Editorial

Mandated emergency care for sepsis: faster might not always be (much) better

Kanwar Sudhir Lather, Win Sen Kuan

Emergency Medicine Department, National University Hospital, National University Health System, Singapore

Correspondence to: Win Sen Kuan. Emergency Medicine Department, National University Hospital, National University Health System, Singapore. Email: win_sen_kuan@nuhs.edu.sg.

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: 21 July 2017; Accepted: 26 July 2017; Published: 11 August 2017.

doi: 10.21037/jeccm.2017.07.03

View this article at: http://dx.doi.org/10.21037/jeccm.2017.07.03

The concept of early goal-directed therapy (EGDT) was originally pioneered by the seminal work of Rivers and colleagues published in 2001. It was a single-center, randomized, controlled trial of EGDT versus usual care in patients presenting with septic shock to an urban emergency department in the United States (1). EGDT was defined as a 6-hour resuscitation protocol for the administration of intravenous fluids, vasopressors, inotropes, and transfusion of red cells to reach prespecified targets for mean arterial blood pressure, central venous pressure, central venous oxygen saturation, and hemoglobin level. In the original study, EGDT achieved 16% reduction in absolute risk of hospital mortality from 46.5% to 30.5%, thus prompting a worldwide rethink in the management of sepsis—emphasizing the need for aggressively seeking, recognizing, and treating severe sepsis. The era of EGDT had commenced.

Shortly afterwards, the Surviving Sepsis Campaign (SSC) was launched, where a consensus group of international experts convened and first published a set of guidelines in 2004 for the care of patients with sepsis. The guidelines recommended a protocolized quantitative resuscitation incorporating some principles from EGDT and introduced the concept of sepsis resuscitation bundles that aimed to simplify the care of patients with severe sepsis and septic shock (2). The SSC guidelines have since been updated thrice in 2008, 2012 and 2016 in keeping with the burgeoning evidence in this field.

The almost decade and a half following the introduction of the concept of EGDT and publication of the first SSC guidelines, the attempts at the clinical care end have been to verify the validity of the components of the original 6-hour bundle; predominantly through observational studies (3,4). Meanwhile, the public health community has focused on the applicability of the sepsis care bundles at the state and national levels (5).

Recently, more than a decade after the original landmark paper, three large multicenter randomized trials have looked into a comparison of EGDT versus usual care or standard therapy (6-8). All 3 trials failed to show mortality reduction in the EGDT arm. However, there were concerns regarding the methodology and inclusion criteria used in the trials, specifically the time from emergency department presentation "time zero" to time to randomization of patients (from 2.5 hours to just over 3 hours); and volume of crystalloids administered prior to randomization (30 mL/kg in the ProCESS and ARISE trials, and approximately 2 liters in the ProMISe trial).

In the domain of health policy, sepsis performance improvement programs have been associated with better patient outcomes. A meta-analysis of 50 observational studies demonstrated that performance improvement programs were associated with significant increase in compliance with the SSC resuscitation bundles and reduction in mortality [odds ratio (OR) 0.66; 95% confidence interval (CI), 0.61–0.72] (9). The largest study to date examined the relationship between compliance with the SSC resuscitation bundles (based on the 2004

guidelines) and mortality. A total of 29,470 patients in 218 hospitals in the United States, Europe and South America were examined over a 7.5-year period (10). Lower mortality was observed in hospitals with higher compliance. Overall hospital mortality decreased 0.7% for every 3 months a hospital participated in the SSC, associated with a 4% decreased length of stay for every 10% improvement in compliance with bundles. Similar results have been observed following mandating the use of specific guideline-based clinical practices as part of state sepsis mandates. One such initiative is a set of New York State regulations implemented in 2013 and collectively known as "Rory's Regulations" (New York Codes, Rules, and Regulations parts 405.2 and 405.4), named after Rory Staunton, who died at 12 years of age from sepsis resulting from a soft-tissue infection. Rory's Regulations mandate that all hospitals in the state use evidence-based protocols for sepsis identification and management, and that they report to the state government data on their sepsis protocol adherence and clinical outcomes.

Data from the above-mentioned New York State Department of Health sepsis database was analyzed, and the results reported by Seymour and colleagues (11). This study published in May 2017 reviewed retrospective data for 49,331 patients who presented with sepsis or septic shock to 149 hospitals in New York, from April 1, 2014, to June 30, 2016. Investigators evaluated the association between in-hospital mortality and time to completion of the 3-hour sepsis bundle (obtaining of blood culture before the administration of antibiotics, measurement of the serum lactate level, and administration of broad-spectrum antibiotics), time to administration of these antibiotics, and time to completion of the initial intravenous fluid bolus. They sought to address the issue of whether more rapid treatment in sepsis improves outcomes in patients.

Time-to-intervention studies are aplenty in medicine; the most widely-mentioned being door-to-balloon time in acute myocardial infarction (12) and door-to-needle time in acute ischemic stroke (13). The most famous example in sepsis is the retrospective cohort time-to-antibiotics in septic shock study published in 2006 that showed an average decrease in survival of 7.6% per hour delay in antibiotics administration from onset of documented hypotension up to 6 hours (14). A subsequent publication in 2014 using a larger dataset collected prospectively as part of the SSC, albeit with inclusion of patients with severe sepsis, had a similar conclusion though not to such a dramatic effect (15).

Seymour and colleagues found that the 3-hour bundle was completed on time for 83% of patients, with a median time to completion of 1.3 [interquartile range (IQR) 0.65 to 2.35] hours. Each additional hour until completion was associated with increased mortality (OR 1.04 per hour; 95% CI, 1.02–1.05). The median time to antibiotic completion was 0.95 (IQR 0.35 to 1.95) hours and each hour delay was also associated with increased mortality (OR 1.04 per hour; 95% CI, 1.03–1.06), which is in congruence with previous studies though with markedly smaller effect size. Finally, the median time to intravenous fluid bolus completion was 2.56 (IQR 1.33 to 4.20) hours, but delay was not associated with increased mortality.

While this was a well-conducted analysis and the results likely represent the importance of early administration of antibiotics in patients with sepsis and septic shock, the fact remains that this is a retrospective analysis and we simply cannot determine the causative effect of timely completion of the 3-hour bundle. Examination of the crude inpatient mortality between the patients who had the 3-hour bundle completed in less than 3 hours compared to those in whom it was completed between 3 and 12 hours showed very little difference (22.6% versus 23.6%, P=0.05). In addition, the authors did not enroll all patients with sepsis, but rather examined the subset of patients with severe sepsis or septic shock as per the Sepsis-2 criteria (16). One could argue that the small improvements in mortality with early aggressive care would vanish when we examine the less critically ill subset of this cohort. The odds ratio for inpatient mortality, when the patients requiring vasopressors are excluded from the analysis, was 1.02 per hour (95% CI, 1.00–1.03). A suggested takeaway of the study's results would be: 1–2 hourly delays in the completion of the bundles matter, ever so slightly, in particular subsets of patients.

Though few would argue that timely administration of broad spectrum antibiotics and aggressive fluid resuscitation are both vital to the management of patients presenting to the emergency department with sepsis or septic shock, the outcome that stands out from this study is the seeming absence of mortality benefit from aggressive hydration with 30ml/kg for all the patients included in the study. As the authors rightly point out, these data should not be interpreted as evidence in favor of abandoning early fluid resuscitation. The analysis of the time to completion of the initial fluid bolus is most prone to confounding by indication; sicker patients will receive fluids sooner and are also more likely to die. Furthermore, the volume of recommended fluid (30 mL/kg) in the bundle has been a subject of great controversy and criticism (17). Also, a

greater volume of fluids given at rapid pace may contribute to adverse effects such as pulmonary edema, volume overload and longer duration of organ support in selected patients (18). Especially relevant to the population of this study were over 20% and 10% with past medical history of congestive heart failure and end-stage renal disease, respectively. This emphasizes the need for bedside means of fluid status evaluation, such as bedside cardiovascular ultrasound and dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge (19,20). Causal inference will require investigation in randomized clinical trials, and the current study contributes to the clinical equipoise needed for such trials.

Though the true burden of disease arising from sepsis remains unknown, the current estimates of 30 million episodes and 6 million deaths per year come from a systematic review that extrapolated from published national or local population estimates to the global population (21). The estimate is based on data on hospital-treated sepsis in high income countries. There is high likelihood that the result was a significant underestimate as no data was available from the low- and middle-income countries where 87% of the world's population resides. The epidemic scale of numbers has prompted the World Health Assembly, the World Health Organization's decision making body, to recently adopt a resolution suggesting recommended actions for reducing the global burden of sepsis (22). Among others, these recommendations urge member states to develop national policy and processes to improve the prevention, diagnosis, and treatment of sepsis; develop and implement measures to recognize and manage sepsis as a core part of national and international health emergency response plans.

With the push from the World Health Organization towards state healthcare system led evidence-based protocols for sepsis identification and management, and the need to meet predetermined outcome 'targets', state sepsis mandates like "Rory's Regulations" are a discussion many healthcare systems will likely have to deal with in the very near future.

Studies similar to Seymour and colleagues will be analyzed to justify and decide upon the wider implementation of sepsis mandates on emergency departments. The implications of such policies could prove to be immensely cumbersome for emergency departments already dealing with increasing patient numbers and overcrowding (23). The decision to proceed with state mandated sepsis care needs to be gradual, nuanced and with maximal in-built flexibility to ensure that departments and hospitals can tailor care to patient needs and respond nimbly to changes in evidence.

Acknowledgements

None.

Footnote

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

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doi: 10.21037/jeccm.2017.07.03
Cite this article as: Lather KS, Kuan WS. Mandated emergency care for sepsis: faster might not always be (much) better. J Emerg Crit Care Med 2017;1:15.

