

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;68:298-311.]

Please see page 299 for the Editor's Capsule Summary of this article.

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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 al⁵ 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 al¹¹

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 in-hospital 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.

demonstrating substantially increased mortality with each hour of antibiotic delay in septic shock patients, the literature expansively explored the association between the 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 guidelines¹⁰ 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 in-hospital 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

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