



Sepsis, the earlier the better, 3- to 1-hour bundle

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Sepsis is life threatening organ dysfunction caused by a dysregulated host response to infection. There is a substantial global burden in sepsis with an estimated 32 million cases and 5.3 million deaths per year (1). Its prevalence is increasing, and it is associated with high costs and poor outcomes. From 2010 to 2015 the proportion of admissions for sepsis in the United States more than doubled from 3.9% to 9.4% (2). This is leading to increasing hospital expenditure, more than \$20 billion per year in the United States (3).

In 2004, the initial Surviving Sepsis Campaign (a global initiative bringing together critical care and infectious disease experts in the diagnosis and management of sepsis with the aim of improving awareness and outcomes in sepsis) guidelines were drafted. Since then guidelines have been revised in 2008, 2012 and 2016 and there has been a recent update in June 2018. The initial guidelines listed key recommendations including early goal directed resuscitation of the patient during the first 6 hours after recognition; appropriate diagnostic studies to ascertain causative organisms before starting antibiotics and early administration of broad spectrum antibiotic therapy. Recommendations were subsequently grouped into 6- and 3-hour bundles. Compliance with these bundles has been shown to improve survival (4). The 3-hour bundle in the 2016 revision comprised of (I) obtain a blood culture before antibiotics, (II) measuring a lactate level, (III) administer broad spectrum antibiotics, and (IV) administer 30 mL/kg of crystalloid fluid for hypotension (mean arterial blood pressure <65 mmHg) or lactate >4 mmol/L within 3 hours

(3-hour bundle) (5).

Possibly in response to this paper, in the 2018 update the 3- and 6-hour bundles have been combined into a single 1-hour bundle. Recommendations 1–4 should be initiated within one hour with the additional recommendation of application of vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP $\geq$ 65 mmHg. The emphasis is on beginning treatment immediately particularly in patients with hypotension. More than 1 hour may be required for resuscitation to be completed but it should be commenced within 1 hour (6,7).

This paper demonstrated that delays in administering all four guideline recommendations, even if they did not exceed the 3-hour window is associated with a significant increase in in-hospital mortality. No delay in implementing the guidelines is safe. The longer the delay the higher the mortality risk. In figures 1–4 the curves rise sharply at first followed by a flattening out. This would suggest that the risk is highest in the beginning even for short delays though we can't rule out a statistical anomaly. This type of analysis can be affected by differences in time interval between control group and treatment group. Delays exceeding 3 hours are associated with little additional harm on top of that experienced within 3 hours. This could partly be explained by the number of events/deaths occurring early. The population group selected may have a high compliance rate with the 3-hour bundle influencing the result by lowering the event rate i.e., sample size too small beyond 3 hours to determine further increased mortality risk (7).

The statistically significant time delay is calculated at

50 minutes for blood cultures and 20 minutes for lactate compared to 125 minutes for antibiotics and 100 minutes for crystalloid infusion. This is surprising as the time delay shown to effect mortality rate is much shorter for the investigations (blood cultures and lactate level) than the treatments (antibiotic administration and fluid resuscitation). One would expect that the magnitude of effect of a treatment to outweigh the magnitude of effect of an investigation. In fact, one could argue that the magnitude of effect by treatment be the only thing that influences outcome in any disease process. However, the complex nature of sepsis and what influences outcomes means a lot of treatments are supportive in nature. In fact, the process of sepsis treatment maybe the thing that is most important in influencing outcomes. Hence the importance of systematic approach to sepsis management and up to date and evidence-based guidelines.

Intuitively one would expect that the quicker the administration of antibiotics and intravenous fluids occurs then the better the outcome. This was not demonstrated in this study possibly due to limitations due to sample size. Referring to the survival probability curves, the difference between the control and treatment group is less than expected for the administering of antibiotics and crystalloid recommendations. There is little difference in the antibiotics recommendation curve in the first 100 minutes and the crystalloid recommendation in the first 50 minutes. There is a difference in survival probability between the control and treatment groups with delays as small as 10–20 minutes in taking blood cultures and measuring the lactate level. Again, this is surprising as the non-treatment parameters measuring a lactate level and obtaining blood cultures prior to administration of antibiotic appear to have a greater survival benefit than the treatment parameters administering of broad spectrum antibiotics and the rapid administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L (7). However, implementation of each of these 4 recommendations are likely interlinked. Crystalloids may not have been started until a lactate level has been measured and the administration of broad spectrum antibiotics after blood cultures taken. A structured approach is important in the management of sepsis. Good quality data collection and analysis provides an opportunity for improving outcomes. If there are no guidelines and protocols in place for treatment this will lead to delays and poor practice resulting in worse outcomes for patients.

Propensity score matching (PSM) was the statistical analysis method used in the study. This was performed at $t = 15, 30, 45, \dots, 360$ minutes. The exposed group consisted of patients that received a guideline recommendation in

less than t minutes versus the control group that received the recommendation with more than t minutes delay. At each point over time the exposed group gets larger and the control group smaller. This variability in size of the control and exposed group at each point impacts on the certainty of the estimates. With PSM analysis there is also potential for confounding unmeasured variables. With these uncertainties in the statistical analysis the findings in this paper may not provide sufficient evidence without other corroborating studies. Although intuitively process delays should worsen outcome we still require more evidence. Further studies with the use of EHR databases looking at time delays in the implementation of guidelines should be performed to confirm, strengthen and further quantify the effect of time delays on outcomes (7). Other limitations in this study are mortality that occurred outside of hospital and re-admission rates are not incorporated. These are of importance as there is an increasing number of re-admissions with sepsis due to improved survival rates (7).

The time of randomised control trials (RCT's) in gathering evidence for the drafting of guidelines in sepsis has passed. Studying the effects of delays in treatment would be unethical and the design of a trial for this purpose would be difficult. Future research is going to be relying more and more on the use of electronic health records (EHR's). There are many advantages to the use of EHR's. It is a very efficient way of retrieving data allowing a larger sample size and improving the power of the study. Researchers in the past had the laborious task of retrieval of data in paper medical charts which is time consuming in terms of the time required to analyse the data collected (8). "Big data" is here to stay. EHR implementation was statistically associated with reductions in central line associated bloodstream infection (CLABSI) rates and surgical intensive care unit (SICU) mortality though several Quality Insurance initiatives geared towards reducing CLABSIs and mortality in the SICU were implemented concurrently with the EHR (9). Limitations to this type of research (versus randomised controlled trials) is that recording of results and clinical practices may be less reliable. This is due to the data being recorded in a busy working environment. The clinical practices may be less reliable for example recalibrating the arterial pressure transducers each shift (10).

This paper should be a call to arms to the governing bodies (for example the SCC) to produce guidelines on what variables should be recorded in the EHR system and there should be consistency across all computer platforms in their implementation. Important variables to be recorded include blood pressure, mean arterial blood pressure, heart

rate, respiratory rate, temperature, white blood cell count, lactate, use baseline vasopressors and mechanical ventilation. These are all predictors of mortality in sepsis patients. Recording of which antibiotic administered and volume and quantity of crystalloid infused would also be useful. This would allow databases to be used interchangeably and a standardised approach in measuring outcomes. In one study over 25% of the clinical data available in the EHR was never used, and only 33% was used greater than 50% of the time by admitting physicians (11). The EHR system needs to be reviewed periodically.

It is important that as more evidence from on-going studies become available we revise and update our guidelines in concordance. The SCC guidelines have been recently updated in June 2018 accordingly. The focus is now on the beginning of management and resuscitation immediately with the combining of a 3- and 6-hour bundle into a single 1-hour bundle. Reviewing outcomes, the in-hospital mortality for hospitalisations secondary to sepsis has declined from 24.1% in 2010 to 14.8% in 2015. With increasing numbers of admissions for sepsis, and lower in-hospital mortality the proportion of medical and surgical discharges at risk for hospital readmission has increased 2.9-fold. However, the 30-day hospital readmission rate declined from 26.4% to 23.1% (2).

The reduction in in-hospital mortality rate and hospital readmission rate confirms that the Surviving Sepsis Guideline revisions and updates are improving patient care resulting in better outcomes. There needs to be a continued emphasis on in future papers and in future guidelines, on beginning treatment immediately and reducing time delays in the management pathway. This paper is a step in the right direction, but more corroborative evidence needs to be accumulated.

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Footnote

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

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