hospitals, costing more than $16 billion annually [7].

Underlying medical conditions and increased age can increase the risk of developing severe sepsis, as well as influence poor outcomes [8]. The highest incidence of severe sepsis occurs among people over 65 years of age. As America's baby boom generation continues to age and the number of patients living with comorbidities such as cancer and HIV continues to increase, the incidence, mortality, and costs associated with severe sepsis will continue rising [9]. The relationship between severe sepsis and underlying co-morbidities is bi-directional. Not only does underlying illness increase the risk for infection and severe sepsis, but survivors are then more likely to suffer a higher burden from their existing comorbid medical conditions [8]. This series of events could be the initial spiral of major morbidity in our country. Epidemiological studies report that the incidence of severe sepsis continues to increase, along with total mortality, while case fatality decreases [10-12].

**Definitions of Sepsis, Severe Sepsis, and Septic Shock**

Severe sepsis is a condition caused by an underlying infection triggering an inappropriate, systemic immune response and resulting in end organ dysfunction. Normally, in response to cellular injury or infection leukocytes and pro-inflammatory mediators such as TNF-α, IFNγ, IL-1, and IL-6, work to kill invading pathogens and repair damaged cells. These pro-inflammatory mediators also play a central role in amplification of the immune response by activating cellular cascades that recruit more immune cells to the site of infection, increase the permeability of the vasculature to allow cell migration to the site of injury, and raise the body's temperature [13]. These basic immune processes are manifested clinically as the systemic immune response syndrome, SIRS. SIRS is a sign of an active immune response and consists of four markers, listed in Figure 1. The combination of two or more SIRS criteria, coupled with a suspected infection, describes a patient with sepsis. A study published in 2015 found that nearly 87.9% of septic patients have two or more criteria [14]. Even though a small proportion of patients, 12%, do not elicit a response to meet the SIRS criteria, SIRS criteria are important early signs of sepsis and have a large role in screening patients for the condition. While mortality rates at this stage are lower than for severe sepsis, at 7-16%, the key to positive outcomes is prevention of progression to the next stage [4].

| | |
|---|---|
| Heart Rate | >90 bpm |
| Respiratory Rate | >20 breaths/min |
| Temperature | $\geq 38^0$C or $\leq 36^0$C |
| White Blood Cell Count | $\geq$ 12,000 or $\leq$ 4,000 cells/mm3 or > 10% bands |

Figure 1. The SIRS Criteria [2]

The next stage after sepsis, severe sepsis, is defined as acute organ dysfunction in the presence of an underlying infection. (Specific acute organ dysfunction sites and descriptions can be found in the appendix.) The immune process described above is highly regulated, ensuring it stays localized and controlled.

For reasons not precisely known, in some situations this response becomes more robust and systemic, involving secondary sites away from the primary site of infection [8]. Pinsky described this robust immune response as a form of malignant intravascular inflammation due to its auto-amplifying nature, spreading uncontrolled within the vascular space and a result of a normal immune response gone awry [15]. It is believed that this systemic vascular inflammation is caused by an excessive amount of inflammatory mediators. These mediators activate the fibrinolytic and coagulation systems causing endothelial damage, increased vascular permeability, decreased perfusion of organs, and at the cellular level causing mitochondrial dysfunction [13]. Regardless of the exact mechanisms, this profound and systemic immune response results in acute organ dysfunction and potentially failure. Mortality estimates for severe sepsis range from 21% to 58% [4]. Eventually, without aggressive treatment, the vascular compromise becomes so significant that the potentially deadly syndrome of septic shock ensues. Septic shock is defined as severe hypotension, refractory to fluid management. This progression and classification of sepsis, severe sepsis, and septic shock was proposed in 1991 by the Society of Critical Care Medicine (SCCM) and the American College of Chest Physicians (ACCP) to help unify the description and diagnosis of these patients and can be visualized in Figure 2 [2].

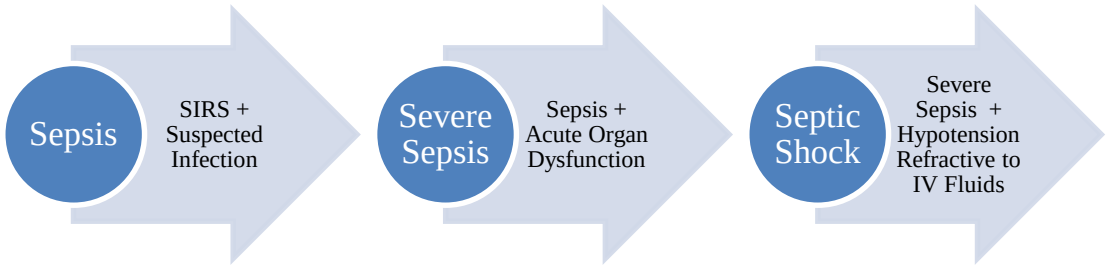


Figure 2. Progression of Sepsis [2]

**Treatment of Severe Sepsis**

Decreased mortality and morbidity in severe sepsis revolves around early recognition and aggressive treatment. A consensus committee of international experts and organizations, the Surviving Sepsis Campaign (SCC), created international guidelines and recommendations for the treatment of severe sepsis and septic shock patients, the Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic shock Patients. Treatment is focused on administration of timely antibiotics, controlling the source of infection, and volume resuscitation with intravenous fluids (IV fluids) [1]. Based on a large retrospective study involving 32,000 patient charts across 17 countries, the SCC committee decided to simplify treatment in 2012 by creating the SCC sepsis 3 and 6 hour treatment bundles. The components of the sepsis bundles can be found in Figure 3. The use of SSC three- and six-hour bundles showed increases in the quality improvement of sepsis care and decreases in mortality.

SSC provides well defined rationale for each bundle component based on the best evidence available. A serum lactate measurement provides information about the level of hypoperfusion in patients who are not yet hypotensive based on mean arterial pressure, but who are at risk. As hyperlactatemia is typically found in septic patients, the lactate level can provide

| Surviving Sepsis Campaign Bundles |
|---|
| To be completed in three hours: |
| 1) Obtain blood cultures prior to antibiotic administration<br>2) Administer broad spectrum antibiotics<br>3) Measure serum lactate levels<br>4) Provide 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L |
| To be Completed within six hours: |
| 1) For hypotension, non-responsive to initial fluid resuscitation, apply vasopressors to maintain a MAP ≥65 mmHg<br>2) If hypotension is persistent after fluid resuscitation, or initial lactate ≥4 mmol/L, reassess volume and tissue perfusion.<br>3) Re-measure lactate if initial lab value was elevated |

Figure 3. Bundle Protocol Components [1]

prognostic information, as those patients with a serum lactate level of ≥4 mmol/L have a 46.1% mortality rate [16]. High lactate levels can also alert a provider to initiate treatment with the recommended six-hour shock bundle despite not having blood pressures ≤70 mmHg. Requirements of a blood culture before antibiotic administration increases the opportunity to identify the causative organism and to use the confirmation to de-escalate antimicrobial therapy to a more selective agent [1]. Additionally, if a blood culture is drawn after antibiotic administration, the likelihood of growing a culture becomes rare, as sterilization of the blood occurs quickly, potentially within an hour of administration of an antibiotic [17].

The two most important components of the bundle, antibiotic administration and IV fluid resuscitation are aimed at therapeutic benefit, rather than for diagnostic purposes as are obtaining a serum lactate and a blood culture. As the most common source of infection in severe sepsis and shock is pneumonia, followed by abdominal infections with Gram-positive and Gram-negative organisms, administration of early antibiotics is appropriate in the majority of patients. Evidence overwhelmingly supports that administration of early antibiotics reduces mortality in severe sepsis patients with a bacterial infection [18]. Kumar showed that patients with septic shock havve a linear relationship between time of antibiotic administration and risk of death among patients with septic shock. Each hour of delay was associated with a 7.6% decrease in survival [19]. Ibrahim found that patients in the intensive care unit (ICU) who received inadequate antibiotic treatment experienced higher hospital mortality [20]. The recommendation that a broad spectrum antibiotic be given first is based on the reduced margin of error when treating critically ill patients. Antibiotic therapy should always be targeted at the suspected pathogen and its sensitivity to coverage, but broad coverage is essential when the pathogen is unknown. SCCM guidelines even recommend storing pre-mixed quantities of broad spectrum antibiotics in the

emergency department to speed in delivery and avoid delays. Lastly, administration of IV fluids is necessary to help restore ineffective arterial blood pressure and perfusion of end organs that contributes to global tissue hypoxia. As the systemic immune response increases in severe sepsis and septic shock, vasodilation, capillary leak, and vascular injury can contribute to significant intravascular volume deficits. Patients with a fluid requirement should receive at least 30mL/kg of a crystalloid fluids to restore perfusion [17].

Another key in fighting this rising epidemic is education. Physician education promoting the recognition of patients meeting criteria, as well as adherence to standardized treatment protocols is essential to prevent unnecessary loss of life. The guidelines recommend screening of all infected patients for severe sepsis to increase early identification of patients with sepsis and begin early interventions to prevent progression [1]. In 2008, results from a nationwide prospective educational intervention in Spain showed that the intervention, aimed at improving screening of patients and completion of the SSC sepsis bundles, was capable of decreasing nationwide severe sepsis mortality rates [21]. An estimated 490 lives were saved by this one year education effort. In the United States, Levy et al. measured treatment compliance rates and mortality over a seven year period after the initiation of the Surviving Sepsis Campaign initiative in 2004. Their analysis involved 218 medical sites from three continents. At sites with high treatment compliance, mortality rates were lower, dropping 0.7% for every quarter of participation. This resulted in a 25% relative risk reduction in mortality, helping prove that standardization and performance markers can help change clinical behaviors that improve care and ultimately decrease mortality [22]. Despite the positive outcomes associated with protocol compliance and early recognition, all epidemiological severe sepsis studies show that the condition remains underdiagnosed and undertreated.

**History of Finding Severe Sepsis Patients Retrospectively in Research**

The majority of published literature relies on retrospective patient cohorts created using data extracted from the electronic medical record (EMR) or administrative billing data. The very first epidemiological study was conducted by the CDC in 1990, using the National Hospital Discharge Survey, estimating 450,000 cases a year, attributing to greater than 100,000 deaths. Since then, a variety of epidemiological methods have been used to produce estimates of severe sepsis burdens; each has its own limitations.

In 2001, Angus became one of the first researchers to describe the epidemiology of severe sepsis, in the United States. He used a more inclusive method that did not require a positive blood culture diagnosis, as only 30-50% of patients have one [1, 23]. Using administrative discharge data from hospitals in seven states, the case definition required that patients have ICD-9 codes for both an infection and acute organ dysfunction within the same encounter. Angus's final cohort was validated against previous prospective clinical trial data and resulted in a relatively simple algorithm that can be used to find an inclusive group of severe sepsis patients [3]. Despite the success of this methodology, as noted by the paper's > 3900 citations (Web-of-Science), Angus's method relies solely on ICD-9 codes, not taking into consideration the clinical components that measure organ dysfunction such as lab values. Without these clinical elements of severe sepsis, elements that may not be reflected within the lists of acute organ dysfunctions, severe sepsis is generally underestimated, only capturing those patients with severe sepsis who were actually treated [8]. Additionally, Angus' method does not require that the organ dysfunction be separate from the site of infection. As the definition of severe sepsis is a systemic immune response, Angus captured a population that consists of patients with mostly single site organ dysfunctions, 73% of his cohort [3].

Following Angus' work, the second most cited methodology for finding severe sepsis patients was created by Martin, who reviewed data from severe sepsis patients from 1979-2000. The Martin method searched the EMR for patients with ICD-9 diagnosis codes for a blood borne infection (septicemia, bacteremia, or fungemia) and ICD-9 diagnosis codes for acute organ dysfunctions. His searches produced a more specific cohort, with mortalities 10% higher than the Angus method and a lower incidence, 140/100,000 cases. As mentioned previously, about 50% of severe sepsis patients do not have laboratory positive blood cultures; among those who do, there is a higher associated mortality rate [23, 24].

Since the publication of these two methods, numerous others have replicated their algorithms to find severe sepsis patients, all resulting in different numbers. The most recent epidemiological studies show annual incidence rates vary 3.5 fold from 300/100,000 to 1,031/100,000 creating a call for a closer look at the methodology and validity of using administrative billing data [25]. Overall, all studies report a rise in incidence and total mortality making this an important area of study. Case fatality rates have been declining around 3% a year since 1991 [26]. Clinicians postulate that these observations arise from improved treatment and identification, as well as an increasing high-risk population [10, 24]. Others believe the rise in incidence is attributable to ICD-9 coding changes, such as increased use of organ dysfunction coding [27]. Stevenson, et al. compared mortality rates from 36 multicenter clinical trials with administrative data to answer the billing changes versus clinical practice improvement debate. They hypothesized that the increase in incidence and decline in case fatality was due to increased organ dysfunction coding, and that capturing a larger, less acutely ill cohort, led to a fall in mortality rates. After standardizing for case-mix differences, they found that from 1991-2009, from all forms of identification (Martin, Angus, and prospectively using clinical trial data), case

fatality rates dropped and incidence rates increased [26]. Additionally, regardless of the method, Angus or Martin, mortality estimates derived from administrative data ICD-9 algorithms are comparable to prospective trial cohorts, and thereby likely are accurate.

## Chapter II: Thesis Introduction

Severe sepsis is a major public health problem in the United States. It is the leading cause of mortality in non-coronary ICUs, as well as the most expensive condition treated in U.S. hospitals [3, 7]. As the population continues to age and the number of people living with comorbid medical conditions continues to increase, the incidence and overall mortality from severe sepsis will likely continue to rise. Although the condition is highly lethal, early recognition and aggressive treatment decrease mortality and morbidity [22, 28]. Despite this fact, studies continue to show that patients meeting severe sepsis criteria are underdiagnosed [3, 25].

In 2004, sepsis-specific ICD-9 codes 995.92 and 785.52 were created to administratively capture patients meeting the international consensus definitions of severe sepsis and septic shock. Multiple studies, as well as local chart review adjudications, continue to show that these explicit sepsis related ICD-9 diagnosis codes are underused by physicians and coders [10, 24, 25, 29, 30]. In Gaieski's study of epidemiological methods to identify severe sepsis patients, he found that patients who met Martin's criteria, requiring presence of a blood borne infection, were more likely to have received a sepsis-related ICD-9 code [25]. In 2013, Whittaker evaluated the sensitivity and specificity for detecting severe sepsis patients by using sepsis related ICD-9 diagnosis codes for cohort extraction. She found that explicit diagnosis codes had a sensitivity of 21% when compared with the Angus method. Both methods showed that patients with a sepsis related diagnosis code represented a more severely ill population, based on higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores, higher serum lactate levels, and higher ICU admission rates [25, 30]. To date, this is the only study that investigated the differences between patients who did or did not receive a sepsis related ICD-9 diagnosis code. We previously showed that of patients meeting clinical criteria for severe sepsis, 48.4% were

never assigned an explicit ICD-9 diagnosis code of 995.92 and/or 785.52 [29]. This led us to question whether these un-coded severe sepsis patients represent an unrecognized, and potentially undertreated group of patients with severe sepsis.

After a physician recognizes that a patient meets criteria for severe sepsis, within three hours the provider should initiate and complete components of the international evidence-based guidelines for treatment of severe sepsis [1]. The combination of drawing a blood culture and a serum lactate, administration of a broad spectrum antibiotic, and administration of fluids if the patient is hypotensive is known as the Surviving Sepsis Three Hour Bundle. Performance of these actions is specifically indicated for patients recognized as having severe sepsis and septic shock.

We hypothesized that a smaller proportion of patients who met clinical criteria for severe sepsis, but who were not specifically given a sepsis-related ICD-9 diagnosis code, would receive care according to these guidelines for treatment in comparison with patients who were specifically diagnosed as having severe sepsis or septic shock using an ICD-9 code. We also hypothesized that the mortality and morbidity would be higher in this un-coded group as measured by hospital and ICU length of stays, 30-day readmission rates, and discharge to locations beyond home. Our primary objective was to compare treatment, mortality, and other patient-centered outcomes among severe sepsis patients with a sepsis related ICD-9 diagnosis code, 995.92 or 785.52, with the same outcomes among patients who met clinical criteria for severe sepsis but did not receive a sepsis specific diagnosis code.

# Chapter III: Methods

## Study Approval

Our study was approved by the University of Kansas Institutional Review Board with a waiver of informed consent, IRB STUDY00001753.

## Data Source

Data were collected from the electronic medical record, (EMR), at the University of Kansas Medical Center using an i2b2 based interface, the Healthcare Enterprise Repository for Ontological Narration (HERON) [31]. Using HERON, a query tool that extracts information from the EMR based on researcher selection of discrete data fields, we created a Boolean search method to find a cohort of severe sepsis patients who entered through the emergency department and were treated between 11/01/2007, the initiation date for the institution's EMR, and 09/30/2015, the last date before conversion to ICD-10 diagnosis codes. Flowsheet data not captured by the HERON interface were electronically obtained after the final cohort of severe sepsis and/or septic shock patients were identified by the Office of Organizational Improvement matching MRN and triage dates.

## Case Selection

All patients were required to meet the following inclusion criteria: ≥ 18 years of age, admission through the emergency department, received an ICD-9 diagnosis code for acute infection, given an antibiotic within 24 hours of triage, and had recorded clinical outcomes, such as hospital length of stay and discharge disposition codes. ICD-9 diagnosis codes for infection can be found in the appendix.

**Case Definitions**

After meeting the above inclusion criteria, patients were retained if they the met case definition of severe sepsis or septic shock. Using a modified Angus method, based on the clinical criteria proposed by the American College of Chest Physicians/Society of Critical Care Medicine Consensus definitions, we defined patients as having severe sepsis if either a diagnosis code of 995.52 was given or there was documented presence of an infection plus ≥2 different sites of organ dysfunction [2]. Acute organ dysfunction was defined by presence of either an acute organ dysfunction code or on the basis of whether the first laboratory or physiologic value recorded in the patient record met the threshold of organ dysfunction [32]. Laboratory threshold values and lists of codes for infections and acute organ dysfunctions can be found in the appendix. Patients with septic shock were similarly defined by having a septic shock specific ICD-9 diagnosis code of 785.52, or if they met severe sepsis criteria and were administered a vasopressor (norepinephrine, epinephrine, vasopressin, or phenylephrine), or met severe sepsis criteria and received a diagnosis of shock unspecified or other shock. Patients were excluded from the final cohort if they were under the age of 18 years, had cardiogenic shock (ICD-9 code of 785.51), did not meet criteria for severe sepsis, or were not given an antibiotic within 8 hours of triage.

**Outcome Measures and Statistical Analysis**

Data cleaning and analysis were performed using SAS software, Version 9.4, using two-sided hypothesis testing (alpha 0.05) (Copyright 2012-2013 SAS Institute Inc., Cary, NC). All binary outcomes were analyzed using chi-square test statistics, and data consisting of numerical continuous data were evaluated using a Student's t-test. Our primary outcomes were treatment completion rates and mortality compared between the groups of patients diagnosed with an ICD-9 code specific to severe sepsis or septic shock (995.92 or 785.52) and the group with no such

ICD-9 code. Outcome measures including information about death, hospital and ICU length of stays, final discharge location, and 30-day readmission rates were calculated using information from the University Health Consortium (UHC) data embedded within the electronic medical record. Treatment completion rates were calculated and analyzed in accordance with the Surviving Sepsis Campaign Three Hour Bundle Guidelines [1]. Each component of the protocol (blood culture ordered, serum lactate ordered, antibiotics administered, IV fluids given) was first analyzed independently and, if completed, the patient received a score of 1 (yes) on that component. All four components were summed for a total treatment score out of 4. If the patient scored a 4, they were considered to have the bundle protocol successfully completed within three hours of triage. If less than four, the patient did not meet bundle completion. The proportion of patients who received the complete bundle was calculated. Additionally, therapeutic components of the bundle, use of broad spectrum antimicrobials within three hours and intravenous fluids if hypotensive, were analyzed together and reported as a frequency.

Patients with the first recorded MAP < 70mmHg or the first serum lactate ≥ 4 mmol/L were classified as having a need for fluids. All patients who had a need and received 30mL/kg within the first 2.5 hours of triage received a fluid completion score of 1, as did patients without a need. We chose to limit fluid times to 2.5 hours within triage time to prevent overestimate of the actual fluid received by a patient. Other outcomes including mortality, 30-day readmission, and discharge location are expressed as a frequencies, while average lengths of stay were reported as an average number of days.

To evaluate potential reasons for coding and treatment differences, we measured presentation illness status by calculating a sequential organ failure assessment (SOFA) score, using the first laboratory and physiological values recorded. Additionally, we calculated the

number of infection sites, number of significant co-morbidities using a Charleson co-morbidity score, and a total number of acute organ dysfunctions.

We conducted multivariate logistic regression analysis to find the most accurate predictors of receiving an ICD-9 diagnosis code of 995.92 or 785.52, as well as independent predictors of receiving complete treatment within the first three hours of admission while controlling for potential confounding. The results are presented as odds ratios and 95% confidence intervals.

Lastly, as outcome differences between severe sepsis and septic shock patients are already known to be significantly different, we analyzed severe sepsis and septic shock patient outcomes separately to prevent confounding by the presence of septic shock.

# Chapter IV: Results

## Cohort Characteristics

A total of 6,885 patients were identified with severe sepsis or septic shock (Figure 4). The mean age was 60.4 ± 16.9 years (mean ± SD), and 51.6% (n=3534) were male. About one-fifth of the total cohort met criteria met criteria for septic shock (n=1254, 18.2%) (Table 1).

Overall, 42.5% of patients (n=2927) had a sepsis related ICD-9 diagnosis code. Those with a diagnosis code had more documented infections (2.4 vs 1.8), were more likely to have a diagnosis of bacteremia or septicemia (93.7% vs 22.2%), and had more organ dysfunction sites (3.2 vs 2.6), (all $p< 0.001$) (Table 2). When further separated based on presence or absence of shock, the significant difference in the number of organ dysfunction sites between ICD-9 positive and negative groups disappeared among patients with severe sepsis, but not patients with septic shock patients (Table 3). Other baseline acute organ dysfunction, as measured by initial lactate levels (2.6 vs 2.2 mmol/L) and SOFA scores (3.9 and 3.1), were higher in the ICD-9 diagnosed group ($p<0.001$) even when separated based on presence of shock (Table 4).

Using multivariate logistic regression (odds ratio: 95% confidence interval), we found that having a diagnosis of bacteremia/septicemia, (OR: 25.1, 17.2-36.7), being admitted to the ICU (OR: 3.3, 2.8-3.8), and having a diagnosis of a respiratory tract infection or respiratory dysfunction, (OR 1.40, 1.2-1.6) were all independently associated with receiving a sepsis-specific ICD-9 diagnosis code. Age, gender, number of comorbidities, and number of organ dysfunction sites were not found to be predictive. Overall model fit was assessed using the Hosmer and Lemeshow Goodness-of-Fit Test, ($p=0.5$). Components of the final model can be found in the appendix.

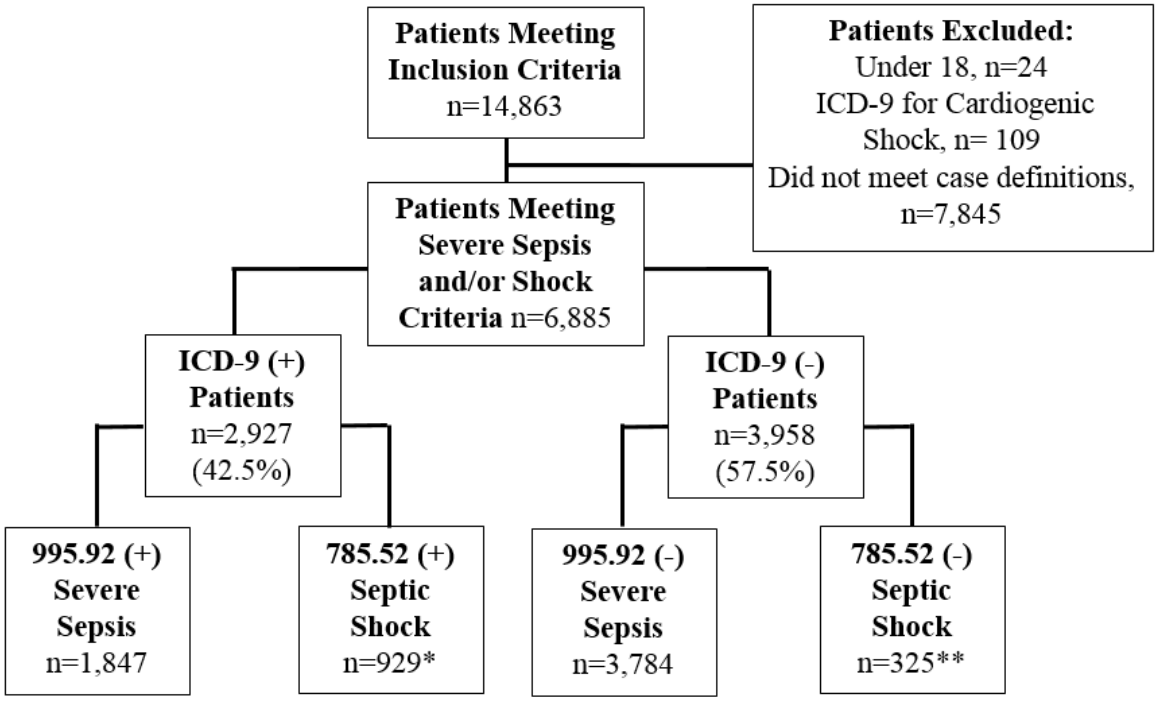


Figure 4. Cohort Organization

*68 patients assigned 785.52 never received 995.92 and 861 received both. **151 patients meeting criteria for septic shock received an ICD-9 diagnosis code of 995.92, but not 785.52. 104 of these patients were identified by administration of a vasopressor and had no other diagnosis code of shock. 37 received a diagnosis of shock unspecified, 785.50 and 16 a diagnosis code of other shock, 795.59.

Table 1. Demographic Characteristics for All Patients with Severe Sepsis and Septic Shock

| | Entire Cohort N=6885 | Patients with sepsis specific ICD-9 codes N=2927 (42.5%) | Patients without sepsis specific ICD-9 codes N=3958 (57.5%) | P values |
|---|---|---|---|---|
| | | | | |
| Age, (mean ± SD) | 60.4 ± 16.9 | 59.5 ± 17.3 | 61.1 ± 16.7 | p=0.03 |
| Gender, male n (%) | 3534 (51.3%) | 1510 (51.6%) | 2024 (51.1%) | p=0.72 |
| Race White, n (%) | 4536 (65.9%) | 1920 (65.6%) | 2616 (66.1%) | p=0.056 |
| Black, n (%) | 1614 (23.4%) | 667 (22.8%) | 947 (23.9%) | |
| Other, n (%) | 725 (10.5%) | 333 (11.4%) | 392 (9.90%) | |
| Charleston Comorbidity Score (out of 21 ± SD) | 6.1 ± 3.6 | 6.2 ± 3.5 | 5.9 ± 3.6 | p<0.001 |

Table 2. Measures of Infection for Patients with Severe Sepsis and Septic Shock

| | Entire Cohort N=6885 | Patients with sepsis specific ICD-9 codes N=2927 (42.5%) | Patients without sepsis specific ICD-9 codes N=3958 (57.5%) | P values |
|---|---|---|---|---|
| **Measures of Infection** | | | | |
| Sites of Infection (mean ± SD) | 2.0 ± 0.9 | 2.4 ± 0.9 | 1.8 ± 0.8 | p<0.001 |
| Infectious Codes (001-0139.99) | 5399 (78.4%) | 2861 (97.8%) | 2538 (64.1%) | p<0.001 |
| Bacteremia/Septicemia | 3624 (52.6%) | 2744 (93.7%) | 879 (22.2%) | p<0.001 |
| Respiratory | 3130 (45.5%) | 1499 (51.2%) | 1631 (41.2%) | p<0.001 |
| Urinary | 2703 (39.3%) | 1199 (41.0%) | 1504 (38.0%) | p=0.01 |
| Soft Tissue Site | 1236 (17.9%) | 561 (19.2%) | 675 (17.1%) | p=0.02 |
| Abdomen | 731 (10.6%) | 385 (13.2%) | 346 (8.74%) | p<0.001 |

Table 3. Presentation Acute Organ Dysfunctions for Severe Sepsis Patients

| | All Severe Sepsis Patients N=5631 | Patients with 995.92 N=1847 (32.8%) | Patients without 995.92 N=3784 (67.2%) | P values |
|---|---|---|---|---|
| First Serum Lactate (mean ± SD) | 2.2 ± 1.6 | 2.3 ± 1.7 | 2.1 ± 1.5 | p<0.001 |
| Average SOFA score | 3.0 ± 2.1 | 2.9 ± 2.2 | 3.1 ± 2.0 | p<0.001 |
| First MAP (mean ± SD) | 92.3 ± 20.3 | 91.8 ± 20.6 | 92.5 ± 20.2 | p=0.23 |
| Organ Dysfunction Sites (mean out of 7 ± SD) | 2.6 ± 1.0 | 2.6 ± 1.3 | 2.6 ± 0.8 | p=0.06 |
| Renal | 3145 (56.8%) | 1024 (58.3%) | 2121 (56.1%) | p=0.12 |
| Hematological | 2922 (52.7%) | 821 (46.7%) | 2101 (55.5%) | p<0.001 |
| Respiratory | 2170 (39.2%) | 849 (48.3%) | 1321 (34.9%) | p<0.001 |
| Cardiovascular | 1444 (26.1%) | 437 (24.9%) | 1007 (26.6%) | p=0.17 |
| CNS | 1665 (30.0%) | 529 (30.0%) | 1136 (30.0%) | p=0.97 |

*105 (1.8%) patients had one or more components necessary to calculate a complete SOFA score missing, 2236, (39.7%) never had a serum lactate taken, and 73 (1.3%) had an unattainable MAP. They were excluded from the respective calculation.

Table 4. Baseline Acute Organ Dysfunctions of Septic Shock Patients

| | All Septic Shock Patients N=1254 | Patients with 785.52 N=929 (74.0%) | Patients without 785.52 N=325 (26.0%) | P values |
|---|---|---|---|---|
| First Serum Lactate (mean ± SD) | 2.97 ± 2.79 | 3.04 ± 2.86 | 2.75 ± 2.55 | p=0.04 |
| SOFA score (mean out of 21 ± SD) | 5.4 ± 3.32 | 5.65 ± 3.39 | 4.68 ± 3.01 | p=0.01 |
| First MAP (mean ± SD) | 81.4 ± 22.1 | 79.7 ± 21.3 | 86.4 ± 23.5 | p=0.03 |
| Organ Dysfunction Sites (mean out of 7 ± SD) | 4.13 ± 1.38 | 4.20 ± 1.43 | 3.95 ± 1.20 | p<0.001 |
| Respiratory | 867 (69.1%) | 628 (67.6%) | 239 (73.5%) | p=0.05 |
| Hematological | 832 (66.3%) | 626 (67.4%) | 206 (63.3%) | p=0.20 |
| Cardiovascular | 1254 (100%) | 929 (100%) | 325 (100%) | p=1.00 |
| CNS | 511 (40.8%) | 385 (41.4%) | 126 (38.7%) | p=0.43 |
| Renal | 882 (70.3%) | 680 (73.1%) | 202 (62.1%) | p<0.001 |

*22 (1.7%) patients had one or more components necessary to calculate a complete SOFA score missing, 326, (26.0%) never had a serum lactate taken, and 22 (1.7%) had an unattainable first MAP. They were excluded from the respective calculation.

**Treatment Differences**

A total of 6885 patients were included in the bundle completion calculation. Those patients with a sepsis related ICD-9 diagnosis code (995.92 and/or 785.52) had higher total bundle protocol completion, all four components met under three hours, than those without a code (9.6% vs 7.9%, p <0.001). Therapeutic component completion rates (a broad spectrum antibiotic and appropriate fluids) were higher than total bundle protocol completion rates for the whole cohort (31.2% vs 8.6%) and also higher for those with an ICD-9 diagnosis code (34.8% vs 28.6%, p<0.001). All individual protocol component completion rates were higher in those with a diagnosis code than those without. The largest percentage of the 1458 (21.2%) patients who required fluid resuscitation were those with a diagnosis code, (58.0%, n=845). A majority of patients without a need for IV fluids (n=5427) did not have a diagnosis code (61.6%). Among

these patients with a fluid need, those with a diagnosis code were more likely to receive appropriate fluids than patients without a code (25.6% vs 11.4%, p<0.001).

Blood culture completion was the most common of all four components completed in both patients with a code and without (76.5% vs 54.4%) and obtaining a serum lactate was the least completed (29.7% vs 27.4%). The average time to first antibiotic administration was 3.6 +/- 1.9 hours for the whole cohort. The group of patients with a diagnosis code were given antibiotics about 45 minutes sooner than patients without a diagnosis code, (3.2 +/- 3.1 hours vs 3.9 +/- 3.9 hours, p <0.002). Only 48.0% of patients received an antibiotic within three hours of triage as recommended, but 75.7% appropriately received a broad spectrum antibiotic as their first dose (Figure 5). When the cohort was divided based on presence or absence of septic shock, similar trends were seen.

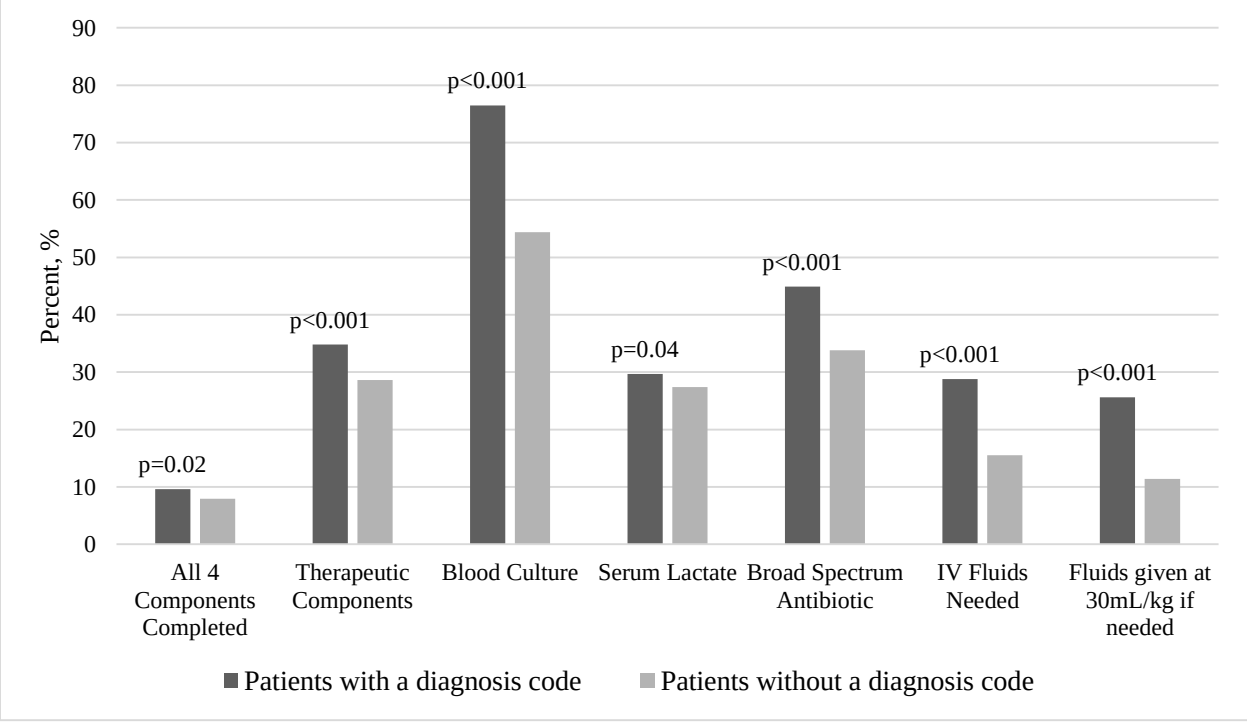


Figure 5. Three Hour Bundle Completion Rates by Presence or Absence of ICD-9 Diagnosis Code Specific to Severe Sepsis or Septic Shock

Using multivariate logistic regression (odds ratio: 95% confidence interval), we found no good model to predict receiving all four components of treatment within three hours. Receiving therapeutic components, a broad spectrum antibiotic and IV fluids, the most significant independent predictors of receiving treatment, completed bundle protocol or therapeutic components alone to be: having a respiratory infection (OR: 1.56, 1.43-1.78), receiving a sepsis specific ICD-9 diagnosis code (OR: 1.24, 1.10-1.36), presence of respiratory dysfunction (OR: 1.25, 1.12-1.40), and age (OR: 1.006, 1.00-1.01). Gender, race, number of comorbidities, and markers of acute organ dysfunction including SOFA scores, first lactates, and total number of organ sites involved were not found to be predictive. Overall model fit was assessed using the Hosmer and Lemeshow Goodness-of-Fit Test, ($p=0.41$). Components of the final model can be found in the appendix.

Due to a higher presence of respiratory infections in patients with a diagnosis code (51% vs 41%, Table 1), and because respiratory infection was independently predictive of receiving treatment, we performed a sub-analysis of treatment rates for patients with and without diagnosis codes while controlling for respiratory infections (Figure 6). 3130 severe sepsis or septic shock patients had a respiratory infection, 52% received a diagnosis code and 48% did not ($p=0.02$). While controlling for the presence of a respiratory infection, differences in overall bundle treatment and therapeutic component treatment rates between patients with and without a diagnosis code no longer differed. Yet, patients with a diagnosis code continued to have higher rates of individual components completed. Time to first antibiotic remained similar, being administered almost 45 minutes earlier in patients with a diagnosis code than those without ($3.2 \pm 1.8$ hours vs $3.9 \pm 2.0$ hours, $p<0.001$).

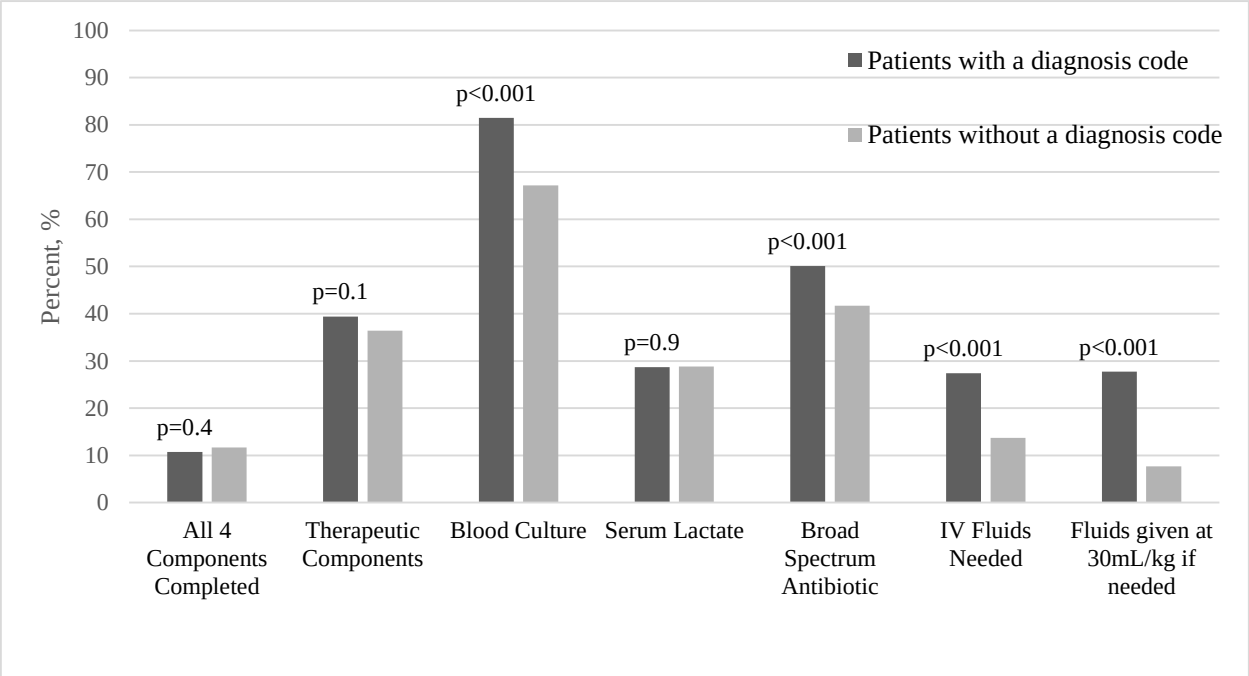


Figure 6. Three Hour Bundle Completion Rates While Controlling for Presence of Pneumonia by Presence or Absence of ICD-9 Diagnosis Code Specific to Severe Sepsis or Septic Shock

## Outcomes for Patients with Severe Sepsis and No Shock

A total of 5631 (81.7%) patients had severe sepsis without shock criteria. Overall severe sepsis mortality was 3.6%. Mortality was significantly higher among those patients with a sepsis-specific ICD-9 diagnosis code (6.3% vs 2.3%, $p<0.001$). Patients with a diagnosis code also had higher rates of ICU admission (44.7% vs 22.5%), longer hospital length of stays (9.2 ± 9.4 vs 6.9 ± 6.7 days), and higher rates of discharge with home healthcare services (22.4% vs 19.5%), (all $p<0.01$). Readmission rates (30-day) were highest among those patients without a diagnosis code, (21.5% vs 25.2%, $p=0.02$).

Table 5. Outcomes of Patients with Severe Sepsis and No Shock

| Outcome Measures | All Patients with Severe Sepsis Criteria | 995.92 (+) Cases | 995.92 (-) Cases | P values |
|---|---|---|---|---|
| | 5631 (81.7%) | 1847 (32.8%) | 3784 (67.2%) | |
| Mortality, % | 204 (3.6%) | 117 (6.3%) | 87 (2.3%) | p<0.001 |
| Hospital Length of Stay (mean days ± SD) | 7.6 ± 7.7** | 9.2 ± 9.4 | 6.9 ± 6.7 | p<0.001 |
| ICU Length of Stay (mean days ± SD) | 3.7 ± 4.2** | 4.0 ± 4.5 | 3.5 ± 3.9 | p=0.02 |
| ICU Admission Rate | 1679 (29.8%) | 826 (44.7%) | 853 (22.5%) | p<0.001 |
| 30-Day Readmission Rate | 1352 (24.0%) | 397 (21.5%) | 955 (25.2%) | p=0.02 |
| Discharge Location | | | | |
| Home | 2771 (49.2%) | 805 (43.6%) | 1966 (52.0%) | p<0.001 |
| Home, with Home Health Services | 1151 (20.4%) | 414 (22.4%) | 737 (19.5%) | p=0.01 |
| Rehab | 129 (2.3%) | 42 (2.3%) | 87 (2.30%) | p=1.0 |
| Acute Nursing Care | 855 (15.2%) | 269 (14.6%) | 586 (15.5%) | p=0.38 |
| Long Term Care | 109 (1.9%) | 46 (2.5%) | 63 (1.7%) | p=0.04 |
| Hospice | 281 (5.0%) | 113 (6.1%) | 168 (4.4%) | p<0.001 |

**Length of stays were calculated excluding patients who died during the encounter. Results were similar when these patients remained included.

## Outcomes for Patients with Septic Shock

A total of 1254 (18.2%) patients met septic shock criteria. Most (69.7%, n=1147) had an ICD-9 code of 785.52 of which 75% (n=861) also were assigned a diagnosis code of 995.92. Overall septic shock mortality was 20.5%. No significant difference in mortality was seen between patients with and without a sepsis-specific ICD-9 diagnosis code (21.7% vs 16.9%, p=0.07). Additionally, no statistically significant differences were seen in 30-day readmission rates (20.9% vs 25.5%, p=0.10) or specific locations of discharge including home, home with home health services, or long term care facilities. Measures of resource utilization were higher in patients who did not receive a diagnosis code including ICU admission rates, (83.8 % vs 90.2%,

p<0.001), ICU length of stay (5.50 ± 6.16 vs 7.73 ± 8.18 days, p<0.001), and hospital length of stay (13.4 ± 12.3 vs 16.7 ± 14.8 days, p<0.001).

Table 6. Outcomes of Patients with Septic Shock

| Outcome Measures | All patients with shock criteria | 785.52 (+) Cases | 785.52 (-) Cases | P values |
|---|---|---|---|---|
| | N=1254 (18.2%) | N=929 (74.1%) | N=325 (25.9%) | |
| Mortality, % | 257 (20.5%) | 202 (21.7%) | 55 (16.9%) | p=0.07 |
| Hospital Length of Stay (mean days ± SD) | 14.3 ± 13.1** | 13.4 ± 12.3** | 16.7 ± 14.8** | p<0.001 |
| ICU Length of Stay (mean days ± SD) | 6.14 ± 6.87** | 5.50 ± 6.16** | 7.73 ± 8.18 ** | p<0.001 |
| ICU Admission Rate | 1071 (85.4%) | 778 (83.8%) | 293 (90.2%) | p=0.005 |
| 30-Day Readmission Rates | 278 (22.2%) | 195 (20.9%) | 83 (25.5%) | p=0.10 |
| Discharge Location | | | | |
| Home | 312 (24.9%) | 230 (24.8%) | 82 (25.2%) | p=0.88 |
| Home, with Home Health Services | 242 (19.3%) | 180 (19.4%) | 62 (19.1%) | p=0.94 |
| Rehab | 50 (3.99%) | 31 (3.34%) | 19 (5.85%) | p=0.07 |
| Acute Nursing Care | 211 (16.8%) | 155 (16.7%) | 56 (17.2%) | p=0.86 |
| Long Term Care | 74 (5.90%) | 50 (5.38%) | 24 (7.40%) | p=0.22 |
| Hospice | 84 (6.70%) | 62 (6.67%) | 22 (6.77%) | p=1.0 |

**Length of stays were calculated excluding patients who died during the encounter. Results were similar when these patients remained included.

## Chapter V: Discussion

We present a retrospective study of 6885 patients with severe sepsis or septic shock admitted through the emergency department at a single academic medical center in Kansas City, KS. It is the largest study to-date investigating treatment and outcome differences between patients with and without sepsis-specific ICD-9 diagnosis codes. We hypothesized that patients with sepsis-specific ICD-9 diagnosis codes, 995.92 or 785.52 represented a formally diagnosed group of severe sepsis patients, and that those severe sepsis and septic shock patients without these codes would be an under recognized and undertreated group of patients. Consistent with previous studies, we found that patients meeting clinical criteria for severe sepsis and septic shock continue to be underdiagnosed as evidenced by over half of the cohort lacking sepsis-specific ICD-9 diagnosis codes (57.5%) [3, 10, 25]. Overall, the highest rate of code assignment was seen among patients with septic shock (74%), but unlike Gaieski's 2013 study, we found high rates of patients who received an ICD-9 for both septic shock and severe sepsis (68.7%) [25]. We believe this reflects increased familiarity with 995.92 and 785.52 by physicians and coders over the last decade.

This is the first study to find that patients without sepsis specific ICD-9 diagnosis codes are undertreated based on the Surviving Sepsis three hour bundle guidelines. We found that patients with a sepsis-specific ICD-9 diagnosis code received individual bundle components and the complete 3-hour bundle protocol more often than those without an ICD-9 diagnosis code, though these are still not optimal among even the patients with a diagnosis code. Having a diagnosis code was also independently associated with receiving treatment after adjusting for other possible factors in multivariate analysis. We believe this signifies that patients without a diagnosis code are not simply un-coded patients, but a group of patients that go under recognized

and undertreated. A potential limitation of our modeling analysis was that overall low treatment rates might have prevented us from capturing the best predictors. We found only one marker of acute organ dysfunction that significantly predicted who received treatment. It's possible that physicians associate severe sepsis with markers of acute inflammation and infection, such as the SIRS criteria, that were not captured in this study and that their presence would have better predicted administration of the bundle treatment protocol. Of interest, the most significant predictor of receiving the three hour bundle was having a respiratory infection. It is well known that the respiratory tract is the most common site of infection in patients with severe sepsis [3]. It is possible that pay for performance initiatives such as PN-5b, requiring early antibiotic administration in patients with pneumonia confound our findings [33]. When controlling for pneumonia, individual treatment rates still remained higher in patients who received a diagnosis code while the complete 3-hour bundle protocol and therapeutic components were no longer significantly different. It's also possible that physicians associate severe sepsis with specific characteristics, such as respiratory infections or advanced age and potentially miss less apparent, but equally important sites of infection such as the urinary tract or soft tissues. However, age was not associated with receiving a diagnosis code in our study.

We additionally focused on the therapeutic components of the three hour bundle protocol. Again, those without an ICD-9 diagnosis code were undertreated when compared to patients with an ICD-9 diagnosis code. Nationwide surveys of emergency department physicians and nurses have identified several barriers to early administration of the three hour bundle protocol. The third most common listed by physicians and the number one described by nurses was lack of identification of patients who meet severe sepsis criteria [34, 35] . This is also the first study to report similar baseline measures of acute organ dysfunction when comparing patients with and

without ICD-9 diagnosis codes. It is possible, as described by these surveys, that severe sepsis patients are a challenging and heterogeneous population to identify in the emergency department.

We also hypothesized that patients without an ICD-9 diagnosis would experience worse outcomes. We found this to be only partially true and specific to patients meeting septic shock criteria. Patients without an ICD-9 diagnosis code of 785.52 had worse outcomes as measured by higher ICU admission rates and hospital and ICU length of stays. Patients without a diagnosis code had statistically equivalent mortality rates compared to those with an ICD-9 diagnosis code. We believe this is a reflection of inadequate treatment rates within the critical hours of presentation. As described by Kumar, the strongest predictor of mortality in patients with septic shock was time to antibiotic [19]. In our cohort, those without an ICD-9 diagnosis code, time to first antibiotic was 1.35 hours later than those with a diagnosis code (Appendix Table 6).

Unlike shock patients, patients with a severe sepsis diagnosis code of 995.92 had worse clinical outcomes compared to patients without a code. We found that all ICD-9 coded patients had a higher number of infections, were more frequently diagnosed with septicemia, and had a higher number of total organ dysfunction sites [25, 36]. It is possible that severe sepsis patients who are not formally diagnosed are a less acutely ill population and, despite being less aggressively treated, experienced better outcomes [36]. Unlike previous studies, beyond baseline differences just described, we demonstrated patients with and without ICD-9 diagnosis codes had similar illness presentations in the emergency room based on first mean arterial pressure and lactate values, as well as SOFA scores using the first recorded laboratory and physiologic measurements. Again, it is possible that better markers of acuity that would prompt treatment or describe predictors of poor outcomes were not included in this study. Despite lower mortality, patients without an ICD-9 code of 995.92 had higher 30-day readmission rates. A known risk

factor for 30-day readmission rates in severe sepsis patients is inadequate treatment during the primary hospitalization [37].

Our study raises more questions than it answers, but the findings from this study provide direction for moving forward. Acknowledging low treatment rates, based on three hour bundle protocol completion, and low identification of severe sepsis patients, the next step is identifying factors that prevent early treatment initiation and recognition of these patients in the emergency department. Educational interventions have been shown to increase recognition, physician adherence to treatment protocols, and ultimately patient outcomes [21].

Finally, financial implications of under coding and long term outcomes beyond 30 days are of interest. The average cost of a sepsis hospitalization is double the cost of a stay for another diagnosis and when not coded correctly, and reimbursement can be significantly lower [38]. Resource utilization by patients, specifically of those with septic shock and without an ICD-9 diagnosis code, was significantly higher based on higher ICU admission rates and longer lengths of ICU and hospital stays and severe sepsis patients without an ICD-9 code had higher 30-day readmission rates. It is possible that our hospital is being under reimbursed due to inadequate physician coding practices. Prior, during a hospital specific chart review, only 2 out of 100 charts had a diagnosis of severe sepsis or septic shock defined by the presence of a written diagnosis of severe sepsis or septic shock, but never received a formal ICD-9 diagnosis code [29]. This, in addition to evidence of under treatment found in this study, supports a hypothesis that physicians are underdiagnosing and undertreating severe sepsis and septic shock cases and it results in worse outcomes.

**Limitations**

Our study has several limitations. Generalizability to other institutions and hospital settings may be restricted as our study was confined to patients admitted through a single center emergency department. As data were extracted from the EMR, quality is limited to the quality of data entry during the initial hospitalization. Our retrospective design also limits our ability to determine a true directional relationship between physician recognition, sepsis specific bundle treatment completion, and ICD-9 diagnosis code assignment. It is also possible that not all patients presented to the ED with criteria for severe sepsis and/or septic shock at the initial triage time, and only developed the condition later during the hospitalization; affecting the accuracy of subsequent analysis. We do believe that requiring patients to have had an antibiotic within 8 hours and ≥ 2 sites of organ dysfunction, using both ICD-9 diagnosis codes and laboratory values, helps increase the likelihood of acute infection and organ dysfunction on presentation. Lastly, due to the large size of our cohort, interpretations of statistically significant findings require clinical judgment when making interpretations about the differences between groups.

**Considerations for Future Research**

This study highlights a concerning finding that severe sepsis and septic shock patients are being underdiagnosed and undertreated within our own facility. It is of interest to measure ICD-9 diagnosis code rates, as well as bundle completion rates after a planned educational intervention to boost provider recognition and treatment based on international guidelines. It would be of use to survey physicians about the assignment of sepsis-related ICD-9 diagnosis codes to further understand why patients are being assigned a code (or not being assigned) and barriers to code use. Lastly, financial implications of under diagnosis are of importance for hospital reimbursement.

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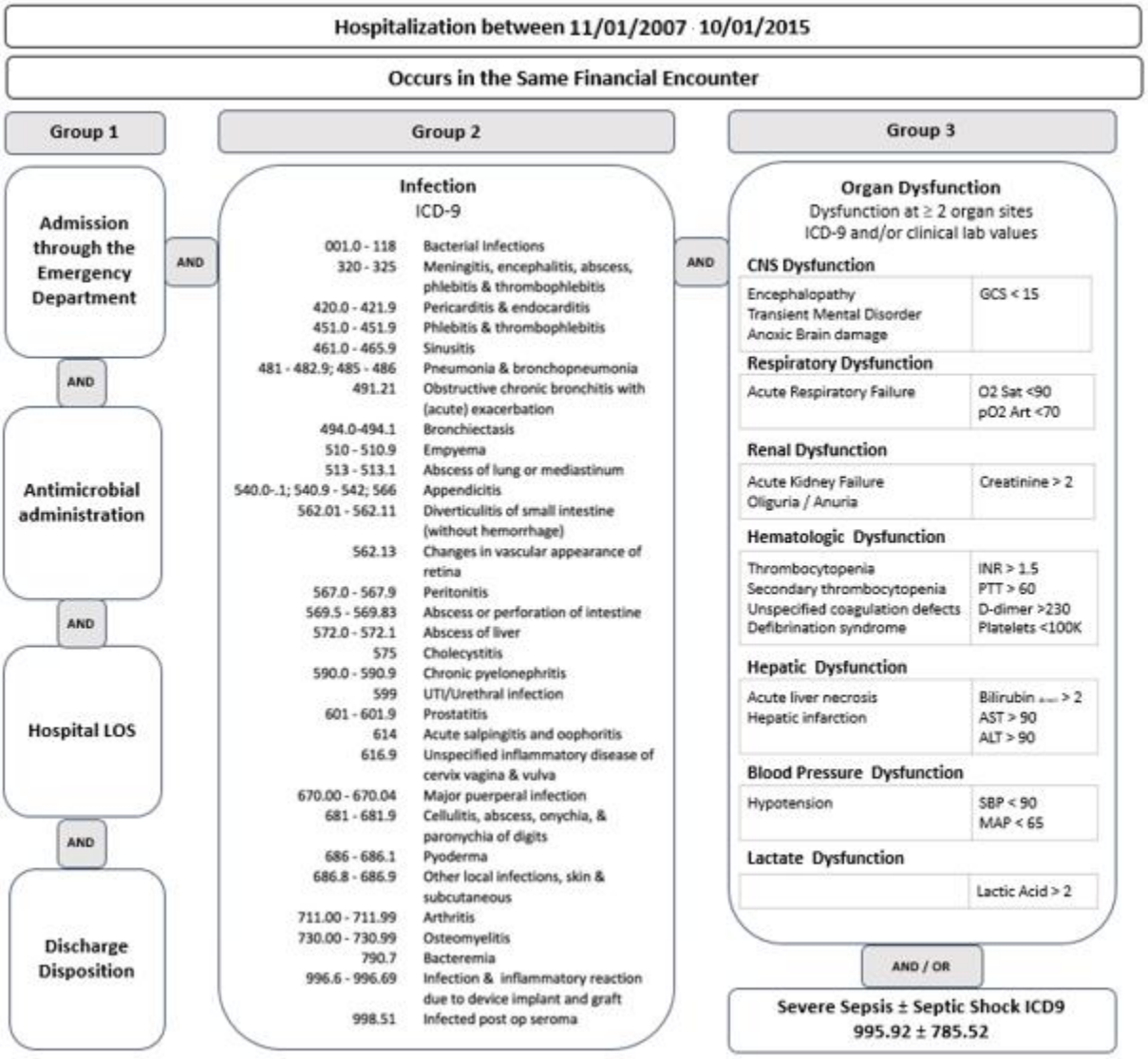
# Appendices

## Appendix A: Heron Search Method and Inclusion Criteria



**Appendix B: ICD-9 Infection List**

| ICD9 Codes | ICD-9 Code Description |
|---|---|
| 001.0 – 139.99 | Infectious & Parasitic Infections |
| 320.0 – 326.99 | Meningitis, encephalitis, abscess, phlebitis and thrombophlebitis |
| 420.0 - 421.9 | Acute pericarditis and endocarditis |
| 451.0 - 451.9 | Phlebitis and thrombophlebitis |
| 461.0 - 465.9 | Sinusitis, pharyngitis, tonsillitis, URI's, laryngitis, bronchitis, and bronchiolitis |
| 481 - 482.9 485 - 486 | Pneumonia and bronchopneumonia |
| 491.21 | Obstructive chronic bronchitis with (acute) exacerbation |
| 494.0 - 494.1 | Bronchiectasis |
| 510 - 510.9 | Empyema |
| 513 - 513.1 | Abscess of lung or mediastinum |
| 540.0, 540.1, 540.9 - 542, 566 | Appendicitis |
| 562.01-562.11 | Diverticulitis of small intestine (without hemorrhage) |
| 562.13 | Changes in vascular appearance of retina |
| 567.0 - 567.9 | Peritonitis |
| 569.5 - 569.83 | Abscess or perforation of intestine |
| 572.0 - 572.1 | Abscess of liver |
| 575 | Cholecystitis |
| 590.0 - 590.9 | Chronic pyelonephritis |
| 599 | UTI/Urethral infection |
| 601 - 601.9 | Prostatitis |
| 614 | Acute salpingitis and oophoritis |
| 616.9 | Unspecified inflammatory disease of cervix vagina and vulva |
| 670.00- 670.04 | Major puerperal infection |
| 681 - 681.9 | Cellulitis, abscess, onychia, and paronychia of digits |
| 686 - 686.1 | Pyoderma |
| 686.8 - 686.9 | Other local infections, skin & subcutaneous |
| 711.00- 711.99 | Arthritis |
| 730.00 -730.99 | Osteomyelitis |
| 790.7 | Bacteremia |
| 996.6 - 996.69 | Infection and inflammatory reaction due to device implant and graft |
| 998.51 | Infected post operative seroma |
| 998.59 | Acute reaction to foreign substance accidentally left during a procedure |
| 999.3 | Infection due to central venous catheter |

**Appendix C: Criteria for Acute Organ Dysfunctions**

| Organ System | Physiological/Lab Markers | Threshold Value | ICD-9 Description & Code |
|---|---|---|---|
| Neurological | Glasgow Coma Scale | < 15 | Encephalopathy Unspecified 384.30<br>Metabolic Encephalopathy, 348.31<br>Other Encephalopathy 348.30<br>Transient Mental Disorder 293.9<br>Anoxic Brain Damage, 348.1 |
| Hematological | Partial Thromboplastin Time<br>Platelet Count<br>INR<br>D-dimer | > 60 sec<br>< 100,000 /μL<br>> 1.5<br>> 230 | Defibrination Syndrome, 286.6<br>Thrombocytopenia, 287.5<br>Secondary Thrombocytopenia, 287.4<br>Other and unspecified coagulation defects, 286.9 |
| Respiratory | Arterial 02 saturation<br>PaO2 | < 90%<br>< 70% | Acute respiratory failure 518.81 |
| Cardiovascular | Systolic Blood pressure<br>MAP<br>Received a vasopressor** | < 90 mmHg<br>< 65 mmHg | Hypotension 458.0<br>Shock w/o trauma 785.5<br>Septic Shock 785.52<br>Other shock, no trauma 785.59 |
| Hepatic | Bilirubin, total<br>ALT<br>AST | > 2 mg/dL<br>> 90 U/L<br>> 90 U/L | Acute and subacute necrosis of the liver, 570<br>Hepatic infarction 573.4 |
| Renal | Creatinine | >2 mg/dL | Oliguria and anuria, 788.5<br>Acute Kidney Failure, 584 |
| Lactic acidosis | Lactate | >2mmol/L | |

*Required 2 or more different organ systems be compromised, from any combination of the 7 systems listed, plus one ICD-9 infection code to meet criteria for severe sepsis. All lab values were sorted by first measurement date and only included as an acute organ dysfunction if it met threshold. **Vasopressor types for cardiovascular dysfunction included dobutamine, dopamine, norepinephrine, epinephrine, vasopressin, or phenylephrine.

**Appendix D: Cohort Characteristics for Patients with Severe Sepsis and No Septic Shock**

| | All Severe Sepsis Patients | Patients with 995.92 | Patients without 995.92 | P values |
|---|---|---|---|---|
| | N=5631 | N=1847 (32.8%) | 3784 (67.2%) | |
| Age, (mean ± SD) | 60.6 ± 17.2 | 61.2 ± 16.7 | 59.5 ± 18.0 | P<0.001 |
| Gender, male n (%) | 2872 (51.0%) | 933 (50.5%) | 1939 (51.2%) | P=0.61 |
| Race White, n (%) | 3710 (65.9%) | 1198 (64.9%) | 2512 (66.4%) | |
| Black, n (%) | 1339 (23.8%) | 436 (23.6%) | 903 (23.9%) | |
| Other n, (%) | 576 (10.2%) | 210 (11.4%) | 366 (9.67%) | |
| Sites of Infection (mean ± SD) | 1.95 ± 0.88 | 2.31 ± 0.82 | 1.78 ± 0.84 | P<0.001 |
| Bacteremia/Septicemia | 4229 (75.1%) | 1806 (97.8%) | 2423 (64.0%) | P=0.001 |
| Respiratory | 2516 (44.7%) | 957 (51.8%) | 1559 (41.2%) | P=0.001 |
| Urinary | 2176 (38.6%) | 741 (40.1%) | 1435 (37.9%) | P=0.11 |
| Soft Tissue Site | 986 (17.5%) | 336 (18.2%) | 650 (17.2%) | P=0.35 |
| Abdomen | 523 (9.29%) | 194 (10.5%) | 329 (8.69%) | P=0.03 |
| First Serum Lactate (missing=2562, 37%) (mean ± SD) | 2.21 ± 1.61 | 2.33 ± 1.73 | 2.13 ± 1.53 | P<0.001 |
| Average SOFA score (missing=105, 1.8%) | 3.02 ± 2.08 | 2.89 ± 2.17 | 3.07 ± 2.03 | P<0.001 |
| First MAP (mean ± SD) (missing=73, 1.0%) | 92.3 ± 20.3 | 91.8 ± 20.6 | 92.5 ± 20.2 | P=0.23 |
| Organ Dysfunction Sites (mean out of 7 ± SD) (missing=89, 1.3%) | 2.58 ± 0.99 | 2.62 ± 1.29 | 2.56 ± 0.82 | P=0.06 |
| Renal | 3145 (56.8%) | 1024 (58.3%) | 2121 (56.1%) | P=0.12 |
| Hematological | 2922 (52.7%) | 821 (46.7%) | 2101 (55.5%) | P<0.001 |
| Respiratory | 2170 (39.2%) | 849 (48.3%) | 1321 (34.9%) | P<0.001 |
| Cardiovascular | 1444 (26.1%) | 437 (24.9%) | 1007 (26.6%) | P=0.17 |
| CNS | 1665 (30.0%) | 529 (30.0%) | 1136 (30.0%) | P=0.97 |
| Charleston Comorbidity Score (out of 21 ± SD) | 6.03 ± 3.59 | 5.64 ± 5.48 | 6.22 ± 6.11 | P=0.32 |

**Appendix E: Cohort Characteristics for Patients Septic Shock**

| | All Septic Shock Patients | Patients with 785.52 | Patients without 785.52 | P values |
|---|---|---|---|---|
| | N=1254 | 929 (74.0%) | 325 (26.0%) | |
| Age, (mean ± SD) | 59.6 ± 15.9 | 59.6 ± 16.1 | 59.7 ± 15.2 | P=0.20 |
| Gender, male n (%) | 662 (52.8%) | 497 (53.5%) | 165 (50.8%) | P=0.42 |
| Race White, n (%) | 826 (65.9%) | 625 (67.3%) | 201 (61.8%) | |
| Black, n (%) | 275 (21.9%) | 194 (20.9%) | 81 (24.9%) | |
| Other n, (%) | 149 (11.9%) | 107 (11.5%) | 42 (12.9%) | |
| Sites of Infection (mean ± SD) | 2.37 ± 0.95 | 2.45 ± 0.92 | 2.14 ± 0.99 | P=0.10 |
| Bacteremia/Septicemia | 1170 (93.3%) | 908 (97.7%) | 262 (22.4%) | P<0.001 |
| Respiratory | 614 (49%) | 466(50.2%) | 148 (45.5%) | P=0.16 |
| Urinary | 527 (42.0%) | 392 (42.2%) | 135 (41.5%) | P=0.85 |
| Soft Tissue Site | 250 (20.0%) | 194 (20.9%) | 56 (17.2%) | P=0.17 |
| Abdomen | 208 (16.6%) | 161 (17.3%) | 47 (14.5%) | P=0.26 |
| First Serum Lactate (missing=2562, 37%) (mean ± SD) | 2.97 ± 2.79 | 3.04 ± 2.86 | 2.75 ± 2.55 | P=0.035 |
| Average SOFA score (missing=105, 1.8%) | 5.4 ± 3.32 | 5.65 ± 3.39 | 4.68 ± 3.01 | P=0.01 |
| First MAP (mean ± SD) (missing=73, 1.0%) | 81.4 ± 22.1 | 79.7 ± 21.3 | 86.4 ± 23.5 | P=0.03 |
| Presence of Shock | 1254 (100%) | 1254 (100%) | 1254 (100%) | |
| Organ Dysfunction Sites (mean out of 7 ± SD) (missing=89, 1.3%) | 4.13 ± 1.38 | 4.20 ± 1.43 | 3.95 ± 1.20 | P<0.001 |
| Respiratory | 867 (69.1%) | 628 (67.6%) | 239 (73.5%) | P=0.05 |
| Hematological | 832 (66.3%) | 626 (67.4%) | 206 (63.3%) | P=0.20 |
| Cardiovascular | 1254 (100%) | 929 (100%) | 325 (100%) | P=1.00 |
| CNS | 511 (40.8%) | 385 (41.4%) | 126 (38.7%) | P=0.43 |
| Renal | 882 (70.3%) | 680 (73.1%) | 202 (62.1%) | |
| Charleston Comorbidity Score (out of 21 ± SD) | 6.26 ± 3.54 | 6.3 ± 3.59 | 6.15 ± 3.40 | P=0.24 |

**Appendix F: Multivariate logistic regression model of adjusted odds ratios for being assigned as sepsis specific ICD-9 diagnosis code of 995.52 or 785.52.**
Overall model choice was based on using Hosmer and Lemeshow Goodness-of-Fit Test, Chi-squared value, 2.7, p=0.53.

| Predictors of a sepsis specific ICD-9 diagnosis code in the final model | Adjusted Odds Ratios | 95% Confidence Interval |
|---|---|---|
| Bacteremia/Septicemia ICD-9 diagnosis code | 25.1 | 17.2 – 36.7 |
| ICU Admission | 3.3 | 2.8 – 3.9 |
| Hypotension | 1.4 | 1.2 – 1.7 |
| Respiratory Infection | 1.4 | 1.2 – 1.6 |
| Respiratory Organ System Dysfunction | 1.4 | 1.2 – 1.7 |
| Total Infection Sum | 1.3 | 1.2 – 1.5 |
| First Lactate Values | 1.1 | 1.1 – 1.2 |

**Appendix G: Multivariate logistic regression model of adjusted odds ratios for receiving therapeutic components of the bundle protocol.**
Overall model choice was based on using Hosmer and Lemeshow Goodness-of-Fit Test, Chi-squared value, 8.24, p=0.410.

| Predictors of receiving therapeutic components of treatment in final model | Adjusted Odds Ratios | 95% Confidence Interval |
|---|---|---|
| Age | 1.01 | 1.00-1.01 |
| Sepsis specific ICD-9 diagnosis code (995.52 or 785.52) | 1.22 | 1.10 – 1.36 |
| Respiratory Infections | 1.60 | 1.42 – 1.78 |
| Respiratory Dysfunction | 1.25 | 1.12 – 1.40 |

**Appendix H. Bundle Protocol Completion Rates for All Patients with Severe Sepsis and No Septic Shock**

| Bundle Protocol Component | Overall Cohort | Patients with sepsis specific ICD-9 code 995.92 | Patients without sepsis specific ICD-9 code 995.92 | P value |
|---|---|---|---|---|
| | 5631 | 1847 (32.8%) | 3784 (67.2%) | |
| All 4 Components | 491 (8.7%) | 189 (10.2%) | 302 (8.0%) | p<0.005 |
| Blood Culture | 3483 (61.9%) | 1411 (76.3%) | 2072 (54.8%) | p<0.001 |
| Lactate measured within 3 hours | 1589 (28.2%) | 541 (29.3%) | 1048 (27.7%) | p=0.23 |
| Broad Spectrum given under three hours | 2087 (37.1%) | 801 (43.4%) | 1286 (34.0%) | p<0.001 |
| Given Under Three | 2593 (46.1%) | 1010 (54.7%) | 1583 (41.8%) | p<0.001 |
| First Dose Broad spectrum | 4271 (75.8%) | 1402 (75.9%) | 2869 (75.8%) | p=0.97 |
| Time to Antibiotic (mean hours ± SD) | 3.7 ± 1.9 | 3.3 ± 1.9 | 3.9 ± 1.9 | p<0.001 |
| Appropriate Fluids | 4825 (85.7%) | 1549 (83.9%) | 3276 (86.6%) | p<0.001 |
| IV Fluids Needed (n=22 missing) | 928 (16.5%) | 371 (20.1%) | 557 (14.8%) | p<0.001 |
| IV Fluids given at 30mL/Kg among only those with a need | 133(14.3%) | 74 (19.6%) | 59 (10.6%) | p<0.001 |
| Therapeutic Components | 1764 (31.3%) | 665 (36.0%) | 1099 (29.0%) | p<0.001 |

**Appendix I. Bundle Protocol Completion Rates for All Patients with Septic Shock**

| Bundle Protocol Component | Overall Cohort | Patients with sepsis specific ICD-9 code 785.52 | Patients without sepsis specific ICD-9 code 785.52 | P value |
|---|---|---|---|---|
| | 1254 | 1080 (86.1%) | 174 (13.9%) | |
| All 4 Components | 103 (8.2%) | 92 (8.5%) | 11 (6.3%) | P=0.37 |
| Blood Culture | 906 (72.3%) | 827 (76.6%) | 79 (45.4%) | P<0.001 |
| Lactate measured within 3 hours | 365 (29.1%) | 327 (30.3%) | 38 (21.8%) | P=0.02 |
| Broad Spectrum given under three hours | 5562 (44.8%) | 512 (47.4%) | 50 (28.7%) | P<0.001 |
| Given Under Three | 713 (56.9%) | 650 (60.2%) | 63 (36.2%) | P<0.001 |
| First Dose Broad spectrum | 938 (74.8%) | 817 (75.7%) | 121 (69.5%) | P=0.09 |
| Time to First Antibiotic (mean hours ± SD) | 3.2 ± 1.9 | 3.0 ± 1.9 | 4.4 ± 2.2 | P<0.001 |
| Appropriate Fluids | 867 (69.1%) | 747 (69.2%) | 120 (69.0%) | P=1.0 |
| IV fluids needed | 530 (42.6%) | 474 (43.9%) | 56 (33.9%) | P=0.02 |
| Fluids given at 30mL/Kg among only those with a need | 153 (28.9%) | 142 (30.0%) | 11 (19.6%) | P=0.12 |
| Therapeutic Components | 383 (30.5%) | 352 (32.6%) | 31 (17.8%) | P<0.001 |