Association of Fluid Resuscitation Initiation Within 30 Minutes of Severe Sepsis and Septic Shock Recognition With Reduced Mortality and Length of Stay

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Study objective: We evaluate the association of intravenous fluid resuscitation initiation within 30 minutes of severe sepsis or septic shock identification in the emergency department (ED) with inhospital mortality and hospital length of stay. We also compare intravenous fluid resuscitation initiated at various times from severe sepsis or septic shock identification's association with the same outcomes.

Methods: This was a review of a prospective, observational cohort of all ED severe sepsis or septic shock patients during 13 months, captured in a performance improvement database at a single, urban, tertiary care facility (90,000 ED visits/year). The primary exposure was initiation of a crystalloid bolus at 30 mL/kg within 30 minutes of severe sepsis or septic shock identification. Secondary analysis compared intravenous fluid initiated within 30, 31 to 60, or 61 to 180 minutes, or when intravenous fluid resuscitation was initiated at greater than 180 minutes or not provided.

Results: Of 1,866 subjects, 53.6% were men, 72.5% were white, mean age was 72 years (SD 16.6 years), and mean initial lactate level was 2.8 mmol/L. Eighty-six percent of subjects were administered intravenous antibiotics within 180 minutes; 1,193 (64%) had intravenous fluid initiated within 30 minutes. Mortality was lower in the within 30 minutes group (159 [13.3%] versus 123 [18.3%]; 95% confidence interval [CI] 1.4% to 8.5%), as was median hospital length of stay (6 days [95% CI 6 to 7] versus 7 days [95% CI 7 to 8]). In multivariate regression that included adjustment for age, lactate, hypotension, acute organ dysfunction, and Emergency Severity Index score, intravenous fluid within 30 minutes was associated with lower mortality (odds ratio 0.63; 95% CI 0.46 to 0.86) and 12% shorter length of stay (hazard ratio=1.14; 95% CI 1.02 to 1.27). In secondary analysis, mortality increased with later intravenous fluid resuscitation initiation: 13.3% (≤30 minutes) versus 16.0% (31 to 60 minutes) versus 16.9% (61 to 180 minutes) versus 19.7% (>180 minutes). Median hospital length of stay also increased with later intravenous fluid initiation: 6 days (95% CI 6 to 7 days) versus 7 days (95% CI 6 to 7 days) versus 7 days (95% CI 6 to 8 days) versus 8 days (95% CI 7 to 9 days).

Conclusion: The time of intravenous fluid resuscitation initiation was associated with improved mortality and could be used as an easier obtained alternative to intravenous fluid completion time as a performance indicator in severe sepsis and septic shock management. [Ann Emerg Med. 2016;■:1-14.]

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INTRODUCTION

Background

Sepsis, severe sepsis, and septic shock are principal drivers of morbidity and mortality worldwide.[1-4] The seminal trial by Rivers et al[5] in 2001 espoused the efficacy of early goal-directed therapy protocols, but 3 recent, multisite, randomized trials failed to demonstrate mortality benefit from such therapy compared with usual care.[6-8] However, in all 3 trials, all patients in both study and control arms received early intravenous fluid resuscitation and intravenous antibiotic administration.

Early intervention is critical in managing severe sepsis and septic shock. Current guidelines from the National Quality Forum and Surviving Sepsis Campaign recommend administration of crystalloid at 30 mL/kg and intravenous broad-spectrum antibiotics within 3 hours of a patient's first meeting severe sepsis or septic shock criteria.[9,10] After the 2006 article by Kumar et al[11] demonstrating substantially increased mortality with each hour of antibiotic delay in septic shock patients, the literature expansively explored the association between the

Editor's Capsule Summary

What is already known on this topic

There remains uncertainty in regard to how the timing of delivery of each component of standard sepsis care affects outcomes.

What question this study addressed

This observational study of 1,866 subjects examined the association between initiation of fluid resuscitation within 30 minutes of severe sepsis identification and hospital mortality and length of stay.

What this study adds to our knowledge

Initiation of fluids within 30 minutes of severe sepsis recognition was associated with lower inhospital mortality and length of stay.

How this is relevant to clinical practice

This article supports the importance of rapid identification and fluid administration for patients with severe sepsis. Studies are needed to measure the causal relationship of this association and the interaction with the timing of other therapeutic interventions.

timeliness of intravenous antimicrobial source-control administration and patient outcomes.[12-17] The importance of providing intravenous fluid resuscitation completed within 3 hours has also been established.[6,18-20] However, the tightly controlled environment of clinical trials starkly contrasts with the emergency department (ED) setting. Although consistent accounting of intravenous fluid completion times is available for patients enrolled in such studies, reliable documentation of these times in practice is another matter. Review of sepsis performance improvement data in the North Shore–LIJ health system, as well as anecdotal discussion with leadership at several New York hospitals, identified documentation of intravenous fluid bolus completion times as frequently inadequate or absent for ED patients at many sites, impeding assessment of provider adherence to current guidelines.

In 2009, based in part on Surviving Sepsis Campaign guidelines[10] and in conjunction with the Institute for Healthcare Improvement, North Shore–LIJ developed an algorithm and basic 3-hour bundle for the early identification and treatment of patients on the sepsis continuum. This 3-hour bundle obligates initiation of a crystalloid intravenous fluid bolus at 30 mL/kg within 30 minutes of severe sepsis or septic shock identification, rather than completion of a bolus within 3 hours. The rationale behind this approach was that any patient receiving intravenous fluid of appropriate volume administered as a bolus initiated within 30 minutes would have fluid resuscitation that not only adhered to 3-hour recommendations but also was likely completed considerably earlier.

Importance

Unlike intravenous fluid completion times, performance improvement data suggested that initiation times were far more consistently and reliably captured. This currently unvalidated measure could therefore prove more generalizable and easier to operationalize in an ED environment as a practice guiding and performance assessment measure, and facilitate yet earlier intervention in the highly time-dependent management of severe sepsis or septic shock patients. We are unaware of any study investigating the association of intravenous fluid initiation time on patient outcomes.

Goals of This Investigation

As the primary objective, we attempt to determine the association of initiating intravenous fluid resuscitation within 30 minutes of severe sepsis or septic shock identification in the ED with inhospital mortality, controlling for demographic, acuity, and treatment factors. Secondary analysis sought to calibrate the 30-minute specification by assessing the relationship between whether intravenous fluid resuscitation initiated within 30 minutes, 31 to 60 minutes, 61 to 180 minutes, or greater than 180 minutes and in-hospital mortality in an adjusted model. In both analyses, we also attempt to determine the association of earlier intravenous fluid initiation with hospital length of stay.

Given the high incidence and mortality rate, even modest improvements in sepsis care translate to substantial absolute effect; eg, even with a conservative 25% mortality rate estimate, a mortality odds ratio (OR) of 0.75 would imply 5% absolute risk reduction and a number needed to treat of 20.[1,2] Considering this, as well as the difficulty in obtaining completion time data and the paucity of literature directly assessing fluid resuscitation and mortality in sepsis, we believe a mortality odds decrease on the order of 0.75 would support 30-minute intravenous fluid initiation as a feasible performance measure that is easier to operationalize in an ED practice environment than 3-hour intravenous fluid completion.

MATERIALS AND METHODS

Study Design

This was an observational cohort study examining data from a prospective performance improvement database, conducted at a single urban tertiary care center with 90,000

ED visits and 360,000 inpatient days per year. The hospital adopted an algorithm and 3-hour bundle in 2010 to screen and treat sepsis patients. To measure bundle compliance and outcomes, data for all consecutive severe sepsis or septic shock patients were captured in real time and entered into an internally managed performance improvement database. Additionally, we abstracted relevant data from the performance improvement database into a distinct, institutional review board–approved, prospective research registry for analysis.

All patients with a severe sepsis or septic shock diagnosis met eligibility for algorithm care (Figure 1). We defined severe sepsis or septic shock as a confirmed or suspected source of infection in addition to greater than or equal to 2 Systemic Inflamatory Response Syndrome (SIRS) criteria[21] and lactate level greater than or equal to 2.2 mmol/L, or evidence of end-organ dysfunction not otherwise explained by the patient's medical history. End-organ dysfunction criteria are outlined in Figure 1. Although current Surviving Sepsis Campaign and National Quality Forum 0500 bundle recommendations use a 4.0 mmol/L lactate-level cutoff,[9,10] 2.2 mmol/L was selected as the inclusion threshold to cast a wider therapeutic net and reflects the algorithm's early recognition focus. This is consistent with measures subsequently adopted by the Centers for Medicare & Medicaid Services, which use lactate level greater than or equal to 2.0.[22] We defined severe sepsis or septic shock identification as the laboratory result or vital sign measurement time that first caused the patient to meet all inclusion criteria. To expedite algorithm inclusion, locally developed consensus criteria nicknamed "Super-SIRS" were used at triage. Patients meeting Super-SIRS criteria had suspected infection and greater than or equal to 2 of the following: pulse rate greater than or equal to 120 beats/min, respiratory rate greater than or equal to 24 breaths/min, rectal or oral temperature less than or equal to 36.0°C (96.8°F) or greater than or equal to 38.3°C (101.0°F), and systolic blood pressure less than 90 mm Hg. All eligible patients were to receive bundle-adherent care, which required an intravenous crystalloid bolus at 30 mL/kg, initiated within 30 minutes of severe sepsis or septic shock identification; lactate result available within 90 minutes of order; blood for cultures drawn before antibiotic administration; and source-directed, broad-spectrum, intravenous antibiotics administered within 180 minutes of sepsis identification (ie, two SIRS criteria and a lactate-level test ordered) or 60 minutes of severe sepsis or septic shock identification (ie, two SIRS criteria and available laboratory results, or vital signs indicating hypoperfusion or organ dysfunction), whichever occurred earlier.

A dedicated team of data abstractors concurrently entered data for all patients eligible for the 3-hour bundle into the performance improvement database, using a standardized data collection form, which they submitted to a centralized data collection unit. The form focused on the uniform abstraction of objective variables. All abstractors received standardized training at the beginning of their involvement. Database managers monitored the quality of data abstraction weekly, and monthly abstractor meetings ensured uniformity in data collection. Abstractors identified eligible patients by screening all patients who had blood gas or lactate laboratory tests ordered in the ED. Abstractors excluded patients younger than 18 years, with advance directives precluding bundle interventions, who declined interventions, who were admitted from the ED directly to palliative care or hospice, or who were enrolled in an institutional review board–approved clinical trial that precluded standard application of the bundle.

Demographic and clinical data obtained included patient age, sex, race, primary payer, initial lactate level, signs of hypoperfusion or organ dysfunction (Figure 1), and Emergency Severity Index scores at triage. Abstractors documented whether care adhered to the 3-hour bundle's four specified procedures and recorded initiation of intravenous fluid resuscitation as the time that a 0.9% normal saline solution bolus of at least 30 mL/kg was administered. In the case of patients receiving multiple boluses, initiation time was the time the first bolus began. Fluid completion times were not reliably documented and subsequently not recorded, reflecting the underlying need for this investigation. Abstractors did not record the volume administered for much of the data collection period because, like intravenous fluid completion times, these data were frequently missing or unreliable. As such, abstractors recorded initiation times as the time the first bolus began only for intravenous fluid administration documented as meeting bundle guidelines, ie, administered or ordered as a bolus and in volumes greater than or equal to 30 mL/kg. Initiation times for fluids administered as an infusion or in inadequate total volumes were not recorded. A bolus was defined as a volume of at least 500 mL, ordered to be administered at a rate of at least 500 mL per 15 minutes.

After discharge, patients' unique encounter identifier numbers allowed autopopulation of diagnosis-related group with corresponding product line (eg, infectious disease, cardiology) and case mix index. Case mix index, also called *service intensity weight* when referring to patient- rather than aggregated hospital-level data, is an index measure of the typical resource use for a given diagnosis-related group, adjusting for the presence of comorbidities and clinical complications.

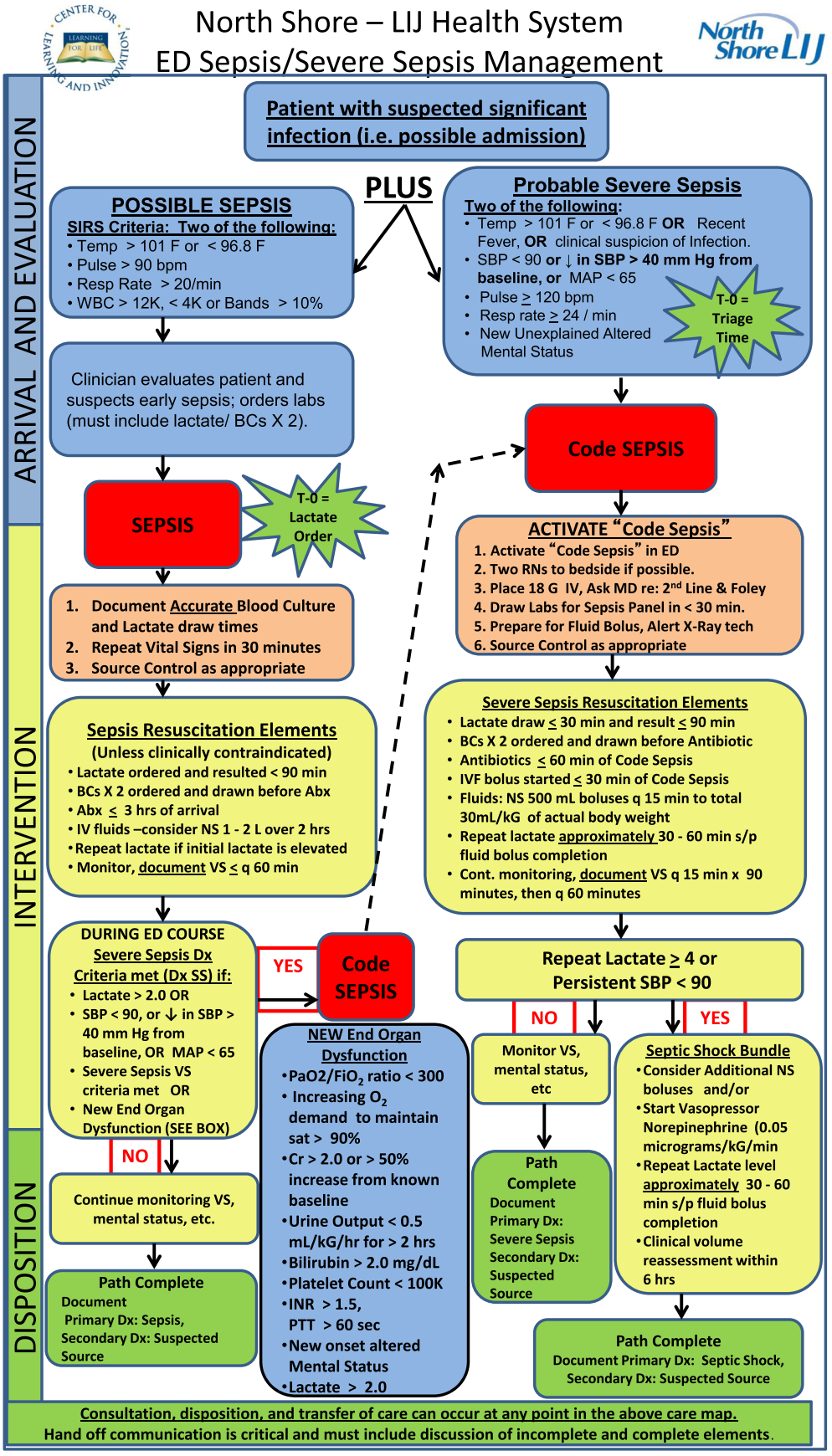


Figure 1. Sepsis algorithm and 3-hour bundle.

SELECTION OF PARTICIPANTS AND DATA COLLECTION AND PROCESSING

We obtained institutional review board approval to abstract relevant data, entered in real time into the quality database, into a distinct research database. Study subjects were all severe sepsis or septic shock patients entered into the quality database during a 13-month period, from September 2013 through September 2014. We excluded database patients who met eligibility only for the "sepsis alert" arm of the algorithm, and not the "code sepsis" arm (Figure 1). The primary exposure of interest was whether a crystalloid bolus at 30 mL/kg was initiated within 30 minutes of severe sepsis or septic shock identification. We grouped patients according to whether this occurred. A secondary analysis parsed subjects receiving fluid initiation at greater than 30 minutes into subgroups according to whether they received intravenous fluid resuscitation 31 to 60 minutes, 61 to 180 minutes, and greater than 180 minutes from severe sepsis or septic shock identification or not at all, respectively. We considered patients receiving adequate intravenous fluid before severe sepsis or septic shock identification in the within 30 minutes group. In accordance with the data abstraction procedure, we considered patients receiving inadequate intravenous fluid volume in the greater than 180 minutes group.

We also abstracted demographic, clinical, and administrative data. Because a composite initial acuity score (eg, Sequential Organ Failure Assessment (SOFA) score) requires variables that are not routinely obtained for this undifferentiated, real-world population (eg, PaO_2, urine output), we could not calculate this type of measure. However, we collected and used measures of initial acute organ dysfunction (Figure 1) to this effect. We also used Emergency Severity Index scores at triage and case mix index in this capacity. Originally designed as a financial measure, case mix index has been increasingly used as a measure of severity of patient illness.[23-28] Timeliness of antibiotic administration has often been shown to be associated with mortality risk in severe sepsis or septic shock patients and was assessed in this study as well.

Outcome Measures

The primary outcome was inhospital mortality. Additional outcomes included ICU admission during stay, hospital length of stay, and ICU length of stay for patients admitted to the ICU.

Because data collection ran in parallel to the health system–wide quality improvement initiative, abstractors were blinded to the study hypothesis. The quality initiative had been operating since early 2010, and we believed the study posed reduced risk for confounding by the initial effects of a Hawthorne effect and denominator expansion.

Primary Data Analysis

We performed all analyses with SAS (version 9.3; SAS Institute, Inc., Cary, NC). We report continuous variables as means and SDs, and categorical variables as proportions; 95% confidence intervals (CIs) are constructed about group differences. There were no missing data entries for any fields included in this study.

We tested 30-minute intravenous fluid resuscitation initiation as a predictor of mortality, using multivariate logistic regression, adjusting for age, sex, administration of antibiotics within 180 minutes, lactate level available within 90 minutes of order, blood cultures before antibiotics, indicators of organ dysfunction at severe sepsis or septic shock identification, Emergency Severity Index score, case mix index and Medicare severity–diagnosis-related group product line. The models did not adjust for vasopressors, inotropes, central line placement, or hemodynamic monitoring measures (eg, central venous pressure). We did not assess variable interactions within the model. Hosmer-Lemeshow's test assessed goodness of fit. The null hypothesis that the model adequately fit the data was accepted for $P>.05$. We used the same model design to test 30-minute intravenous fluid's association with ICU admission.

To assess 30-minute intravenous fluid's association with hospital length of stay, we used a proportional hazard (Cox) model that censored for mortality and adjusted for the same covariates as the logistic mortality model, as well as payer class. Because a subject being discharged alive was the "event" in the model, a hazard ratio (HR) greater than 1.0 indicated faster rate of live discharge (shorter hospital length of stay), and the inverse HR was the hospital length of stay ratio between groups.

In the secondary analysis, we examined time to intravenous fluid initiation as an ordinal variable, grouping patients according to whether intravenous fluid resuscitation began within 30 minutes, 31 to 60 minutes, or 61 to 180 minutes, or at greater than or equal to 180 minutes or not at all. We selected these group distinctions to ensure sufficient sample size in each. Logistic regression models adjusting for the same covariates as the primary analysis compared these groups as predictors of inhospital mortality and ICU admission. A Cox model compared hospital length of stay between all groups. After completing data collection, we decided not to assess ICU length of stay in multivariate regression in the secondary analysis for sample size considerations.

RESULTS

Characteristics of Study Subjects

We abstracted data for 1,866 severe sepsis or septic shock patients into the registry from the performance

improvement database and did not exclude any cases. In the primary analysis, 1,193 subjects (64%) had intravenous fluid resuscitation initiated within 30 minutes of severe sepsis or septic shock identification. Patient characteristics are summarized in Table 1. The within 30 minutes group had a greater frequency of lactate greater than or equal to 4.0 mmol/L, hypotension, and thrombocytopenia, but lower incidence of acute kidney injury or altered mental status at severe sepsis or septic shock identification. Subjects in the within 30 minutes group were more likely to have blood for cultures drawn before antibiotics and antibiotics administered in compliance with 3-hour bundle requirements. They had lower case mix index and comparable Emergency Severity Index scores.

Main Results

Mortality was lower for within 30 minutes initiation subjects (159 [13.3%] versus 123 [18.3%]; 95% CI 1.4% to 8.5%), as was ICU admission (313 [26.2%] versus 216

Table 1. Primary analysis: univariate comparisons of demographic factors and outcomes.

Variable	All Subjects	≤30-Minute Fluids	>30-Minute Fluids
Characteristics			
N	1,866	1,193	673
Male sex (%)	1,000 (53.6)	650 (54.5)	350 (52.0)
Age (SD), y	72 (16.7)	72 (16.7)	72 (16.6)
White (%)	1,353 (72.5)	865 (72.5)	488 (72.4)
Black (%)	184 (9.9)	104 (8.7)	80 (11.9)
Medicare (%)	1,345 (72.1)	864 (70.9)	499 (74.1)
Medicaid (%)	151 (8.1)	96 (8.0)	55 (8.2)
Initial lactate level (SD), mmol/L	2.8 (0.1)	3.0 (0.1)	2.6 (0.2)
Initial lactate level ≥2.2 (%), mmol/L	1,160 (62.1)	783 (65.6)	377 (56.0)
Initial lactate level ≥4.0 (%), mmol/L	291 (15.6)	208 (17.4)	83 (12.3)
sBP <90 or MAP <65 (%), mm Hg	260 (13.9)	186 (15.6)	74 (11.0)
Acute kidney injury (%)*	412 (22.1)	245 (20.5)	167 (24.8)
Coagulopathy (%)†	370 (19.8)	227 (19.0)	143 (21.2)
Platelets <150 (%), cells/μm^3	264 (14.1)	189 (15.8)	75 (11.1)
Total bilirubin >2.0 (%), mg/dL	111 (5.9)	72 (6.0)	39 (5.8)
Acutely altered mental status (%)	166 (8.9)	95 (8.0)	71 (10.5)
Compromised oxygenation (%)‡	46 (2.5)	25 (2.1)	21 (3.1)
ESI score at triage (%)			
1	14 (0.8)	10 (0.8)	4 (0.6)
2	615 (33.0)	393 (32.9)	222 (33.0)
3	1,174 (62.9)	760 (63.7)	414 (61.5)
CMI (SD)	2.03 (0.08)	1.91 (0.08)	2.25 (0.17)
DRG product line (%)			
Infectious disease	901 (48.3)	633 (53.0)	268 (39.8)
Cardiology§	86 (4.6)	33 (2.8)	53 (7.9)
Gastroenterology	121 (6.5)	88 (7.4)	33 (4.9)
Hematology	80 (4.3)	53 (4.4)	27 (4.0)
General surgery	160 (8.6)	102 (8.5)	58 (8.6)
Bundle interventions§			
Median IVF initiation time (IQR)	10 (0, 32)	8 (0, 12)	72 (45, 120)
Blood cultures before antibiotics (%)§	1,438 (77.0)	940 (78.7)	498 (74)
Lactate result ≤90 min (%)	1,813 (97.1)	1,159 (97.1)	654 (97.2)
Median lactate result time (IQR)	23 (14, 37)	25 (15, 38)	21 (13, 37)
Antibiotics ≤180 min (%)§	1,605 (86.0)	1,061 (88.9)	544 (80.8)
Median antibiotic time (IQR)	48 (13, 110)	39 (10, 90)	66 (20, 144)
Unadjusted outcomes			
Inhospital mortality (%) [95% CI]	282 (15.1)	159 (13.3) [±1.9]	123 (18.3) [±2.9]
ICU admission (%) [95% CI]	528 (28.3)	313 (26.2) [±2.5]	216 (32.1) [±3.5]
Median LOS (95% CI), days	7	6 (6–7)	7 (7–8)
Median ICU LOS (ICU admissions only) (95% CI), days	3	3 (3–4)	4 (4–5)

SD, Standard deviation; *sBP*, systolic blood pressure; *MAP*, mean arterial pressure; *ESI*, Emergency Severity Index; *CMI*, case mix index; *DRG*, diagnosis-related group; *IVF*, intravenous fluid; *IQR*, interquartile range; *ICU*, intensive care unit; *LOS*, length of stay.

±Indicates the 95% CI for unadjusted outcomes.

*Acute kidney injury defined as creatinine level greater than 2.0 mg/dL or 50% increase from a known baseline.

†Coagulopathy defined as an international normalized ratio greater than 1.5 or a partial thromboplastin time greater than 60 seconds.

‡Compromised oxygenation defined as PaO_2/FiO_2 less than 300 or an increased oxygen requirement to maintain SaO_2 greater than 90%.

§All times are in minutes.

[32.1%]; 95% CI 1.6% to 10.3%). The within 30 minutes group had lower median hospital length of stay (6 days [95% CI 6 to 7 days] versus 7 days [95% CI 7 to 8 days]) and median ICU length of stay (3 days [95% CI 3 to 4 days] versus 4 days [95% CI 4 to 5 days]).

In multivariate logistic regression adjusting for sex, age, lactate level, organ dysfunction at severe sepsis or septic shock identification, Emergency Severity Index score, case mix index, other 3-hour bundle interventions, and infectious disease, cardiology, gastroenterology, hematology, and general surgery product lines (Hosmer-Lemeshow χ^2=6.72; P=.57), within 30 minutes initiation patients had 0.63 the mortality risk compared with greater than 30 minutes (OR 0.63; 95% CI 0.46 to 0.86) (Table 2). Hypotension, initial lactate, blood cultures before antibiotics, age, Emergency Severity Index score, case mix index, and a diagnosis-related group within the infectious disease or cardiology product lines were all significantly associated with mortality. Receiving antibiotics greater than 180 minutes from identification was not associated with increased mortality risk (OR 1.03; 95% CI 0.67 to 1.59) in the model. Patients treated within 30 minutes did not have significantly reduced likelihood of ICU admission compared with all others in a multivariate model (OR 0.84; 95% CI 0.65 to 1.08), nor did the goodness-of-fit test render the results meaningful (Hosmer-Lemeshow χ^2=15.35; P=.05).

Table 2. Primary analysis: logistic regression output for variables as a predictor of mortality.

Variable	OR	95% CI	
IVF resuscitation initiated ≤30 min	0.63	0.46	0.86
Age	1.03	1.02	1.04
Male sex	0.88	0.65	1.18
Blood drawn for cultures before antibiotics	0.63	0.45	0.88
Lactate result available within 90 min of order	1.33	0.51	3.49
Antibiotics administered in <180 min	1.03	0.67	1.59
Initial lactate level	1.17	1.1	1.24
sBP <90 or MAP <65 mm Hg	2.04	1.41	2.96
Acute kidney injury*	1.32	0.95	1.84
Platelets <150 cells/μm^3	1.23	0.82	1.86
Coagulopathy†	1.28	0.91	1.81
Total bilirubin >2.0 mg/dL	1.43	0.82	2.48
Compromised oxygenation‡	1.85	0.78	4.37
Acutely altered mental status	1.39	0.9	2.14
CMI	1.4	1.26	1.55
Infectious disease MS-DRG	2.22	1.48	3.32
Cardiology MS-DRG	3.09	1.59	5.97
Gastroenterology	1.59	0.77	3.26
Hematology MS-DRG	1.49	0.63	3.49
General surgery MS-DRG	0.56	0.26	1.18

MS-DRG, Medicare severity diagnosis related group.
*Acute kidney injury defined as creatinine level greater than 2.0 or 50% increase from a known baseline.
†Coagulopathy defined as an international normalized ratio greater than 1.5 or a partial thromboplastin time greater than 60 seconds.
‡Compromised oxygenation defined as PaO_2/FiO_2 less than 300 or an increased oxygen requirement to maintain SaO_2 greater than 90%.

In a multivariate Cox proportional hazards model adjusting for the same covariates and censoring for mortality (Figure 2; Table 3), receiving intravenous fluid within 30 minutes was associated with 12% shorter hospital length of stay (HR=1.14; 95% CI 1.02 to 1.27). Association of receiving antibiotics in 180 minutes with 14% shorter hospital length of stay approached but did not reach significance (HR=1.16; 95% CI 0.99 to 1.34).

When examining time to initiation as an ordinal variable, we grouped patients by whether intravenous fluid was initiated within 30 minutes, 31 to 60 minutes, or 61 to 180 minutes from severe sepsis or septic shock identification, or either greater than 180 minutes or not at all. We report group characteristics in Table 4. Earlier fluid resuscitation initiation showed higher frequency of lactate level greater than or equal to 4.0 mmol/L, hypotension, thrombocytopenia, bundle-compliant antibiotic administration, and having blood for cultures drawn before antibiotics.

Mortality increased with later initiation of intravenous fluid in the 4 groups: 13.5% versus 16.0% versus 16.9% versus 19.7%. ICU admission was higher in the later groups compared with the within 30 minutes and 31 to 60 minutes groups (313 [26.2%] versus 46 [26.0%] versus 53 [29.9%] versus 117 [36.7%]). Initiation within 30 minutes was associated with median hospital length of stay of 6 days (95% CI 6 to 7 days) versus 7 days (95% CI 6 to 7 days) in the 31 to 60 minutes group, 7 days (95% CI 6 to 8 days) in the 61 to 180 minutes group, and 8 days (95% CI 7 to 9 days) in the greater than 180 minutes group. In the same analysis for patients admitted to the ICU, the within 30 minutes group had a median ICU length of stay of 3 days (95% CI 3 to 4 days) versus 4 days in both the 31 to 60 minutes group (95% CI 3 to 7 days) and the 61 to 180 minutes group (95% CI 2 to 5 days), and 5 days (95% CI 4 to 6 days) for patients receiving intravenous fluid initiated in greater than 180 minutes or not at all.

In the multivariate logistic regression analysis of time to fluid resuscitation initiation (Hosmer-Lemeshow χ^2=7.02; P=.54), the within 30 minutes group had 0.59 the mortality likelihood of the reference group (patients receiving fluids >180 minutes from severe sepsis or septic shock identification or not at all) (OR 0.59; 95% CI 0.39 to 0.87), adjusting for age, lactate level, organ dysfunction, Emergency Severity Index score, case mix index, MS–diagnosis-related group product line, and other 3-hour bundle measures. The 31 to 60 minutes group had three quarters the mortality risk of the reference group, but this difference was not significant (OR 0.78; 95% CI 0.44 to 1.38). Receiving fluids 61 to 180 minutes after severe sepsis or septic shock identification was also associated with decreased mortality likelihood that was not statistically

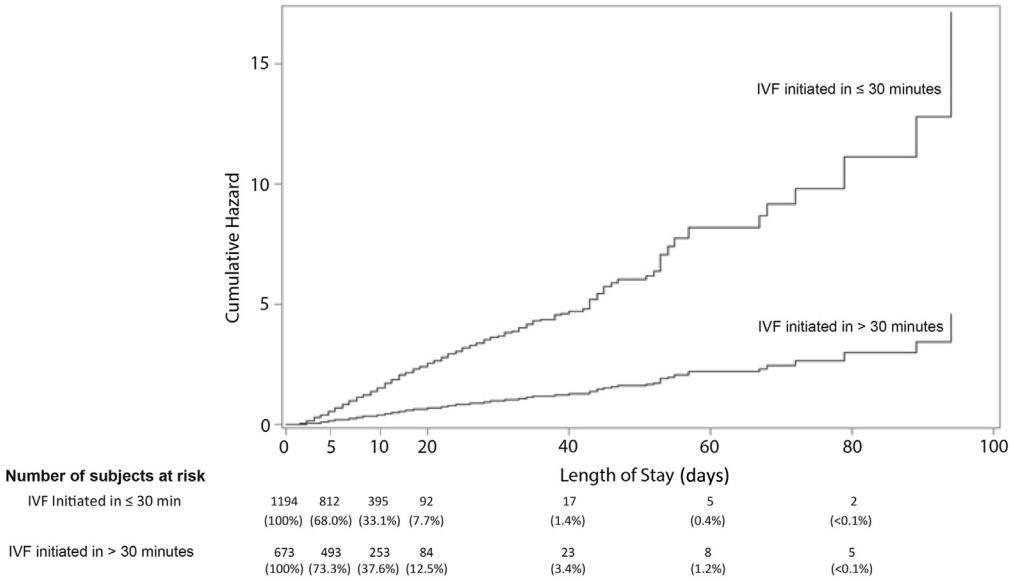


Figure 2. Cumulative hazard and number at risk table for primary analysis.

significant. Receiving antibiotics within 180 minutes was not significantly associated with mortality risk. There was significantly reduced ICU admission likelihood for the within 30 minutes groups (≤30 minutes OR 0.71; 95% CI 0.50 to 0.99), although the Hosmer-Lemeshow goodness-of-fit test approached the threshold to reject the null hypothesis that the model adequately fit the data (χ^2=14.86; P=.06).

In the adjusted Cox proportional hazards model (Figure 3), initiation of fluid resuscitation within 30 minutes was associated with 18% shorter hospital length of stay compared with initiation in greater than 180 minutes or no resuscitation (HR 1.22; 95% CI 1.06 to 1.42). Fluid resuscitation from 31 to 60 minutes was associated with 19% shorter length of stay compared with the referent (HR 1.24; 95% CI 1.00 to 1.52). Association of intravenous fluid within 61 to 180 minutes with a shorter hospital length of stay was not significant (HR 1.08; 95% CI 0.88 to 1.34). Association of receiving antibiotics within 180 minutes with 13% shorter hospital length of stay approached significance (HR 1.15; 95% CI 0.99 to 1.027). We summarize adjusted regression model results in Figure 4.

LIMITATIONS

Our study had a number of important limitations. First, we used the time at which intravenous fluid resuscitation was initiated as the exposure of interest, but did not consider volume of fluids and the time of intravenous fluid administration completion. This stems from the operational challenges in capturing both of these data fields, a problem that we believe to be widely encountered, and one that reflects the principal need and fundamental motivation for this study. We recognize that intravenous fluid volume could confound our analysis of initiation time and that allocation of patients documented as being volume nonadherent to the reference group could overstate results. However, the rationale behind our proposed aggressive 30-minute initiation measure is that such patients would not only have intravenous fluid administration completed earlier but also in general receive more intravenous fluid. Furthermore, a recent prospective observational study of EMS encounters of 1,350 patients with severe sepsis found those who received out-of-hospital fluids had less than 0.6 odds of mortality compared with those who did not.[29] Subjects in the aforementioned study received only a mean volume of 500 mL, suggesting initiation time specifically may be predictive, independent of volume administered.

Second, because of our study's observational design and ED setting, we did not capture sufficient data to calculate composite severity scores (eg, Acute Physiology And Chronic Health Evaluation score, SOFA). However, these scores are difficult to apply to an ED cohort population, and although it was not ideal, we attempted to use multiple surrogates to address this, including initial lactate level, Emergency Severity Index score, case mix index, and measures of organ dysfunction.

Third, the lactate-level threshold of 2.2 mmol/L or new organ dysfunction criteria included patients who may have been inherently less sick than subjects in other studies (eg, ProCESS, ProMISE). However, although literature reports lower mortality for patients with lactate level less than 4.0 mmol/L, "intermediate" hyperlactemia

Table 3. Primary analysis: Cox proportional hazards output for variables as a predictor of length of stay.*

Variable	HR	95% CI	
IVF resuscitation initiated ≤30 min	1.14	1.02	1.27
Age	1	0.99	1
Male sex	0.96	0.87	0.17
Medicare	[Reference]	[Reference]	[Reference]
Medicaid	1.02	0.84	1.25
Commercial I	1.3	1.09	1.55
Commercial II†	1.08	0.88	1.32
Blood drawn for cultures before antibiotics	0.9	0.8	1.02
Lactate result available within 90 min of order	0.89	0.67	1.19
Antibiotics administered in <180 min	1.16	0.99	1.34
Initial lactate level	1.01	0.98	1.04
sBP <90 or MAP <65 mm Hg	0.73	0.62	0.86
Acute kidney injury‡	0.81	0.72	0.92
Platelets <150 cells/μm^3	1.1	0.95	1.28
Coagulopathy§	1.02	0.89	1.16
Total bilirubin >2.0 mg/dL	0.88	0.7	1.1
Compromised oxygenation‖	0.93	0.64	1.36
Acutely altered mental status	0.88	0.73	1.07
CMI	0.65	0.61	0.69
Infectious disease MS-DRG	0.94	0.83	1.06
Cardiology MS-DRG	0.77	0.6	1.01
Gastroenterology MS-DRG	0.94	0.75	1.16
Hematology MS-DRG	0.55	0.42	0.73
General surgery MS-DRG	1.34	1.06	1.71

*Because being discharged alive is the "event" in the model, HR greater than 1.0 indicates a shorter LOS.
†Commercial II refers to commercial insurers considered "high reimbursing" at the study site (high reimbursing defined as >75% higher than the commercial payer average).
‡Acute kidney injury defined as creatinine level greater than 2.0 or 50% increase from a known baseline.
§Coagulopathy defined as an international normalized ratio greater than 1.5 or a partial thromboplastin time greater than 60 seconds.
‖Compromised oxygenation defined as PaO_2/FiO_2 less than 300 or an increased oxygen requirement to maintain SaO_2 greater than 90%.

has been associated with mortality risk.[30] This also likely explains the large volume for a single site throughout the study period.

Fourth, patients receiving intravenous fluid initiated within 30 minutes were more likely to receive other 3-hour-bundle-compliant interventions and had lower case mix index and lower frequency of some organ dysfunction criteria (eg, acute kidney injury, altered mental status). However, they conversely had higher initial lactate level and were more likely to present with hypotension or thrombocytopenia. This is not surprising because sicker patients are more easily identified and would be more likely to receive appropriate ED care. Because these patients are also initially more likely to die, the observed benefits of intervention may even be understated, although we attempted to control for these discrepancies with multivariate regression modeling.

Fifth, as with all sepsis studies and despite our use of objective clinical measures to determine the time to "start the clock," distinguishing gradual clinical development of sepsis from gradual physician recognition and intervention remains a significant limitation.

Sixth, data collection did not differentiate severe sepsis from septic shock patients. Seventh, because of the study site's high compliance with the 30-minute fluid target, sample sizes in the subgroups of the secondary analysis were substantially smaller, and we did not construct a multivariate model to examine ICU length of stay in the secondary analysis for sample size considerations.

Seventh, because this was not a randomized trial, our findings cannot indicate causality. However, this analysis examined prospectively captured observational data of all severe sepsis or septic shock encounters at the study site and may be more reflective of a true emergency medicine practice environment, and could have greater generalizability than a more methodologically rigorous randomized controlled trial.

DISCUSSION

Patients with intravenous fluid resuscitation initiated within 30 minutes had 5% lower mortality and 1 day shorter median hospital length of stay versus those with resuscitation initiated in greater than 30 minutes. In adjusted regression, initiating intravenous fluid resuscitation within 30 minutes of severe sepsis or septic shock identification was associated with 0.63 odds of inhospital mortality and more than 12% shorter hospital length of stay compared with initiation after 30 minutes (Figure 4). The adjusted models showed no significant differences in mortality for fluids initiated at any point from 30 to 180 minutes compared with greater than 180 minutes or not at all. Hospital length of stay was significantly shorter only for patients with fluids initiation within 30 minutes or 31 to 60 minutes compared with the referent in an adjusted model that censored for mortality. All models adjusted for whether antibiotics administration adhered to 3-hour sepsis bundle specifications.

The timeliness of sepsis recognition and intervention is essential in managing patients with a diagnosis on the sepsis continuum.[12,13,15-17,23,31] Protocolized approaches to sepsis care require completion of bundle goals within explicit time limits, and current Surviving Sepsis Campaign guidelines recommend that lactate-level measurement, blood collection for culture, intravenous antibiotic administration, and intravenous fluid resuscitation (30 mL/kg) be completed within 180 minutes of identification.[9,10] The ProCESS, ARISE, and ProMISE trials, 3 multisite

Table 4. Secondary analysis: univariate comparisons of demographic factors and outcomes.

Variable	All Subjects	≤30 Minutes	31–60 Minutes	61–180 Minutes	>180 Minutes
Characteristics					
N	1,866	1,193	177	177	319
Male sex (%)	1,000 (53.6)	650 (54.5)	59 (50.3)	85 (47.8)	178 (55.8)
Age (SD), y	72 (16.7)	72 (16.7)	72 (16.2)	71 (16.7)	73 (16.8)
White (%)	1,353 (72.5)	865 (72.5)	128 (72.3)	130 (73.4)	230 (72.1)
Black (%)*	184 (9.9)	104 (8.7)	19 (10.7)	20 (11.3)	41 (12.9)
Medicare (%)	1,345 (72.1)	864 (70.9)	126 (71.2)	136 (76.8)	237 (74.3)
Medicaid (%)	151 (8.1)	96 (8.0)	14 (7.9)	15 (8.5)	26 (8.2)
Initial lactate level (SD), mmol/L*	2.8 (0.1)	3.0 (0.1)	2.6 (0.2)	2.7 (0.3)	2.5 (0.3)
Initial lactate level ≥2.2 (%), mmol/L	1,160 (62.1)	783 (65.6)	109 (61.6)	104 (58.8)	164 (61.4)
Initial lactate level ≥4.0 (%), mmol/L	291 (15.6)	208 (17.4)	21 (11.9)	23 (13.0)	39 (12.2)
sBP <90 or MAP <65 (%), mm Hg	260 (13.9)	186 (15.6)	22 (12.4)	14 (7.9)	38 (11.9)
Acute kidney injury (%)†	412 (22.1)	245 (20.5)	45 (25.4)	44 (24.9)	78 (24.5)
Coagulopathy (%)‡	370 (19.8)	227 (19.0)	43 (24.3)	42 (23.7)	58 (18.2)
Platelets <150 (%), cells/μm^3	264 (14.1)	189 (15.8)	23 (13.0)	15 (8.5)	37 (11.6)
Total bilirubin >2.0 (%), mg/dL	111 (5.9)	72 (6.0)	10 (5.6)	6 (3.4)	23 (7.2)
Altered mental status (%)	166 (8.9)	95 (8.0)	15 (8.5)	29 (11.9)	35 (11.0)
Compromised oxygenation (%)§	46 (2.5)	25 (2.1)	3 (1.7)	0	18 (5.6)
ESI score at triage (%)					
1	14 (0.8)	10 (0.8)	1 (0.6)	0	3 (0.9)
2	615 (33.0)	393 (32.9)	56 (31.6)	63 (35.6)	103 (32.3)
3	1,174 (62.9)	760 (63.7)	114 (64.4)	110 (62.1)	190 (59.6)
CMI (SD)*	2.03 (0.08)	1.91 (0.08)	2.19 (0.30)	1.96 (0.20)	2.43 (0.25)
DRG product line (%)					
Infectious disease*	901 (48.3)	633 (53.0)	85 (48.0)	85 (48.0)	98 (30.7)
Cardiology*	86 (4.6)	33 (2.8)	8 (4.5)	6 (3.4)	39 (12.2)
Gastroenterology*	121 (6.5)	88 (7.4)	9 (5.1)	5 (2.8)	19 (6.0)
Hematology	80 (4.3)	53 (4.4)	9 (5.1)	5 (2.8)	13 (4.1)
General surgery	160 (8.6)	102 (8.5)	14 (7.9)	10 (5.6)	34 (10.7)
Bundle interventions*					
Median IVF initiation time (IQR)	10 (0, 32)	8 (0, 12)	42 (36, 50)	91 (75, 123.5)	261 (201, 452)
Blood cultures before antibiotics (%)*	1,438 (77.0)	940 (78.7)	138 (78.0)	142 (80)	218 (68.3)
Lactate result ≤90 (%), min	1,813 (97.1)	1,159 (97.1)	173 (97.7)	173 (97.7)	308 (96.6)
Median lactate result time (IQR)	23 (14, 37)	25 (15, 38)	20 (13, 36)	22 (14, 35)	20 (12, 37.5)
Antibiotics ≤180 (%), min*	1,605 (86.0)	1,061 (88.9)	148 (83.6)	152 (85.9)	244 (76.5)
Median antibiotic time (IQR)	48 (13, 110)	39 (10, 90)	59 (25.5, 133)	75 (32, 133)	68.5 (1, 155)
Unadjusted outcomes					
Inhospital mortality (%) [95% CI]	282 (15.1)	159 (13.3) [±1.9]	30 (16.9) [±5.6]	30 (16.9) [±5.6]	63 (19.7) [±4.4]
ICU admission (%) [95% CI]	528 (28.0)	313 (26.2) [±2.5]	46 (26.0) [±6.5]	53 (29.9) [±6.8]	117 (36.7) [±5.3]
Median LOS (95% CI), days	7	6 (6–7)	7 (6–7)	7 (6–8)	8 (7–9)
Median ICU LOS (ICU admissions only) (95% CI), days	3	3 (3–4)	4 (3–7)	4 (2–5)	5 (4–6)

±Indicates the 95% CI for unadjusted outcomes.
*All times are in minutes.
†Acute kidney injury defined as creatinine level greater than 2.0 mg/dL or 50% increase from a known baseline.
‡Coagulopathy defined as an international normalized ratio greater than 1.5 or a partial thromboplastin time greater than 60 seconds.
§Compromised oxygenation defined as PaO_2/FiO_2 less than 300 or an increased oxygen requirement to maintain SaO_2 greater than 90%.

randomized controlled trials, failed to demonstrate mortality benefits for patients receiving protocolized care in accordance with early goal-directed therapy bundles compared with usual care.[6-8] This raises the question of whether the mortality benefits that Rivers et al[5] observed lie in invasive hemodynamic monitoring and rigid protocolization, or perhaps in early recognition and intervention afforded by protocol adherence. Although the standard of care may have changed during the last 13 years, barring direct comparison, all subjects in both experimental and control groups for all 3 recent trials received early intravenous fluid and antibiotics.[6-8]

Numerous studies have also attempted to quantify "golden hours" for antibiotic administration since Kumar et al demonstrated increased mortality risk with each hour of antibiotic delay for septic shock patients. Findings are not unanimous,[32,33] and no subsequent studies demonstrated as substantial an effect as the investigation by Kumar et al. Nevertheless, several large studies reported increased mortality risk with increasing antibiotic

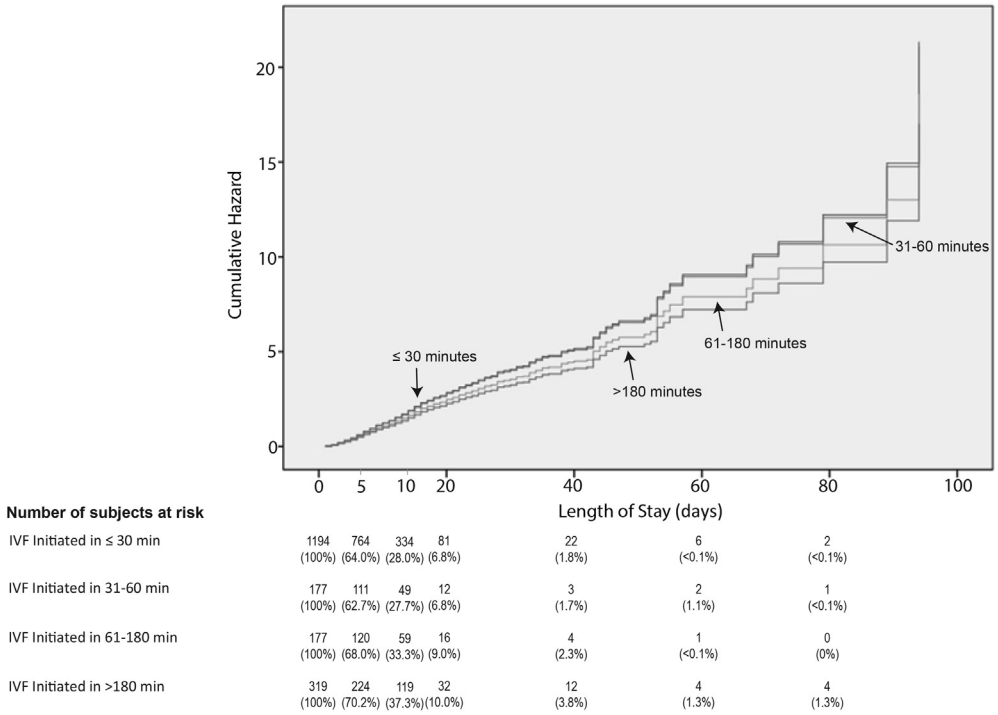


Figure 3. Cumulative hazard and number at risk table for subgroup analysis.

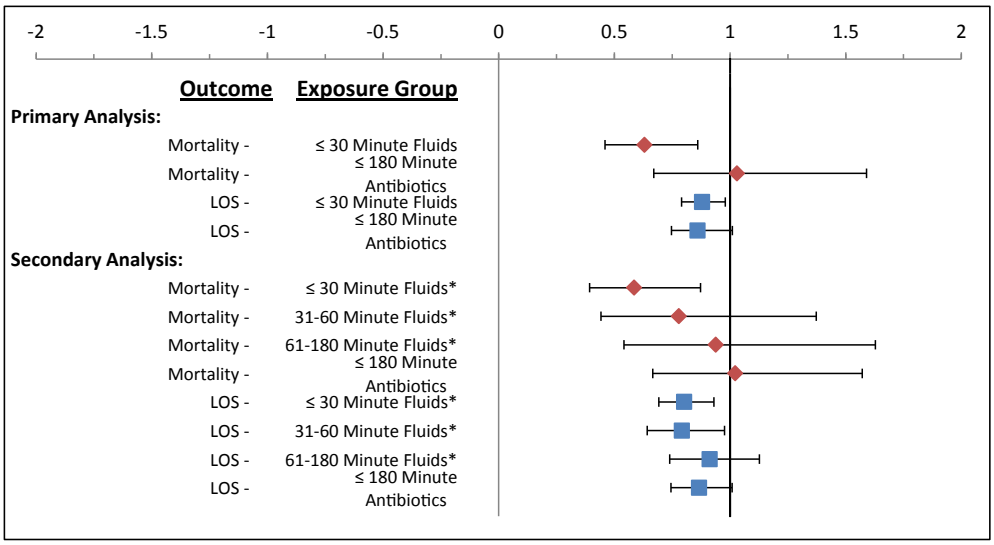
delay.[11-17,33-35] Nearly all of these studies do not take into account whether an appropriate, timely fluid bolus was administered in their analyses, and to our knowledge no study has considered the time of initiation for fluid resuscitation.

The association of time to intravenous fluid resuscitation has been investigated less extensively despite the current consensus on a hypoxemic or hypoperfusive mechanism of injury and disease progression in sepsis.[10,36-38] Although several studies demonstrate mortality benefits for increased intravenous fluid administration within 3 hours, more comprehensive stratification of time to resuscitation remains sparse in the literature. To our knowledge, no study has examined the association of intravenous fluid resuscitation initiation times with patient outcomes. Our adjusted regression models found that the most aggressive 30-minute initiation goal was associated with the most robust mortality and hospital length-of-stay benefits, even when controlling for the timeliness of antibiotic administration. When tested simultaneously in regression models with fluid initiation timeliness, bundle-adherent antibiotic administration failed to demonstrate significant, independent association with reduced mortality. We suspect this may be related to binary treatment of the variable in the analysis and 3-hour cutoff, and although unexpected, this finding is not inconsistent with that in some more recent literature.[32,33]

We draw several inferences from this study. Most important, adhering to an initiation time, rather than completion time, as an intravenous fluid resuscitation compliance measure in severe sepsis or septic shock care may be sufficient to drive mortality and use improvements. Although generalizable data on the availability of completion time documentation would be difficult to capture, in the wake of both New York State and Centers for Medicare & Medicaid Services' sepsis data reporting regulations, discussion at statewide and national meetings has repeatedly raised the issue of reliably capturing intravenous fluid completion times. As such, we suspect that operational difficulties with this measure are not unique to the study site, and this modified approach to everyday severe sepsis or septic shock management may be of wide interest.

Next, although we think it unlikely that earlier antibiotic administration does not independently confer mortality benefit, the absence of this association in our results suggests that both early intravenous fluid and antibiotics may engender improved survival.

Finally, the majority of subjects receiving intravenous fluid initiated within 30 minutes would likely have had administration completed substantially earlier than the current 180-minute recommendation, and in the adjusted models, we observed substantial improvements only in the group with the earliest intravenous fluid initiation. Together with the results of the study by Seymour et al[29] of



	Outcome	Exposure Group	Model Output	Ratio	Lower CI	Upper CI
Primary Analysis:						
	Mortality	≤ 30 Minute Fluids*§	OR	0.63	0.46	0.86
	Mortality	≤ 180 Minute Antibiotics§	OR	1.03	0.67	1.59
	LOS	≤ 30 Minute Fluids*†‡	HR^{-1}	0.88	0.79	0.98
	LOS	≤ 180 Minute Antibiotics†‡	HR^{-1}	0.86	0.75	1.01
Secondary Analysis:						
	Mortality	≤ 30 Minute Fluids°§	OR	0.59	0.39	0.87
	Mortality	31-60 Minute Fluids°§	OR	0.78	0.44	1.37
	Mortality	61-180 Minute Fluids°§	OR	0.94	0.54	1.63
	Mortality	≤ 180 Minute Antibiotics§	OR	1.02	0.67	1.57
	LOS	≤ 30 Minute Fluids°†‡	HR^{-1}	0.80	0.69	0.93
	LOS	31-60 Minute Fluids°†‡	HR^{-1}	0.79	0.64	0.98
	LOS	61-180 Minute Fluids°†‡	HR^{-1}	0.91	0.74	1.13
	LOS	≤ 180 Minute Antibiotics†‡	HR^{-1}	0.87	0.75	1.01

Results with 95% CI are tabulated above
* The referent group is the >30 minute IVF group
° The referent group is the >180 minute IVF group

† This result is reported as the inverse HR. A HR is the ratio of 'events' per unit time and the 'event' in the model is live hospital discharge. The HR-1 is the ratio of time per live hospital discharge: ie, the LOS of the study groups relative to the LOS of the reference groups. A HR^{-1} = 0.88 indicates LOS was 88% as long as the reference group.

‡ Model also adjusted for age, sex, payer-class, initial lactate, hypotension, AKI, thrombocytopenia, coagulopathy, total bilirubin >2.0mg/dL, compromised oxygenation, AMS, blood cultures prior to antibiotics, lactate available within 90 miutes, ESI score, CMI and MS-DRG product line.

§ Model also adjusted for age, sex, initial lactate, hypotension, AKI, thrombocytopenia, coagulopathy, total bilirubin >2.0mg/dL, compromised oxygenation, AMS, blood cultures before antibiotics, lactate available within 90 minutes, ESI score, CMI and MS-DRG product line.

Figure 4. ORs and inverse HRs for mortality and LOS from multivariate models. *AKI*, Acute kidney injury; *AMS*, altered mental status.

out-of-hospital intravenous fluid resuscitation for severe sepsis or septic shock patients, this could suggest that current 3-hour guidelines for fluid resuscitation may be too conservative and that a critical window for intervention may be narrower than current recommendations call for. Therefore, although further investigation should be considered to further validate our approach or to compare it with current metrics, we believe our results demonstrate strong initial evidence that 30-minute intravenous fluid initiation may be an adequate and more pragmatic sepsis performance measure.

In conclusion, we found association between adhering to a requirement to initiate intravenous fluid resuscitation within 30 minutes of severe sepsis or septic shock identification and decreased inhospital mortality and hospital length of stay in a cohort of 1,866 patients. Fluid

resuscitation initiation time may be an appropriate alternative to completion time in guiding management of severe sepsis and septic shock patients.

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Author contributions: DL, BW, MFW, and JAZD conceived of the study and designed it. MD, MFW, JKD, and JAZD were responsible for the development of the original performance improvement initiative, including the data collection process. DL and BW oversaw the research registry's data management. MA was the primary statistician consultant. DL and MA determined the analytic strategy and performed all analyses. DL wrote the initial draft of the article, which all authors reviewed and contributed to before submission. DL revised the article, and all authors subsequently reviewed it. MFW and JAZD mentored the project throughout. DL and BW are co-first authors on this study. DL takes responsibility for the paper as a whole.

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