Editorial

From Barcelona to New York: 15 years of transition of sepsis performance improvement

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Provenance: This is an invited Editorial commissioned by Section Editor Dr. Ming Zhong (Department of Critical Care Medicine, Zhongshan Hospital Fudan University, Shanghai, 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.

Submitted Aug 05, 2017. Accepted for publication Aug 11, 2017.
doi: 10.21037/jtd.2017.08.144
View this article at: http://dx.doi.org/10.21037/jtd.2017.08.144

Sepsis is a major health crisis effecting more than 1.5 million Americans each year, with an annual cost over $20 billion (1,2). Sepsis is also the highest condition driving readmissions and a leading contributor to healthcare costs (3).

In 2002, the European Society of Intensive Care Medicine (ESICM), the International Sepsis Forum (ISF), and the Society of Critical Care Medicine (SCCM) launched the Surviving Sepsis Campaign (SSC or "the Campaign") with the Barcelona Declaration at the annual meeting of ESICM in Barcelona (4) with the first SSC guidelines for sepsis management published in 2004.

In 2005 the SSC created a multifaceted model for sepsis performance improvement intended to change bedside practice to be consistent with the SSC guidelines recommendations for patients with severe sepsis and septic shock, collectively known as the SSC Care Bundles (4). Key elements of the guidelines were identified and organized into these "bundles" of care.

The SSC Care Bundles were comprised of two sets of evidence-based goals for care targeted for completion within 6 hours and within 24 hours of presentation for patients with severe sepsis and septic shock. The 6 hours bundle included: measuring serum lactate, obtaining blood cultures, appropriate antibiotic administration, initial 20 cc/kg crystalloid bolus for hypotension or lactate >4 mmol/L, vasopressor use in patients remaining hypotensive after fluid bolus. In the event of hypotension persisting despite fluid resuscitation it was recommended to maintain CVP ≥8 mmHg and $ScVO_2$ ≥70%. The second bundle (known as the management bundle) was to be completed over first 24 hours. It included consideration of steroids for septic shock, consideration of rhAPC for severe sepsis and septic shock, glucose control and limitation of inspiratory plateau pressure in mechanically ventilated patients.

Over the ensuing years the 24-hour bundle was de-emphasized and eventually abandoned with additional evidence based medicine. In the updated 2012 SSC-guidelines, the bundles were revised: the resuscitation bundle was broken into two parts (3- and 6-hour) (5). The 3-hour bundle included: measuring serum lactate, obtaining blood cultures prior to antibiotics, appropriate antibiotic use, initial 30 cc/kg crystalloid bolus in hypotensive patients. The 6-hour bundle prompted application of vasopressors to maintain MAP ≥65 mmHg and measuring CVP and $SCVO_2$ in persistent hypotension.

In 2014, Centers for Medicare & Medicaid Services (CMS) measures were released in the U.S. and were patterned after the 2012 SSC bundles (6). All hospitals in the U.S. were mandated to collect and report performance with these quality measures. The 3-hour bundle included: measuring lactate, obtaining blood cultures, broad spectrum antibiotics, 30 cc/kg crystalloid for hypotension or lactate ≥4 mmol/L. The 6-hour bundle included administration of vasopressors if needed to maintain MAP ≥65 mmHg following fluid challenge, re-evaluation of volume status and tissue perfusion after fluid administration for persistent hypotension or initial

lactate of ≥4 mmol/L, and re-measuring the lactic acid if initial lactate was elevated.

In 2013, in the state of New York, a major initiative known as "Rory's regulations" was introduced. Rory Staunton was a 12-year-old boy who died following delayed diagnosis and treatment of severe sepsis and septic shock (7). Rory's Regulations mandate that each hospital in NY adopt evidence based protocols for diagnosis and management of severe sepsis and septic shock and to report performance on sepsis bundles to the state government. The NY sepsis bundles are again patterned after the 2012 SSC guidelines and include the following quality indicators which must be addressed in the protocol 3 hours following presentation: serum lactate must be drawn, blood cultures collected prior to antibiotics and administration of appropriate antibiotics. The 6-hour bundle must include administration of a bolus of 30 mL of intravenous fluids per kilogram of body weight in patients with hypotension or a serum lactate level of ≥4.0 mmol/L, the initiation of vasopressors for refractory hypotension, and the re-measurement of the serum lactate level if initial value is elevated.

In the May 2017 issue of *NEJM*, Seymour *et al.* report the results of the first 49,331 patients entered into the NY state database (8). There was a strong association in achieving all quality indicators in the bundles and risk adjusted survival. In addition there was an association between achieving each single element in the bundles and risk adjusted survival with the exception of 30 mL/kg crystalloid within the first 6 hours.

It important to note that the link between achieving the quality indicators of the bundles and survival is an association and not cause and effect. However the strength of this study is that all patients enrolled were on the basis of institution of a sepsis protocol and since this was not a before and after study, the likelihood of this effect being due to the protocol institution itself is not germane.

Why might quality indicators included in the NY sepsis bundles be associated with improved outcome?

Earlier antibiotics in severe sepsis and septic shock might produce a favorable outcome through various mechanisms. Antibiotics decrease pathogen burden thus decreasing the upstream stimulus that is driving toxin and mediation production. This effect should favorably modify host inflammatory response. In 2006, Kumar *et al.* reported a 7.6% increase in mortality in patients with sepsis for each hourly delay after the onset of shock (9).

Obtaining serum lactate allows early identification of tissue hypoperfusion that may not have been suspected if serum lactate was not measured. In addition more aggressive resuscitation has been applied for patients with lactate ≥4 mmol/L with encouraging outcomes (10-12).

Blood cultures prior to antibiotic administration allow modification of antibiotic coverage based on sensitivities when an organism is grown.

In the study by Seymour *et al.* longer time to completion of intravenous fluids was not associated with higher risk-adjusted in-hospital mortality. A number of factors may have influenced this finding. Fluid given prior to presentation to the emergency department was not evaluated, and not added to fluid totals. However, since the study was very large it is unlikely that an imbalance in comparison groups would occur. Another possibility is that patients who were judged by clinicians to be in more need of aggressive fluid administration were prioritized for early fluid administration. These patients were also more likely to die and created a link between more aggressive fluid administration and bad outcomes that was an association and not cause and effect. However, it could have prevented showing an overall benefit of early fluids. Another possibility is that early fluid treatment is good for some patients and bad for others. Therefore, showing an overall neutral effect. The only true way to assess benefit or lack of benefit of early fluid resuscitation in patients with septic shock would be to conduct a randomized controlled trial.

Sepsis related mortality has been noted to be decreasing before the introduction of 2013 NY state health regulations, as noted by Gaieski *et al.* (13). Is the observed mortality lowered because of protocolized management or because of intuitive management of sepsis learned from the earlier trials and from worldwide awareness on importance of early diagnosis and treatment of severe sepsis and septic shock?

In 2014 the SSC reported the results of 30,000 patients enrolled in the SSC performance improvement program showing an association over time between increased compliance with the sepsis bundles and survival (14). When this result was adjusted for time of entry into the performance improvement collaborative, there was no evidence that mortality at the time of entrance was decreasing over time for participating sites. This would support participation in the SSC program as a potential reason for decreased mortality.

There is considerable controversy surrounding US state and government involvement in mandatory reporting of sepsis quality metrics. The controversy centers on the strength of evidence that is utilized for the selection of the quality indicators that are mandatorily reported. In the

case of the Centers for Medicare and Medicaid Services (CMS) the decision was made to implement mandatory reporting of sepsis quality measures likely based to some degree on patient advocacy group pressure and public awareness of this devastating disease process. In the case of New York it was driven by public and legislative response to a high profile bad outcome case of severe sepsis. For whatever reason it is likely that implementation of the sepsis protocols, sepsis bundles and mandatory reporting leads to an increase in attention and emphasis on the early diagnosis and management of severe sepsis and septic shock. How important individual quality indicators are in this process is debated. The importance of early identification and antibiotics are now generally accepted. Timing and amount of fluids remain controversial and the Seymour study does not clarify this issue. Randomized trials are needed to sort out the good and bad (or indifference) of fluid administration but how to design such studies will be challenging.

Quality indicators of sepsis bundles are and may always be a work in progress. They will however, be aided by continued publication of original science that will facilitate application of evidence based medicine to bundle modifications.

Acknowledgements

None.

Footnote

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

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Cite this article as: Dellinger RP, Hussain S. From Barcelona to New York: 15 years of transition of sepsis performance improvement. J Thorac Dis 2017;9(10):3453-3455. doi:10.21037/jtd.2017.08.144

