CHEST

Increased Fluid Administration in the First Three Hours of Sepsis Resuscitation Is Associated With Reduced Mortality

A Retrospective Cohort Study

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BACKGROUND: The surviving sepsis guidelines recommend early aggressive fluid resuscitation within 6 h of sepsis onset. Although rapid fluid administration may offer benefit, studies on the timing of resuscitation are lacking. We hypothesized that there is an association between quicker, adequate fluid resuscitation and patient outcome from sepsis onset time.

METHODS: This is a retrospective cohort study of consecutive adults with severe sepsis and septic shock admitted to a quaternary care medical ICU between January 2007 and December 2009. Data were collected from a previously validated electronic medical database. Multivariate regression modeling was performed, adjusting for age, admission weight, Sequential Organ Failure Assessment score, APACHE (Acute Physiology and Chronic Health Examination) III score, and total fluid administration within the first 6 h of sepsis onset time.

RESULTS: Of 651 patients with severe sepsis and septic shock screened, 594 had detailed fluid data. In a univariate analysis, the median amount of fluid within the first 3 h for survivors at discharge was 2,085 mL (940-4,080 mL) and for nonsurvivors, 1,600 mL (600-3,010 mL; $P = .007$). In comparison, during the latter 3 h, the median amount was 660 mL (290-1,485 mL) vs 800 mL (360-1,680 mL; $P = .09$), respectively. After adjusting for confounders, the higher proportion of total fluid received within the first 3 h was associated with decreased hospital mortality (OR, 0.34; 95% CI, 0.15-0.75; $P = .008$).

CONCLUSIONS: Earlier fluid resuscitation (within the first 3 h) is associated with a greater number of survivors with severe sepsis and septic shock. CHEST 2014; 146(4):908-915

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ABBREVIATIONS: APACHE = Acute Physiology and Chronic Health Evaluation; CVP = central venous pressure; EGDT = early goal-directed therapy; MAP = mean arterial pressure; ProCESS = Protocol-Based Care for Early Septic Shock; $Scvo_2$ = central venous oxygen saturation; SOFA = Sequential Organ Failure Assessment

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Sepsis is the leading cause of death in noncoronary ICUs, with a fatality rate of 20% to 40%,[1,2] and is the 11th leading cause of death overall in the United States.[3] Furthermore, the incidence of sepsis and sepsis-related deaths has increased in the past 2 decades, despite the decrease in overall in-hospital mortality.[2,4] Those who survive sepsis were more likely to require long-term care than those recovering from other acute conditions.[5] The estimated cost of sepsis burden in the United States was $14.6 billion in 2008 and has risen annually by 11.9%.[1,5]

More than 1 decade ago, the term "early-goal directed therapy" (EGDT) was introduced, a protocol for resuscitation within the first 6 h of hospitalization for patients with severe sepsis and septic shock.[6] A mortality benefit was found that resulted in global educational efforts and bundled recommendations from the Surviving Sepsis Campaign to help manage severe sepsis and septic shock. Adherence to these bundled recommendations has been associated with improved outcomes, including decrease in-hospital mortality from sepsis.[6-10]

Despite proven benefits, there continues to be debate on which elements of EGDT actually prevent mortality. Optimal fluid resuscitation is recognized as a critical component, and studies have addressed the crystalloid/colloid debate.[11-15] However, limited data guide fluid management in the ICU in a time-sensitive manner. Multiple studies have demonstrated harm with standardizing liberal fluid resuscitation, notably when given beyond the initial hours of EGDT.[16-19] On the contrary, anecdotal experience and a few studies show the benefit of out-of-hospital fluid resuscitation by emergency medical services, which suggest that early fluid resuscitation might be better.[20,21] The present study is the first, to our knowledge, to examine the timing of fluid resuscitation in patients with severe sepsis and septic shock within the first 6 h in the ICU. The aim was to evaluate for mortality differences in patients who received adequate fluid resuscitation within the first 3 h (hours 0-3) compared with the latter 3 h (hours 3.1-6) of EGDT.

Materials and Methods

Design and Selection

In a single-center retrospective cohort study, consecutive adults aged > 18 years were screened for severe sepsis or septic shock after admission to a medical ICU of a quaternary care academic hospital between January 2007 and December 2009. The study period was selected based on the completeness and accuracy of the available data, which took several years to collect, recheck, and validate against errors. The diagnosis of severe sepsis or septic shock was made based on the 2003 International Sepsis Definitions Consensus Conference.[22] We included patients who had suspected infection and one of the following: (1) fluid-resistant hypotension of < 90 mm Hg systolic BP after an initial 20 mL/kg fluid bolus, (2) lactate level > 4 mmol/L, or (3) vasopressor initiation.[22] Sepsis onset time was based on when the patient met any of these criteria (Fig 1). Two independent reviewers manually appraised the medical charts for accuracy in meeting the inclusion criteria and determining the sepsis onset time. Discrepancies were resolved by consensus. We excluded mixed shock states (ie, hypovolemia due to hemorrhage or trauma, cardiogenic, neurogenic), patients aged < 18 years, and patients placed on comfort care.

The requirement for consent was waived because of the observational nature of the study. Patients were treated according to the institution's sepsis protocol, and all were given antibiotics and fluids. The study was approved by the Mayo Clinic Institutional Review Board (IRB # 277-04).

Data Collection

The data were derived from a previously validated database, the ICU datamart, which is a real-time relational database generated from the electronic medical record.[23] Baseline demographics, BMI on admission, Sequential Organ Failure Assessment (SOFA) score over the first 24 h of sepsis onset time, APACHE (Acute Physiology and Chronic Health Evaluation) III score, Charlson comorbidity index, and hemodynamic variables measured in the sixth hour of sepsis resuscitation, including central venous pressure (CVP), central venous oxygen saturation ($Scvo_2$), and mean arterial pressure (MAP), were collected. Length of hospital stay, duration of mechanical ventilation, presence of oliguria (urine output < 0.5 mL/kg/h), and in-hospital mortality data were also collected. After the initial bolus of 20 mL/kg fluid, the total amount of fluid in milliliters was tallied from the electronic medical record and calculated for the first 3 h and then the latter 3 h for all patients in the cohort. All patients received lactated Ringer's solution, 0.9% normal saline, or albumin for fluid resuscitation. No starches, dextrans, or gelatins were given. The reported fluid amounts were unbalanced.

Statistical Analysis

Quantitative variables are reported as median with interquartile range. Categorical variables, such as sex, vasopressor use, and presence of oliguria, are reported as the percentage of patients within the subgroup of survivors or nonsurvivors. The primary hypothesis was tested using multivariate logistic regression modeling, adjusted for age, admission weight, SOFA score, APACHE III score, and total fluid given within the first 6 h of sepsis onset time. For univariate analysis, Student *t* test, χ^2 test, and Wilcoxon signed rank test were used as appropriate. The covariates identified in the univariate analysis were adjusted in the multivariate logistic regression model. Total amount of fluid given in the first 3 h and later 3 h had a skewed distribution, so they were log-transformed to satisfy regression assumptions. SAS/JMP, version 9.1 (SAS Institute Inc) software was used for data analysis. CIs and *P* values were calculated using the standard *t* test, with $P < .05$ considered statistically significant.

Results

Of the 651 patients who met the inclusion criteria, 57 (8.7%) were excluded due to incomplete data (Fig 2). The median age was 70 years (range, 58-80 years) and 54% (n = 326) were men. Among the cohort, 452 patients survived to discharge and 142 died, resulting in 24% all-cause in-hospital mortality. Table 1 shows the baseline demographics. On the basis of univariate analysis, the