



Progression in optimal sepsis care: the sooner, the better?

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Provenance: This is a Guest Editorial commissioned by Executive Editor Zhongheng Zhang, MD, MM (Department of Emergency Medicine, Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China).

Comment on: Seymour CW, Gesten F, Prescott HC, *et al.* Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. *N Engl J Med* 2017;376:2235-44.

Received: 25 July 2017; Accepted: 27 July 2017; Published: 11 August 2017.

doi: 10.21037/jeccm.2017.08.01

View this article at: <http://dx.doi.org/10.21037/jeccm.2017.08.01>

After the landmark study of Rivers *et al.* (1) proposed the concept of the “golden hour” in the management of severe sepsis and septic shock, early goal-directed therapy (EGDT) became the practice in emergency departments (EDs). EGDT includes the early detection of sepsis, early obtainment of blood culture and administration of broad spectrum antibiotics, risk stratification using lactate measurement and fluid challenge for hypotensive patients, and hemodynamic optimization guided by pre-determined targets for preload (central venous pressure), afterload (mean arterial pressure), and finding a balance between oxygen delivery and oxygen consumption reflected by central venous oxygen saturation. However, three recent large studies, ProCESS (Protocolized Care for Early Septic Shock), ARISE (Australasian Resuscitation in Sepsis Evaluation), and ProMISe (Protocolized Management in Sepsis) have challenged the benefits of this approach to improving survival in severe sepsis (2). Although there have been concerns about protocolized therapy, recent guidelines still recommend the prompt identification of sepsis and treatment with broad-spectrum antibiotic agents and intravenous fluids (3). However, considerable controversy exists over how rapidly sepsis must be treated.

Hospitals in New York are required to adopt, implement, and update evidence-based protocols for the early diagnosis and treatment of sepsis (Rory’s Regulations) due to the occurrence of the preventable death of a 12-year old boy caused by sepsis in 2012 (4). These protocols must

include processes for the early recognition of patients with sepsis, guidelines for hemodynamic support, and the early administration of antibiotics. In a recent issue of *New England Journal of Medicine*, the results of a study of the relation of time to the completion of sepsis bundle with mortality during mandated (law-driven) care for sepsis have been published (5). The authors examined data from 49,331 patients seen at 149 EDs from April 2014 to June 2016. The median time to complete the 3-hour bundle was 1.30 h, the median time to administer broad-spectrum antibiotics was 0.95 h, and the median time to complete the initial fluid bolus (30 cc/kg) was 2.56 h. They also found that each hour required to complete the 3-hour bundle [odds ratio (OR) 1.04/hour (95% CI: 1.02–1.05)], time to administration of broad spectrum antibiotics, time to completion of blood cultures, and time to obtain serum lactate were associated with a statistically significant increase in mortality (OR 1.04/hour, 95% CI: 1.03–1.06; OR 1.04/hour, 95% CI: 1.02–1.06; OR 1.04/hour, 95% CI: 1.02–1.06, respectively, all $P < 0.001$). However, this association was not demonstrated when the time to completion of a fluid bolus was examined in isolation (OR 1.01/hour, 95% CI: 0.99–1.02, $P = 0.21$). It is meaningful to demonstrate the fact that the timing of treatment during the resuscitative phase is a major determinant for the survival outcome for other time-sensitive diseases, such as acute myocardial infarction (“time is muscle”) and acute stroke (“time is brain”). The authors found a relationship between more rapid

administration of antibiotics and lowering risk-adjusted in-hospital mortality. This is a well-done retrospective study with a large sample size and the result is consistent with a study of the importance of the early administration of antibiotics in patients with sepsis and septic shock, which found that hour-long delays in antibiotic administration were associated with increased odds of hospital mortality (6). We do not think anyone would argue “the sooner the better” is inevitable for the early management of patients with severe sepsis or septic shock in EDs. However, “minutes matter” is to be interpreted with caution. The authors found that failure to complete the 3-hour bundle increased mortality in a statistically significant fashion. The OR was 1.04, which means the difference in mortality between the bundle completed in 3 and 3–12 h was very little (22.6% *vs.* 23.6%). In fact, one could argue that when applied, its implication will be unhelpful clinically, because of its small improvements in mortality and the potential resulting harm to other patients in ED, which are already overburdened. The effort to identify patients with severe sepsis or septic shock may be more valuable than the effort to finish the 3-hour bundle sooner. In addition, this study showed an overall 82.5% compliance rate for the 3-hour bundle, despite only half the hospitals included in this study performing above a 75% compliance rate for the 3-hour bundle. A multicenter quality improvement study showed that an increased compliance rate for sepsis bundles was associated with a substantial reduction of in-hospital mortality, and compliance with the early resuscitation bundle predicted ineligibility for later resuscitation and elements of the maintenance bundle through decreasing progression to more severe disease (7). However, data from the New York State Department of Health showed that compliance with the 3-hour bundle increased from 41.5% to 55.2% among adult sepsis patients, while mortality fell from 30.2% to 25.4% in adult sepsis in this study area over 2 years (8). It may not be possible to attribute this result to mandated sepsis care, if the trend of decreasing mortality of sepsis throughout the United States is considered, and the causal inference for mandated sepsis care will require further study (8).

This study failed to show a survival benefit of time for the completion of the initial fluid bolus. We agree with the authors, who state in the discussion that this result should not be used to support opinions to abandon early aggressive fluid resuscitation (fluid bolus) in the management of sepsis-induced hypoperfusion. We further consider that this result should be interpreted with caution. The fluid bolus

could be defined as a defined volume of a defined fluid administered over a defined time period (9). In this study, the volume of the fluid bolus (30 mL/kg per kilogram of body weight) was described but the specific uniform manner of the fluid bolus, such as whether it was a continuous or intermittent bolus and its end point, were not specified. Thus, the practice of fluid bolus therapy could differ by hospital or even by treating physician. These factors could influence the end time for the fluid bolus. In addition, more hypotensive patients tend to have their fluid bolus reception started and completed earlier (10). The initiation and termination of fluid bolus could be slower in patients with co-morbidity (heart failure, renal failure). The end of the fluid bolus might be delayed in fluid-responsive patients to less than 30 mL/kg of fluid for those whose cases are less severe. This unmeasured treatment selection bias might not entirely be removed by logistic regression (11). Moreover, the agreement of the data for the fluid bolus completion in the sample of the audit database is 75.2%, which is the lowest value among bundle elements. There may be a difficulty in reliably capturing the intravenous fluid completion time (12). Receiving fluid resuscitation within 30 min of identification of severe sepsis and septic shock for patients in EDs was associated with lower mortality and hospital length of stay, and these patients were likely to receive full resuscitation volumes earlier than the current 3-hour recommendation (13). This study suggested that the initiation time of resuscitation fluid may be an appropriate alternative for completion time in guiding the management of severe sepsis and septic shock. All together, fluid therapy is a cornerstone therapy in the early management of severe sepsis or septic shock; it remains reasonable that the initial fluid bolus should be started as soon as possible at shock recognition, although the optimal amount and type of initial fluid are under debate.

As evidence that speedy completion of the 3-hour sepsis bundle and antibiotic administration are associated with decreased mortality in patients with severe sepsis and septic shock stacks up, the use of strategy of “the sooner, the better” has become evident to improve sepsis survival. However, there remains considerable controversy over how rapidly sepsis must be treated, and this has created unintended side effects, such as over-diagnosis of sepsis and inappropriate use of antibiotics in busy EDs. Therefore, faster bundle completion should have the flexibility to be adopted depend on the situation of the hospital, and the rate of early recognition and completion of the sepsis bundle within 3 hours must be improved to increase survival in sepsis patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/jeccm.2017.08.01

Cite this article as: Yoon JC, Kim WY. Progression in optimal sepsis care: the sooner, the better? *J Emerg Crit Care Med* 2017;1:14.