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

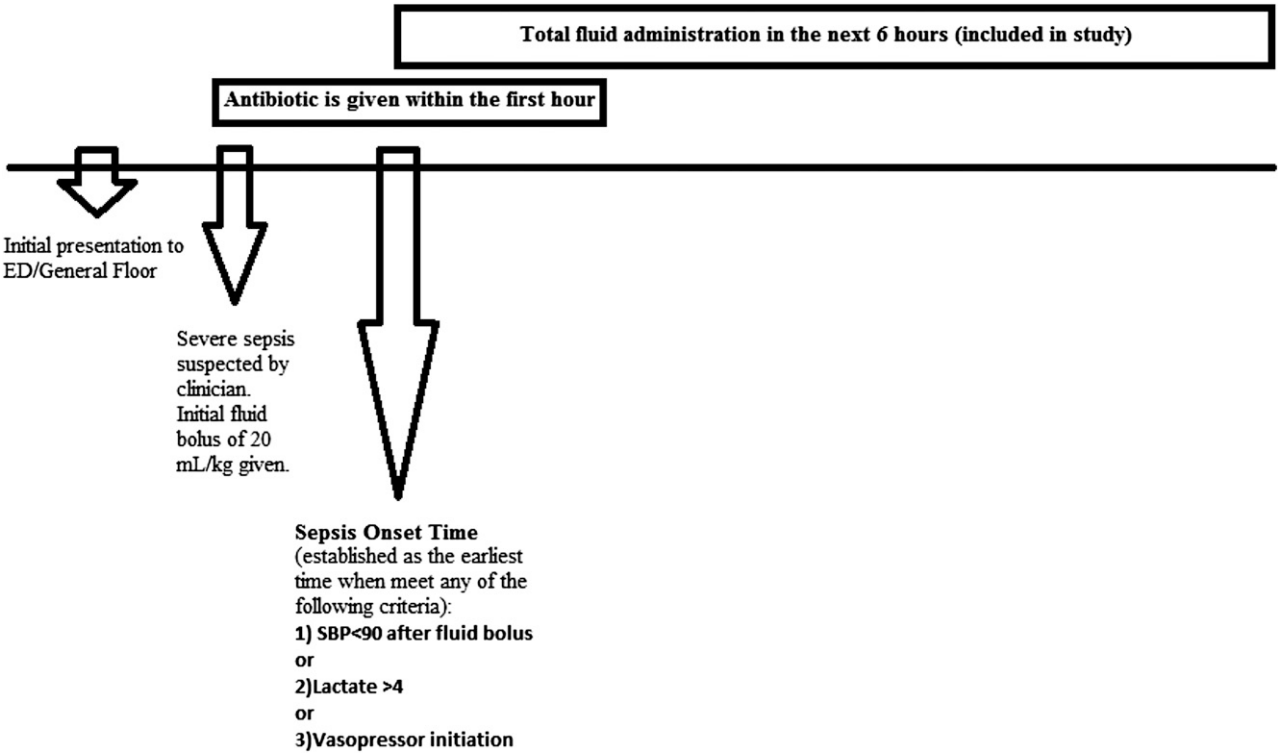

Figure 1 – *Timeline and definition of sepsis onset time. SBP = systolic BP.*

survivors were younger, male, and had lower APACHE III scores than nonsurvivors. There was no difference in BMI, timing of antibiotic initiation relative to sepsis onset time, percentage of central venous catheter use, or hospital length of stay between survivors and nonsurvivors. Total amount of fluids given in the first 6 h, age, and APACHE III score were later adjusted in multivariate logistic regression. All patients received resuscitation that complied with the 2008 protocol, which is to give antibiotics within the first hour, start fluid resuscitation as soon as IV access can be established, measure hemodynamic variables as soon as a central venous catheter is placed, and aim for EGDT by 6 h.

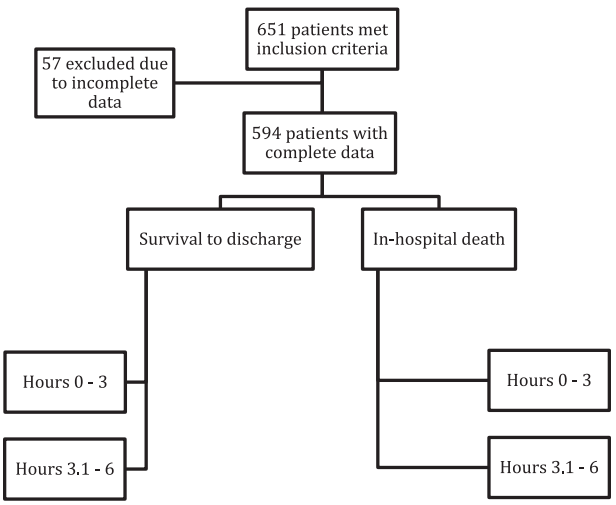

Figure 2 – *Study flowchart.*

In univariate analysis, the median amount of fluid within the first 3 h for survival at discharge vs nonsurvival was 2,085 mL (interquartile range, 940-4,080 mL) vs 1,600 mL (600-3,010 mL; $P = .007$). In comparison, during the latter 3 h, the median amount of fluid administered was 660 mL (290-1,485 mL) vs 800 mL (360-1,680; $P = .09$), respectively. The optimal cut point from receiver operating characteristic analysis that jointly maximizes sensitivity and specificity for numbers of survivors based on fluid administration was 1.5 h from sepsis onset time. Table 2 shows hemodynamic variables comparing the survivors and nonsurvivors according to the institutional protocol for sepsis resuscitation. There was no statistical significance between the two groups regarding CVP measured at 6 h from sepsis onset time. However, the nonsurvivors had significantly lower MAP, lower $Scvo_2$, more vasopressor use in the initial 24 h, more oliguria, and higher SOFA scores. In other words, the nonsurvivor group at the end of 6-h resuscitation exhibited worse clinical markers than the survivor group. Although survivors and nonsurvivors did not differ in the number of hospital days, survivors had more ICU-free days and spent more of their hospitalization on a general care floor (Table 3).

TABLE 1] Baseline Characteristics of Study Participants

Variable	Nonsurvivors (n = 142)	Survivors (n = 452)	*P* Value
Male sex	64 (45)	262 (58)	< .01[a]
Age, y	74 (60 to 82)	69 (58 to 80)	.04[a]
Weight, kg	82 (65 to 92)	77 (66 to 99)	.26
BMI, kg/m^2	28.1 (22.7 to 33.5)	27.9 (23.7 to 34.4)	.37
APACHE III score	60 (46.8 to 75.5)	56 (42 to 70)	.045[a]
Charlson comorbidity index	5 (3 to 7)	5 (3 to 7)	.2
Time to antibiotic initiation relative to sepsis onset time, h	0.13 (−2.2 to 1)	0.28 (−1.9 to 1.3)	.23
Fluid received in hours 0-3, mL	1,600 (600 to 3,010)	2,085 (940 to 4,080)	.007[a]
Fluid received in hours 3.1-6, mL	880 (360 to 1,680)	660 (290 to 1,485)	.09
Total fluid received in 6 h, mL	2,875 (1,390 to 47,20)	3,150 (1,630 to 5,665)	.10
Net positive fluid balance hours 0-3, mL	1,460 (550 to 2,815)	1,790 (705 to 3,665)	.051
Net positive fluid balance hours 3.1-6, mL	665 (250 to 1,595)	465 (100 to 1,170)	.0032[a]

Data are presented as No. (%) or median (interquartile range). APACHE = Acute Physiology and Chronic Health Evaluation.
[a]$P < .05$.

Furthermore, the data were incorporated into a multivariate logistic regression adjusting for total fluid administration, age, admission weight, APACHE III score on admission, and SOFA score. There was a statistically significant difference for the amount of fluid given within the first 3 h between survivors and nonsurvivors. 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; $P = .008$) (Table 4).

Discussion

In this retrospective cohort study of fluid resuscitation in patients with severe sepsis and septic shock, survivors were likely to receive a larger amount of fluid in the first 3 h than nonsurvivors from sepsis onset time. Nonsurvivors were older with higher APACHE III scores, indicating a greater burden of chronic illness. Nonsurvivors had more oliguria, more vasopressor use, worsened hypotension, and lower SOFA scores at the end of 6-h resuscitation. After multivariate adjustment, more fluid resuscitation within the first 3 h was associated with those who survived with severe sepsis and septic shock, even when adjusted for the total amount of fluid in the first 6 h.

This study was performed before the revised guidelines were published[24,25]; however, to our knowledge, the study is the first to show evidence supporting the new recommendation that initial fluid bolus should be increased from 20 to 30 mL/kg.[25] The importance of fluid resuscitation in the first hour has been recognized since the inception of sepsis as a definition and the knowledge of adequate tissue perfusion pressure.[26,27] Oliveira et al[28] found in children with septic shock who received a < 20 mL/kg dose of fluid in the first hour had a significantly higher mortality rate than those who received 40 mL/kg fluid (73% vs 33%, $P < .05$).

TABLE 2] Clinical Hemodynamic Outcomes

Variable	Nonsurvivors	Survivors	*P* Value
CVP in hour 6, cm H_2O	10 (5-16) (n = 88)	10 (5-14) (n = 279)	.52
MAP in hour 6, mm Hg	64.5 (59-72) (n = 142)	68.5 (62-77) (n = 452)	< .01[a]
$Scvo_2$ in hour 6	68.5 (61-78) (n = 75)	73 (68-78) (n = 252)	< .01[a]
Vasopressor use in first 24 h, %	76 (n = 108)	54 (n = 242)	< .01[a]
Oliguria in hour 6, %	71 (n = 101)	41 (n = 186)	< .01[a]
SOFA score day 1	8 (6-12) (n = 142)	6 (4-9) (n = 452)	< .01[a]

Data are presented as median (interquartile range) or % unless otherwise indicated. CVP = central venous pressure; MAP = mean arterial pressure; $Scvo_2$ = central venous oxygen saturation; SOFA = Sequential Organ Failure Assessment.
[a]$P < .05$.

TABLE 3] Secondary Outcomes

Outcome	Nonsurvivors (n = 142)	Survivors (n = 452)	*P* Value
ICU length of stay, d	4.6 (2.2-8.3)	2.1 (1.2-4.2)	<.001[a]
ICU-free days	2.8 (0-9.4)	6.1 (3.1-11.9)	<.001[a]
Hospital length of stay, d	9.16 (5.58-16.6)	9.55 (5.5-17.1)	.87

Data are presented as median (interquartile range).
[a]*P* < .05.

Ospina-Tascon et al[29] found that fluids improved sublingual microcirculation perfusion in the early (within 24 h of severe sepsis diagnosis) but not late phase (> 48 h after diagnosis) of sepsis. Furthermore, there is mounting evidence that late sepsis resuscitation results in harmful effects, such as increased mortality and worsening lung and renal function.[18,30-33]

Debate continues on how best to assess fluid status during resuscitation. CVP is widely used, but studies have shown that CVP poorly predicts a sustained and significant hemodynamic response to a fluid challenge as defined by an increase in cardiac output or MAP.[34,35] The present findings neither support nor contradict the use of CVP as a predictor for outcome because the goal of CVP was achieved in both survivors and nonsurvivors. This is in accordance with the recently published Protocol-Based Care for Early Septic Shock (ProCESS) trial, a randomized controlled trial in 31 EDs across the United States that assigned 1,341 patients to three groups of resuscitation methods.[36] The ProCESS investigators found no difference in mortality between usual-care resuscitation, which is bedside, physician-directed care, and the two protocolized methods studied, including EGDT with central venous catheter monitoring and a standardized protocol model that used adequate peripheral venous access for resuscitation with optional central venous access if peripheral access could not be obtained. The present findings support using $Scvo_2$,

TABLE 4] Multivariate Regression

Variable	OR (95% CI)	*P* Value
Proportion of fluid in first 3 h	0.34 (0.15-0.75)	.0076
Total fluid in 6 h	1.00 (1.00-1.00)	.0138
Age	1.02 (1.01-1.04)	.0050
Weight	1.00 (0.99-1.01)	.7008
Admission APACHE III score	1.00 (0.98-1.01)	.4670
SOFA score on day 1	1.20 (1.14-1.27)	<.0001[a]

See Table 1 and 2 legends for expansion of abbreviations.
[a]*P* < .05.

MAP, or both as surrogate hemodynamic markers for resuscitation.[24] Some nonsurvivors did not reach the goal $Scvo_2$ or MAP by the end of the sixth hour for EGDT, which was statistically significant. Oliguria was significantly more prevalent in the nonsurvivor group, further indicating that fluid resuscitation did not achieve adequate tissue perfusion and probably resulted in end-organ damage. Nonsurvivors had a larger fluid balance in hours 3.1 to 6 than survivors. Total fluid administration was not different between the two groups, which likely reflects the decreased urine output of the nonsurvivors (Table 2).

The ProCESS trial also measured hourly fluid volume administration, and the total volume of fluid given in the 6 h of initial resuscitation varied among the three groups (protocol-based standard therapy, 3.3 L; protocol-based EGDT, 2.8 L; usual care, 2.3 L; *P* < .0001).[36] The standard therapy group received the most fluid initially compared with the usual-care and EDGT groups, and the EGDT group received fluid at the most consistent rate (*P* = .007). The present study had similar inclusion criteria to the ProCESS trial; however, some key differences may account for the conclusions. In the ProCESS trial, fluid volume was tracked from the time of randomization into the study, which may have been up to 2 h after the sepsis onset time or time of initial shock. By then, subjects had already received 20 to 30 mL/kg fluid before randomization. Additionally, all three arms of the ProCESS trial received more fluid in the earlier part of the 6 h, with less fluid given over time. The earlier fluid resuscitation may account for the lack of outcome differences in the trial and may have contributed to the overall low 60-day in-hospital mortality rate of 19%.

Another retrospective cohort study found that there were more nonsurvivors than survivors with a higher fluid balance after 8 days and a trend with higher fluid balance in the first 24 h from septic shock onset.[37] The authors found an association between normal and slightly elevated left ventricular function in nonsurvivors, suggesting the presence of vasoplegia.[37] This study correlates with the present findings in that nonsurvivors

required more vasopressors and had worsened SOFA scores in the initial 24 h from sepsis onset time. It is possible that nonsurvivors exhibited multiorgan dysfunction and vasoplegia beyond EGDT and, therefore, received more fluid after initial resuscitation and throughout the following days, resulting in more total fluid after ≥ 24 h.

The major strengths in this study are the intentionally broad inclusion criteria to be sensitive in capturing the most patients with severe sepsis and septic shock and minimal loss of data due to use of ICU Datamart database, resulting in a large cohort. The 8.7% excluded because of data incompleteness was due to computer medical error. ED fluid resuscitation was included in the calculation of initial fluid bolus. Because laboratory and fluid data from the ED are integrated into the database with review of the electronic medical record, the sepsis onset time could be determined systematically and based on each patient's clinical parameters. The secondary outcome of survivors having more ICU-free days despite a similar number of overall hospitalization days has implications for health-care costs because higher costs are incurred in the ICU.[38] Further study on cost-effectiveness is warranted.

This study is limited in that the prehospital fluid resuscitation and fluid administration before progression to severe sepsis and septic shock may not be consistently reported and accounted for. Furthermore, we do not have an explanation documented in the charts for unachieved resuscitative goals in the nonsurvivor group at the end of the 6-h resuscitation. We conjecture that a predominate factor for unachieved goal resuscitation was lack of timely, adequate vascular access because there was missing CVP and $Scvo_2$ data, measurements that require a central venous catheter. It is possible that attempts were made to achieve venous access when a diagnosis of severe sepsis or septic shock was made; however, variability in patient anatomy and operator skill may have led to lack of timely central venous access, EGDT goal measurements, and resuscitation. Alternatively, nonsurvivors had higher APACHE III and SOFA scores than survivors, indicating a greater burden of critical illness, which may not have been reversible with resuscitation and antibiotic treatment. We incorporated APACHE III and SOFA scores into the multivariate logistic regression model, but unknown confounding factors and bias may not be fully accounted for by the measurements in the retrospective analysis. We also did not stratify the fluid amounts hour by hour because this would require a much larger study to achieve significant power. The data were limited to 3 years and collected before the current guidelines were published because it took several years to collect and validate the data against errors. It is unknown whether a maximum ceiling dose of fluid exists in sepsis resuscitation such that it becomes harmful with subsequent complications, such as brisk electrolyte shifting, ischemic-reperfusion injuries, abdominal compartment syndrome, cerebral edema, or other dangerous edematous states.[3,39-42] Furthermore, this is a single-center study at an academic quaternary center, so the results may not be generalizable to community-based and other models of ICU care. Finally, the study does not prove causality or reduction in mortality, limitations inherent to a retrospective analysis, and these will require prospective validation. The observed association may have been due to an unmeasured risk factor, thereby confounding results. However, the association was present in univariate and multivariate analyses. It is interesting to note that the two study groups (survivors and nonsurvivors) stratified by the end of the 6-h time frame of EGDT, which supports the notion that early intervention is key to prevent sustained organ damage and may set the course for the rest of the hospitalization. We hope that this article is hypothesis generating for future studies on the timing of fluid resuscitation in sepsis.

Conclusions

The purpose of this study is to aid intensivists in the management of fluid resuscitation in sepsis by focusing on the timing of administration. In this multivariate logistic regression analysis adjusting for the total amount of fluid given and severity of illnesses, survivors received more fluid resuscitation within the first 3 h after diagnosis of severe sepsis and septic shock than did nonsurvivors. To our knowledge, this study is the first of its kind to examine the timing of fluid resuscitation within an EGDT time frame for critically ill adults with severe sepsis and septic shock. The findings support the recently published guidelines recommendation of increasing the initial fluid bolus to 30 mL/kg for sepsis resuscitation.

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