Editorial

In sepsis, beyond adherence, timeliness matters

Voon Shiong Ronnie Tan, Jason Phua, Tow Keang Lim

Division of Respiratory & Critical Care Medicine, University Medicine Cluster, National University Health System, Singapore

Correspondence to: Professor Tow Keang Lim. Division of Respiratory & Critical Care Medicine, University Medicine Cluster, National University Health System, NUHS Tower Block Level 10, 1E Kent Ridge Road, Singapore 119228. Email: mdclimtk@nus.edu.sg.

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Sepsis is a major healthcare concern, and remains a leading cause of mortality and critical illness worldwide (1). The global healthcare burden is astronomical; in the largest systematic review that extrapolated data from published national and local population estimates, an estimated 50 million cases and 3 million deaths are associated with sepsis yearly (2). In addition, sepsis is also associated with significant long-term cognitive and functional disability in survivors (3). Recognizing the disease importance and burden, the World Health Assembly, the World Health Organization's decision-making body, adopted a resolution on improving the prevention, diagnosis and management of sepsis recently on 26th May 2017 (4).

In the fight against sepsis, the Surviving Sepsis Campaign (SSC) was initiated in 2002 to promote the adoption of evidence-based performance measures, with the latest guidelines published in 2016 (5). With the publication of 3 landmark studies, namely, ProCESS, ARISE and ProMISe (6-8), the SSC bundles have been updated (9). These include the measurement of serum lactate, obtaining blood cultures prior to the administration of antibiotics, administration of broad spectrum antibiotics and 30 mL/kg crystalloid intravenously for hypotension or lactate ≥4 mmol/L within 3 hours of time of presentation. The SSC bundles also recommend, within 6 hours of presentation, the use of vasopressors to maintain a mean arterial pressure ≥65 mmHg, frequent re-assessment of volume status and tissue perfusion, and re-measurement of serum lactate. Adoption of the sepsis bundles led to a significant mortality reduction in the last decade (10). The early administration of appropriate antibiotics has been associated with improved survival in sepsis (11,12). In a retrospective cohort study by Kumar *et al*., it was found that each hour of delay in appropriate antibiotic administration reduced survival by 8% in patients with septic shock (13). While the ProCESS, ARISE, ProMISe and most recently, the PRISM (14) studies have suggested that early goal-directed therapy (EGDT), in terms of invasive interventions such as the use of the central venous catheter to monitor central venous pressure and central venous oxygen saturation to achieve pre-specified resuscitation targets, does not confer mortality benefit compared to usual care, these studies show that a simplified sepsis management protocol with aggressive treatment in terms of fluid administration and early antibiotics is still needed in sepsis. On the other hand, there also exists considerable debate on how rapidly sepsis should be managed. A recent systematic review of 11 studies which reported the time from recognition of sepsis or septic shock to antibiotic administration did not find such an association (15). However, this should be interpreted with prudence due to the lack of microbiological data, selection bias from excluded studies, and the lack of confidence that all patients had bacterial sepsis.

Seymour *et al*. in their study, "*Time to Treatment and Mortality during Mandated Emergency Care for Sepsis*" published in the *New England Journal of Medicine* (16), have added some new evidence to this ongoing controversy. This was a retrospective study involving 49,331 patients across

149 hospitals in the New York State Department of Health database, including data from 1 April 2014 to 30 June 2016. Hospitals were mandated by the state to adhere to evidence-based protocols for the early identification and treatment of severe sepsis or septic shock, including both a 3-hour bundle and a 6-hour bundle similar to the SSC bundles. The study revealed that the median time to completion of the 3-hour bundle was 1.30 (interquartile range, 0.65 to 2.35) hours, the median time to the administration of antibiotics was 0.95 (interquartile range, 0.35 to 1.95) hours, and the median time to completion of the fluid bolus was 2.56 (interquartile range, 1.33 to 4.20) hours. In their multivariate analysis, the authors found an association between risk-adjusted in-hospital mortality and each hour of time to completion of the bundle [odds ratio, 1.04 per hour; 95% confidence interval (CI), 1.02 to 1.05; P<0.001], as well as time to the administration of antibiotics (odds ratio, 1.04 per hour; 95% CI, 1.03 to 1.06; P<0.001). Surprisingly, the time to completion of the initial bolus of intravenous fluids was not associated with in-hospital mortality (odds ratio, 1.01 per hour; 95% CI, 0.99 to 1.02; P=0.21).

The strengths of this study lie in its large sample size and the high compliance rate to the 3-hour bundle. However, it will be prudent to recognize the limitations of the study for accurate interpretation of the results in the appropriate clinical context. First, the database employed older criteria based on the 2001 International Sepsis Definitions Conference (Sepsis-2) in the definition of patients with severe sepsis or septic shock, and a threshold serum lactate of 4 mmol/L instead of 2 mmol/L was used before initiating fluid resuscitation. In the setting of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (17), it remains to be seen whether these findings are applicable to the new definitions on sepsis. Second, as there is a paucity of data on positive culture results, the appropriateness of broad-spectrum antibiotics administered cannot be determined. This is important as local microbial and antibiotic resistance profiles differ across hospitals and geographical regions. Third, Seymour *et al*. started timing when the bundle was initiated. While a sensitivity analysis performed showed results similar to that in the primary analyses, one wonders if the start time should be the triage time or the earliest time of reaching the emergency department instead, so that the start time for measuring delays would have been accurate and consistent in all cases. Last, perhaps one of the contentious results in this study was the lack of an association between the time to completion of the initial bolus of intravenous fluids and mortality. Yet, the time to obtaining a blood culture and serum lactate measurement respectively, were associated with mortality. The authors are right to point out that this should not be interpreted as evidence that early fluid resuscitation has no role in sepsis management; there may be confounding by indication, i.e. sicker patients will receive fluids earlier and are also at a higher risk of mortality. However, does this argument not apply to the 3-hour bundle too? This is one of the major limitations of this retrospective observational study with results which are prone to confounding. Such questions contribute to clinical equipoise and require answers from randomized controlled trials.

So, what do the results mean? Certainly, we need more robust studies in the Sepsis-3 era. We will also need to increase our understanding of sepsis as a dynamic and heterogeneous clinical syndrome, and the interaction between disease severity and therapeutic responses. For instance, do patients with milder sepsis respond differently to the SSC bundles compared to those with more severe disease? Liu *et al*. reported that the implementation of a treatment bundle for patients with sepsis and intermediate lactate values led to decreased hospital mortality, mediated partly by increased fluid administration among patients with a history of heart failure and/or chronic kidney disease (18). On the other hand, a recent study employing a combined Bayesian and frequentist methodological approach to evaluate 12 randomised trials and 31 observational studies found that any benefit of EGDT was significantly reduced—and potentially harmful—when disease was severe based on the Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment, and the presence of shock (19).

In addition, rather than continued debate on issues like timing, we should focus on facilitating the prompt recognition and earlier treatment of sepsis as far as possible. Seymour *et al*. have shown that with a systematic approach and with commitment, it is possible to achieve a high compliance rate to evidence-based sepsis bundles; 82.5% of patients in this study completed the 3-hour bundle. While challenging, emphasis should also be placed on establishing evidence-based, user-friendly protocols and effective training methods to enhance the early detection and treatment of sepsis. For instance, Lim *et al*. have shown that using a simplified protocol in the emergency department consisting of a score to identify patients with severe community acquired pneumonia, prompt initiation of aggressive resuscitation reduced mortality and intensive care unit admissions (20). In addition, whenever feasible,

we should aim to move treatment upstream and initiate the sepsis resuscitation bundles in places that can perform them. Seymour himself has demonstrated in earlier studies the importance and feasibility of resuscitation with paramedics in the community, and not just in the emergency department setting (21,22). These interventions will not be easy to formulate and implement, but will offer vast potential for enhanced patient outcomes if executed well.

On the other side of the spectrum, in resource-limited settings, we will still need to implement cost-effective sepsis care systematically and with tenacity. Ultimately, it is reassuring that interventions which are relatively inexpensive and simple like antibiotics and adequate fluid resuscitation can truly save lives.

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Footnote

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

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