7-24-2014

Correspondence: Protocol-Based Care for Early Septic Shock

Hans-Joachim Priebe
*University of Freiburg, Germany*

Angel Coz-Yataco
*University of Kentucky, angel.coz@uky.edu*

Stephen Trzeciak
*Cooper University Hospital*

Antonio J. Dajer
*New York Presbyterian-Lower Manhattan Hospital*

Derek C. Angus
*University of Pittsburgh*

*See next page for additional authors*

Click here to let us know how access to this document benefits you.

Follow this and additional works at: [https://uknowledge.uky.edu/internalmedicine_facpub](https://uknowledge.uky.edu/internalmedicine_facpub)

Part of the [Medicine and Health Sciences Commons](https://uknowledge.uky.edu/internalmedicine_facpub/66)

Repository Citation

Priebe, Hans-Joachim; Coz-Yataco, Angel; Trzeciak, Stephen; Dajer, Antonio J.; Angus, Derek C.; Yealy, Donald M.; Kellum, John A.; and Lilly, Craig M., "Correspondence: Protocol-Based Care for Early Septic Shock" (2014). *Internal Medicine Faculty Publications*. 66. [https://uknowledge.uky.edu/internalmedicine_facpub/66](https://uknowledge.uky.edu/internalmedicine_facpub/66)

This Letter to the Editor is brought to you for free and open access by the Internal Medicine at UKnowledge. It has been accepted for inclusion in Internal Medicine Faculty Publications by an authorized administrator of UKnowledge. For more information, please contact UKnowledge@lsv.uky.edu.
Authors
Hans-Joachim Priebe, Angel Coz-Yataco, Stephen Trzeciak, Antonio J. Dajer, Derek C. Angus, Donald M. Yealy, John A. Kellum, and Craig M. Lilly

Correspondence: Protocol-Based Care for Early Septic Shock

Notes/Citation Information
Published in New England Journal of Medicine, v. 371, no. 4, p. 384-387.


Digital Object Identifier (DOI)
http://dx.doi.org/10.1056/NEJMc1406745

This letter to the editor is available at UKnowledge: https://uknowledge.uky.edu/internalmedicine_facpub/66
Protocol-Based Care for Early Septic Shock

TO THE EDITOR: In the Protocolized Care for Early Septic Shock (ProCESS) study (May 1 issue),\(^1\) the investigators report that protocol-based early goal-directed therapy (EGDT) did not improve the outcome in patients with septic shock. Since fluid therapy is an essential component of EGDT, it would be useful to know what types of fluid were administered. During the first 72 hours of care, patients received about 6.5 liters of intravenous fluids, and there was a mean increase in the serum chloride level from 100 mmol per liter to between 106 and 108 mmol per liter. In a recent study,\(^2\) a similar increase in the serum chloride level from 103 to 108.5 mmol per liter 60 minutes after the infusion of 2 liters of 0.9% sodium chloride in healthy participants was associated with a 40% decrease in renal blood-flow velocity (as measured in centimeters per second) and the perfusion of renal cortical tissue. Additional evidence supports the adverse renal effects of hyperchloremia.\(^2-5\) Since such adverse effects might have modified the findings, and since the administration of large amounts of hyperchloremic 0.9% sodium chloride is the probable cause of the reported hyperchloremia, can the authors provide information on the types of fluid that were administered?

Hans-Joachim Priebe, M.D.
University of Freiburg
Freiburg, Germany
hans-joachim.priebe@uniklinik-freiburg.de

No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMc1406745

TO THE EDITOR: In the ProCESS study, all three study groups had an improvement in the rate of death (ranging from 17 to 19 percentage points), as compared with values predicted by their score on the Acute Physiology and Chronic Health Evaluation (APACHE) II, which shows that protocolized care does work. As compared with the patients in the Early Goal-Directed Therapy study,\(^1\) the patients in the ProCESS study had a lower severity of illness because the initial lactate values were lower and the inclusion criteria included a 1-liter fluid bolus instead of 20 to 30 ml per kilogram of body weight.\(^2\) The majority of the study sites had preexisting sepsis programs that were influenced by the Surviving Sepsis Campaign, as shown by the rate of early central-catheter placement of 57% in the usual-care group, a procedure that has been associated with a 10% reduction in mortality.\(^1\) Even the delayed introduction of monitoring of central venous pressure and central venous oxygen saturation after the 6-hour avoidance period can still give rise to improved outcomes.\(^4\) Moreover, the high
likelihood that the usual-care group received pre-existing protocol-driven care, as outlined in the Surviving Sepsis Campaign, could explain the low mortality and small between-group differences (Table 1). Does it make sense to change a historically successful protocol that has improved patient outcomes? The recent continued endorsement of EGDT by the Surviving Sepsis Campaign supports the status quo.5

Angel Coz Yataco, M.D.
University of Kentucky
Lexington, KY
angel.coz@uky.edu

No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMc1406745

Table 1. Differences in Mortality and Key Clinical Values in the EGDT Study and the ProCESS Study.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>EGDT Study</th>
<th>Control Group</th>
<th>EGDT Group</th>
<th>Protocol-Based Standard-Therapy Group</th>
<th>Usual-Care Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted mortality on the basis of APACHE II score (%)</td>
<td>40.3</td>
<td>36.9</td>
<td>38.2</td>
<td>37.5</td>
<td>37.9</td>
</tr>
<tr>
<td>Actual mortality (%)</td>
<td>30.5</td>
<td>46.5</td>
<td>21.0</td>
<td>18.2</td>
<td>18.9</td>
</tr>
<tr>
<td>Lactate (mmol/liter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 0 hr</td>
<td>7.7</td>
<td>6.9</td>
<td>4.8</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>At 6 hr</td>
<td>4.3</td>
<td>4.9</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Central venous oxygen saturation (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 0 hr</td>
<td>48.6</td>
<td>49.2</td>
<td>71.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>At 6 hr</td>
<td>77.3</td>
<td>66.0</td>
<td>NR</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Central-catheter rate at 6 hr (%)</td>
<td>100</td>
<td>100</td>
<td>93.6</td>
<td>56.5</td>
<td>57.9</td>
</tr>
</tbody>
</table>

* APACHE denotes Acute Physiology and Chronic Health Evaluation, NA not applicable, and NR not reported.

TO THE EDITOR: Although it is indeed good news that advances in the field have decreased short-term sepsis-related mortality over time since the original report of EGDT,1,2 and that this lower mortality may have influenced the ProCESS trial results to some extent, it is important to recognize that only half the patients in the ProCESS population were able to be discharged home from the hospital, and the 1-year mortality appears to be nearly double the short-term mortality. Other recent studies have found similar discordance. As highlighted in the Journal,3 chronic critical illness (i.e., critically ill in patients who neither die in the acute phase nor recover) is an emerging public health problem that is both created and sustained by advances in critical care medicine. How many patients in the ProCESS study received the diagnosis of chronic critical illness? And should the primary outcome in sepsis trials incorporate the occurrence of chronic critical illness as a “poor” outcome?

Stephen Trzeciak, M.D., M.P.H.
Cooper University Hospital
Camden, NJ
trzeciak-stephen@cooperhealth.edu

No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMc1406745
TO THE EDITOR: The ProCESS trial represents a little-understood paradigm shift. Twenty years ago, when I began practicing emergency medicine, the administration of antibiotics without an identified source of infection violated accepted practice. We can quibble over monitoring of central venous pressure and lactate clearance. The critical change, though, is that in this “new era,” as described in the editorial accompanying the article on the ProCESS trial, we are urged to treat sepsis quickly on clinical evidence rather than on delayed bacteriologic evidence.

Antonio J. Dajer, M.D.
New York Presbyterian–Lower Manhattan Hospital
New York, NY
tonydajer@aol.com
No potential conflict of interest relevant to this letter was reported.

DOI: 10.1056/NEJMc1406745

THE AUTHORS REPLY: We agree with Priebe that saline can cause hyperchloremia and acidosis. In our study, we did not evaluate different fluid formulations. Saline comprised 93% of intravenous fluids (range, 92 to 96% in the three study groups) during the first 6 hours and 83% (range, 80 to 86%) from 6 hours to 72 hours, which we consider within the scope of usual U.S. practice.1 We also agree with Dajer regarding the importance of the early use of antibiotics in patients who appear to be sick and infected, such as patients enrolled in our study, although use of these drugs in less sick patients may enhance antibiotic resistance.

Modern studies typically report outcomes better than those predicted by the APACHE II score, presumably because of the many advances in care since the original APACHE II calibration 30 years ago.2 Coz Yataco notes that our cohort had some features that suggested a lower severity of illness than that in the study by Rivers et al.3 However, in our reported subgroup analyses, the sickest third of patients on the basis of lactate levels or APACHE II scores, who were sicker than patients in the cohort study by Rivers et al., showed no benefit from EGDT. Thus, we do not believe that differences in severity of illness explain the differences in results between the two trials.

We disagree that central-catheter use in 57% of patients in the control group is evidence that sites all followed the EGDT-based resuscitation guidelines of the Surviving Sepsis Campaign. Central-catheter use is extremely common, especially for patients admitted to the intensive care unit. Furthermore, as we reported, only 3.5% and 4.0% of patients in the two control groups underwent monitoring of central venous oxygen saturation,1 a prerequisite for EGDT. Coz Yataco suggests that the resuscitation bundle that is recommended by the Surviving Sepsis Campaign should remain intact because observational studies report good outcomes. We contend that clinical guidelines should be modified as robust data emerge from randomized trials, and the Surviving Sepsis Campaign bundles have undergone numerous changes in the past on the basis of just such a process.4

We agree with Trzcinski that enthusiasm for the decline in hospital mortality from sepsis must be tempered by concern that many patients who are discharged may die in the following months, as we reported, or suffer protracted sequelae. That said, in our study, only 45 of 1341 patients (3.4%) were still undergoing mechanical ventilation at the time of discharge. We agree that assessing outcomes beyond short-term mortality are key considerations for future sepsis trials.

Derek C. Angus, M.D., M.P.H.
Donald M. Yealy, M.D.
John A. Kellum, M.D.
University of Pittsburgh
Pittsburgh, PA
angusdc@upmc.edu

for the ProCESS Investigators

Since publication of their article, the authors report no further potential conflict of interest.

DOI: 10.1056/NEJMc1406745

THE EDITORIALIST REPLIES: Dajer astutely points out that the one key element that the ProCESS trial procedures shared with those in the preceding EGDT trial was that antimicrobials were administered within the first 2 hours after sepsis was identified in circulatory failure. The practice
of deferring antimicrobial therapy in favor of a prolonged search or unassailable evidence of the source of the infection has been difficult to justify given studies in patients with septic shock that documented mortality benefits from the administration of antimicrobials to which the pathogenic organism was sensitive,^2^ better outcomes with combination therapy as compared with monotherapy therapy,^3^ and particularly the realization that each hour that antimicrobial therapy is deferred has been associated with a 7.6% decrease in survival for patients with septic shock.\(^4\) The training we received to identify the source of any serious infection is as valid today as it was when it was first brought to our attention; what has changed is the amount of time allotted for performing investigations before starting antibiotic therapy.

**Case 9-2014: A Woman with Increasing Dyspnea**

**TO THE EDITOR:** Saukkonen et al. (March 20 issue)\(^1\) describe a 34-year-old woman with severe pulmonary hypertension and Raynaud’s phenomenon due to mixed connective-tissue disease. However, the authors never identified the cause of severe systemic hypertension (which is not typically seen in mixed connective-tissue disease) in this patient. Particularly in light of her autoimmune disease, I wonder whether she was tested for the antiphospholipid syndrome. In one of his early descriptions of this syndrome in 1984, Hughes reported labile hypertension, often with associated livedo reticularis, Raynaud’s phenomenon, or both.\(^2\) Indeed, since then, hypertension — often severe — has been observed in as many as 40 to 50% of patients with primary antiphospholipid syndrome. Hypertension in this syndrome is most often renovascular in origin, including not only thrombosis or focal arterial stenosis of the renal artery, but also intrarenal thrombotic microangiopathy (antiphospholipid syndrome nephropathy), and severe hypertension may be the initial manifestation of the antiphospholipid syndrome in these patients.\(^3\) Hypertension in this syndrome may also occur as a result of an associated autonomic disorder (e.g., hyperadrenergic postural tachycardia syndrome), and these patients also often have livedo reticularis, Raynaud’s phenomenon, or both.\(^4\)

Craig M. Lilly, M.D.
University of Massachusetts Medical School
Worcester, MA
craig.lilly@umassmed.edu

Since publication of his article, the author reports no further potential conflict of interest.


DOI: 10.1056/NEJMc1406745

**TO THE EDITOR:** We would like to raise two issues with regard to the Case Record by Saukkonen et al. First, pulmonary veno-occlusive disease should be considered in the differential diagnosis of pulmonary arterial hypertension associated with connective-tissue diseases. Pulmonary arterial hypertension and pulmonary veno-occlusive disease share predisposing conditions and clinical and hemodynamic features. The exclusion of pulmonary veno-occlusive disease is crucial, since patients with pulmonary veno-occlusive disease, besides having a worse prognosis, may...