Higher Fluids in the First Three Hours of Sepsis Resuscitation? Too Soon to Conclude

To the Editor:

It is with great interest that we read the retrospective study published by Lee et al1 in a recent issue of CHEST (October 2014) that showed a significant decrease in hospital mortality in patients who received early fluid resuscitation within the first 3 h of onset of severe sepsis or septic shock. However, some important points related to this study need to be addressed.

The authors used electronic medical records (EMRs) to identify patients with severe sepsis and septic shock. "Sepsis onset time" was determined by fluid-resistant hypotension, vasopressor use, or a lactate level > 4 mmol/L.1 The reliability and validity of the outcome data in EMR-based interventional studies depend on the accuracy of data collection, entry, and storage. A study conducted on the Veterans Administration's EMRs, a highly integrated and standardized EMR system, showed that 60% of the patients had one or more input-related errors, with an average of 7.8 errors per patient.2

The use of EMRs in observational studies is subject to selection bias and confounding.3 In the study by Lee et al,1 nonsurvivors were significantly older, had a higher severity of illness, and more organ dysfunction. Nonsurvivors also had lower net-positive fluid balance in the first 3 h of resuscitation. The authors suggested the unavailability of a central venous catheter as a possible explanation for underachieved resuscitation goals. However, the presence of certain medical conditions, such as congestive heart failure or chronic kidney disease, can also limit liberal fluid use. Patients with congestive heart failure and chronic kidney disease were not excluded in the study by Lee et al.1

Physicians may also limit aggressive care when presence of advanced medical illness or prior advance directives precludes this approach, thereby introducing treatment bias. In the recently published Protocolized Care for Early Septic Shock (ProCESS) trial, there were no outcome differences among the study groups despite receiving significantly different fluid volumes.4 In this randomized trial, patients with acute pulmonary edema, do-not-resuscitate status, or those deemed unsuitable for aggressive care were excluded.4

In a retrospective observational study, treatment selection bias can influence both the choice for a particular treatment and the outcome of interest. The confounding introduced by this type of bias cannot be adjusted with traditional logistic regression analyses.5 Adequate adjustment for treatment selection and confounding bias requires inclusion of variables that may be unknown or unavailable in a retrospective cohort. As appropriately indicated by Lee et al,1 their results need to be validated with a prospective study.

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FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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DOI: 10.1378/chest.14-1256

References
Response

To the Editor:

We thank Drs Adrish and Soto for their comments on our recent article in CHEST. We agree that electronic medical records, especially progress notes, are subject to human entry error. However, the data in the study were gathered in near real-time entry into the ICU Datamart database as hemodynamics were monitored and fluids were given by providers. Vital signs, laboratory findings, and medication administration are automatically captured and also validated by ICU nurses at hourly intervals. The study period was selected for completeness and accuracy of the data, which took several years to collect, recheck, and validate against any errors.

We agree that retrospective studies have limitations compared with prospective randomized controlled trials. The weaknesses of the observational study design have been outlined in the discussion of our article. It is possible that fluid was conservatively given to some patients per the individual clinician’s decision-making. However, it is unlikely that fluid was systematically withheld to a group of patients with select chronic conditions as that would be inconsistent with the institution’s sepsis resuscitation protocol. Furthermore, we incorporated into the logistic regression analysis age and APACHE (Acute Physiology and Chronic Health Evaluation) and Sequential Organ Failure Assessment (SOFA) scores to account for chronic medical conditions and severity of acute illness. Nevertheless, we cannot exclude potential bias resulting from unmeasured confounders.

In regard to the Protocolized Care for Early Septic Shock (ProCESS) trial, enrollment into the study occurred within (or up to) 2 h of sepsis recognition and within (or up to) 12 h after ED admission. By the time of enrollment into the study, patients had already received 2.2 L or about 29 mL/kg (30.5 ± 22.3 in early goal-directed therapy, 29.2 ± 19.1 in protocol, and 28 ± 21 in usual care group). Given that all three groups initially received similar amounts of fluids early in their resuscitation (prior to randomization), ProCESS trial results do not necessarily seem to refute our findings.

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FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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DOI: 10.1378/chest.14-1712

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