

## CORRESPONDENCE



## Protocol-Based Care for Early Septic Shock

**TO THE EDITOR:** In the Protocolized Care for Early Septic Shock (ProCESS) study (May 1 issue),<sup>1</sup> 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,<sup>2</sup> 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.<sup>2-5</sup> 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?

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

1. The ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014;370:1683-93.
2. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and Plasma-Lyte 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg* 2012;256:18-24. [Erratum, *Ann Surg* 2013;258:1119.]
3. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. *Clin Sci (Lond)* 2003;104:17-24.
4. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012;308:1566-72.
5. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Ann Surg* 2012;255:821-9.

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,<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> Moreover, the high

### THIS WEEK'S LETTERS

- 384 **Protocol-Based Care for Early Septic Shock**
- 387 **A Woman with Increasing Dyspnea**
- 389 **A Randomized Trial of Robot-Assisted Laparoscopic Radical Cystectomy**

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

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

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

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.<sup>5</sup>

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

1. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
2. Mikkelsen ME, Miltiades AN, Gaieski DE, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med* 2009;37:1670-7.
3. Walkey AJ, Wiener RS, Lindenauer PK. Utilization patterns and outcomes associated with central venous catheter in septic shock: a population-based study. *Crit Care Med* 2013;41:1450-7.
4. Castellanos-Ortega A, Suberviola B, García-Astudillo LA, Ortiz F, Llorca J, Delgado-Rodríguez M. Late compliance with the sepsis resuscitation bundle: impact on mortality. *Shock* 2011;36:542-7.
5. Surviving Sepsis Campaign. Surviving Sepsis Campaign responds to ProCESS trial. Updated May 19, 2014 (<http://www.survivingsepsis.org/SiteCollectionDocuments/SSC-Responds-Process-Trial.pdf>).

DOI: 10.1056/NEJMc1406745

**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,<sup>1,2</sup> 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*,<sup>3</sup> chronic critical illness (i.e., critically illness 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?

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

1. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
2. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA* 2014;311:1308-16.
3. Lamas D. Chronic critical illness. *N Engl J Med* 2014;370:175-7.

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,<sup>1</sup> we are urged to treat sepsis quickly on clinical evidence rather than on delayed bacteriologic evidence.

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

1. Lilly CM. The ProCESS trial — a new era of sepsis management. *N Engl J Med* 2014;370:1750-1.

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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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,<sup>1</sup> 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.<sup>4</sup>

We agree with Trzeciak 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.

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

1. Jones D, McEvoy S, Merz TM, et al. International albumin use: 1995 to 2006. *Anaesth Intensive Care* 2010;38:266-73.

2. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818-29.

3. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.

4. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.

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<sup>1</sup> 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,<sup>2</sup> better outcomes with combination therapy as compared with monotherapy therapy,<sup>3</sup> 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.<sup>4</sup> 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.

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

1. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
2. Kumar A, Ellis P, Arabi Y, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest* 2009;136:1237-48.
3. Kumar A, Zarychanski R, Light B, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. *Crit Care Med* 2010;38:1773-85.
4. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;34:1589-96.

DOI: 10.1056/NEJMc1406745

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

**TO THE EDITOR:** Saukkonen et al. (March 20 issue)<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup>

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

1. Case Records of the Massachusetts General Hospital (Case 9-2014). *N Engl J Med* 2014;370:1149-57.
2. Hughes GRV. The Prosser-White oration 1983: connective tissue disease and the skin. *Clin Exp Dermatol* 1984;9:535-44.
3. Karim MY, Alba P, Tungekar ME, et al. Hypertension as the presenting feature of the antiphospholipid syndrome. *Lupus* 2002;11:253-6.
4. Schofield JR, Blitshteyn S, Shoenfeld Y, Hughes GRV. Postural tachycardia syndrome (POTS) and other autonomic disorders in antiphospholipid (Hughes) syndrome (APS). *Lupus* 2014; 23:697-702.

DOI: 10.1056/NEJMc1404715

**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