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ORIGINAL

The Surviving Sepsis Campaign bundles and outcome: results from the International Multicentre Prevalence Study on Sepsis (the IMPreSS study)

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Abstract *Introduction:* Despite evidence demonstrating the value of performance initiatives, marked differences remain between hospitals in the delivery of care for patients with sepsis. The aims of this study were to improve our understanding of how compliance with the 3-h and 6-h

Surviving Sepsis Campaign (SSC) bundles are used in different geographic areas, and how this relates to outcome. *Methods:* This was a global, prospective, observational, quality improvement study of compliance with the SSC bundles in patients with either severe sepsis or septic shock. *Results:* A total of 1794 patients from 62 countries were enrolled in the study with either severe sepsis or septic shock. Overall compliance with all the 3-h bundle metrics was 19 %. This was associated with lower hospital mortality than non-compliance (20 vs. 31 %, $p < 0.001$). Overall compliance with all the 6-h bundle metrics was 36 %. This was associated with lower hospital mortality than non-compliance (22 vs. 32 %, $p < 0.001$). After adjusting the crude mortality differences for ICU admission, sepsis status (severe sepsis or septic shock), location of diagnosis, APACHE II score and country, compliance remained independently associated with improvements in hospital mortality for both the 3-h bundle (OR = 0.64 (95 % CI 0.47−0.87), $p = 0.004$)) and 6-h bundle (OR = 0.71 (95 % CI 0.56−0.90), $p = 0.005$)). *Discussion:* Compliance with all of the evidence-based bundle metrics was not high. Patients whose care included compliance with all of these metrics had a 40 % reduction in the odds of dying in hospital with the 3-h bundle and 36 % for the 6-h bundle.

Keywords Sepsis · Quality improvement · Surviving Sepsis Campaign · Bundle

Introduction

Despite many advances in our understanding of sepsis [1] and recent reports of improved outcomes from the condition [2], the disorder remains of epidemic incidence with an unacceptably high death rate and devastating long-term effects. Quality improvement efforts through the application of sepsis care bundles have reduced mortality, but the number of hospitals participating in such initiatives remains low [3, 4].

The Surviving Sepsis Campaign (SSC) was developed to reduce the mortality from severe sepsis and septic shock. SSC activities directed towards this goal included the development of evidence-based guidelines [5–7], educational packages to improve the awareness and understanding of the condition and a quality improvement initiative to help healthcare professionals adopt the identified best practice [4, 8, 9]. A recent analysis covering a 7.5-year period demonstrated that active participation in the SSC was associated with increased guideline adherence, as evidenced by improved compliance with established performance metrics. Additionally, these improvements were in themselves associated with reductions in sepsis-related mortality [4]. Finally, the longer hospitals participated in the campaign and the more they improved their performance, the greater were the observed outcome improvements.

Despite evidence demonstrating the value of such performance initiatives, marked differences remain between hospitals in the delivery of care for patients with sepsis. Reviewing the inconsistent application of measures identifies an important opportunity to reduce sepsis-induced mortality further. It is recognized that the penetration of the SSC to hospitals around the world is limited. To inform current and future quality improvement efforts in sepsis, there is a need to better understand how widely and well the evidence-based SSC bundles are used in different geographic areas, and how these relate to outcome. In particular, it is necessary to assess the compliance with the 2012 guidelines and associated bundles as all previous data assessed compliance with the previous iterations. A critical step in quality improvement efforts is a thorough assessment of current practice in order to identify ongoing gaps in clinical processes. This study was designed to address this need.

Methods

Study design and participants

This was a global, prospective, observational, quality improvement study of the prevalence of patients with either severe sepsis or septic shock, with evidence-based practices. On 7 November 2013 (0000 to 2400 hours), consecutive patients presenting to either the emergency department (ED) or being cared for in an ICU (either intermediate care or intensive care) with severe sepsis or septic shock were enrolled. To be eligible patients had to have a high clinical suspicion of an infection, together with a systemic inflammatory response and evidence of acute organ dysfunction and/or shock [10]. Patients were excluded if they were less than 18 years of age. Participating hospitals were identified through membership of the European Society of Intensive Care Medicine (ESICM), the Society of Critical Care Medicine (SCCM) and the SSC and through the networks of national and local coordinators. The project was approved as a quality improvement initiative in each participating country, thus precluding the necessity for written informed consent from participants. All demographic and clinical information were de-identified as part of data collection processes so that patient anonymity was strictly maintained throughout the study.

Procedures

Local investigators were identified and were supported by a network of national coordinators. Key study information was provided through a website (http://impress-ssc.com/) which included the protocol, answers to key questions and access to the electronic case report form (eCRF). Upon entry into the eCRF, each patient was assigned a unique study identifier. No patient identifiable data was submitted to the online database housed on a secure server in Germany.

A multi-continental panel of critical care experts iteratively developed a "realistic data set". These data elements included all key and relevant clinical and demographic data points whilst not discouraging centres from participating because of an excessive burden of data collection (see Electronic supplementary material, ESM). The data collected were all part of routine clinical care. Patients were followed up until 30 days after study enrolment or hospital discharge, whichever occurred first.

Data were collected for every patient, on whether their management fulfilled the requirements of the SSC bundles [7]. The 3-h bundle for patients with severe sepsis/septic shock (i.e. elements completed within 3 h) includes a lactate level measurement; blood cultures obtained prior to the administration of antibiotics; the intravenous administration of broad-spectrum antibiotics; and, intravenous administration of 30 mL/kg of crystalloid if hypotension was present or the lactate level was at least 4 mmol/L (36 mg/dL). The 6-h bundle for patients with severe sepsis/septic shock (i.e. elements completed within 6 h) includes a remeasurement of lactate if it was initially raised; the application of vasopressors when hypotension (mean arterial pressure [MAP] at most 65 mmHg) is persistent despite initial fluid resuscitation; and, measurement of central venous pressure (CVP) and central venous oxygen saturation ($ScvO_2$) when there is persistent arterial hypotension despite volume resuscitation or the initial lactate concentration is at least 4 mmol/L. The 6-h bundle was reported for all patients in the study and also just for those who remain with persistent hypotension and/or hyperlactataemia following volume resuscitation within the 6-h period.

Statistical analysis

Categorical variables are described using frequencies and proportions and are compared using Fisher's exact test. Comparisons between geographic regions have been made excluding the data from Oceania, owing to the low numbers of patients enrolled from this region making the estimates less reliable. Continuous variables are described as mean and standard deviation if normally distributed or median and interquartile range if not. A generalized estimating equation (GEE) population-averaged logistic regression was used to assess the association between prognostic factors and mortality where country was the clustering or panel variable with an exchangeable correlation structure. Both unadjusted and adjusted odds ratios are presented along with their associated 95 % confidence intervals. The following adjustment variables of age, ICU admission (yes vs. no), sepsis status (severe vs. shock), location (ED, ward, ICU, OR, unknown), sepsis origin (community, health care, hospital, or ICU acquired), and APACHE II were determined a priori. All analyses were run using Stata 13.1, StataCorp, College Station, TX.

Results

We collected data describing patients presenting with severe sepsis and/or septic shock in 618 hospitals from 62 countries. Data were returned on 1927 patient records of which 133 were removed having been identified as duplicates or having missing hospital outcome data, leaving 1794 for analysis (ESM Fig. 1). A median number of 9 (3−25) patients were included per country and 2 (1−4) per site. The two biggest participating regions were Western Europe (623 (34.7 %)) and North America (501 (27.9 %)). The highest enrolling countries were the USA (489 (27.3 %)), UK (199 (11.1 %)), Malaysia (144 (8.0 %)), Spain (141 (7.9 %)) and India (70 (3.9 %)) (ESM Table 1). Oceania had only 14 observations; thus, their results have very wide confidence intervals.

Table 1 and ESM Tables 2 and 3 show the baseline data and outcomes. Overall, 47 % of the patients were over 65 years old and 59 % presented with at least one co-morbid illness (ESM Tables 1 and 2). The majority of patients were diagnosed in the ED (54 %) and the most frequent presentations were of community-acquired sepsis (59.9 %) and pneumonia (40 %). The most common organ dysfunctions at presentation were hypotension (66 %), acute respiratory distress syndrome [11] (57 %) and acute kidney injury (46 %). In 39 % of the patients the sepsis progressed to septic shock (ESM Table 2). A total of 1545 (86 %) of the patients were admitted to an ICU and the overall hospital mortality was 28 % with a median (IQR) length of hospital stay of 13.7 (6.5–24.6) days.

Demographic and clinical details of patients presenting by region are described in Table 1. Patients were more likely to be older in Western Europe and present with chronic illnesses in North America. The diagnosis of severe sepsis/septic shock was most likely to be made in the ED in North America (64 %), the ward in Asia (24 %) and the ICU in Eastern Europe (44 %). Unadjusted hospital mortality was highest in Eastern Europe (44 %) and lowest in Oceania (14 %). When the crude mortality rates for each region were compared against North America and adjusted for ICU admission, sepsis status, location of

Table 1 Presenting characteristics and outcomes for patients enrolled into the IMPreSS study split by geographic region

Detail	Asia	Oceania	West Europe	East Europe	North America	Central/South America	Africa and Middle East
N	344	14	623	100	501	147	65
Age >75 years	53 (15.4)	0 (0.0)	192 (30.9)	18 (18.1)	118 (23.7)	27 (18.4)	13 (20.0)
Presenting with chronic illness	101 (29.4)	5 (35.7)	239 (38.4)	40 (40.0)	253 (50.5)	60 (40.8)	33 (50.8)
Location in hospital of diagnosis							
Emergency department	180 (52.3)	7 (50.0)	324 (52.0)	26 (26.0)	318 (63.5)	84 (57.1)	33 (50.8)
Ward	82 (23.8)	2 (14.3)	136 (21.8)	18 (18.0)	72 (14.4)	29 (19.7)	13 (20.2)
Intensive care unit	66 (19.2)	1 (7.1)	135 (21.7)	44 (44.0)	100 (20.0)	27 (18.4)	10 (15.4)
Source of infection							
Abdominal	75 (21.8)	6 (42.9)	162 (26.0)	33 (33.0)	84 (16.8)	32 (21.8)	10 (15.4)
Respiratory	152 (44.2)	3 (21.4)	251 (40.3)	32 (32.0)	188 (37.5)	66 (44.9)	24 (36.9)
Urinary tract	14 (4.1)	0 (0.0)	81 (13.0)	7 (7.0)	104 (20.8)	18 (12.2)	10 (15.4)
Community-acquired	221 (64.4)	12 (85.7)	352 (56.7)	41 (41.0)	322 (64.4)	87 (60.4)	30 (52.6)
Septic shock	153 (45.8)	2 (15.4)	218 (36.0)	43 (43.0)	171 (35.9)	60 (42.0)	27 (48.2)
Baseline lactate (mmol/L) (mean (SD))	3.1 (2.7)	2.2 (1.5)	3.1 (3.4)	3.9 (3.4)	3.0 (4.2)	3.2 (3.6)	4.0 (2.9)
APACHE II score (mean (SD))	22.2 (8.5)	23.5 (9.7)	21.5 (8.2)	22.5 (9.7)	22.5 (9.1)	19.8 (8.2)	24.1 (8.8)
SOFA score	8.1 (3.2)	8.9 (3.8)	6.8 (3.4)	7.9 (3.2)	6.5 (3.2)	6.8 (3.0)	8.2 (2.9)
ICU admission	328 (95.4)	12 (85.7)	488 (78.3)	97 (97.0)	445 (88.8)	125 (85.0)	50 (76.9)
Hospital length of stay, days (median (range))	13.4 (7.0–22.2)	19.9 (7.3–26.2)	14.4 (7.2–28.1)	22.9 (14.2–36.4)	10.5 (5.0–19.4)	15.5 (8.0–27.0)	14.1 (5.3–24.0)
Hospital mortality (all patients)	106 (30.8)	2 (14.3)	160 (25.7)	44 (44.0)	121 (24.2)	54 (36.7)	23 (35.4)
Hospital mortality (septic shock)	42 (27.5)	0 (0)	59 (27.1)	21 (48.8)	43 (25.2)	29 (48.3)	13 (48.2)

All numbers are presented as *n* (%) unless otherwise stated

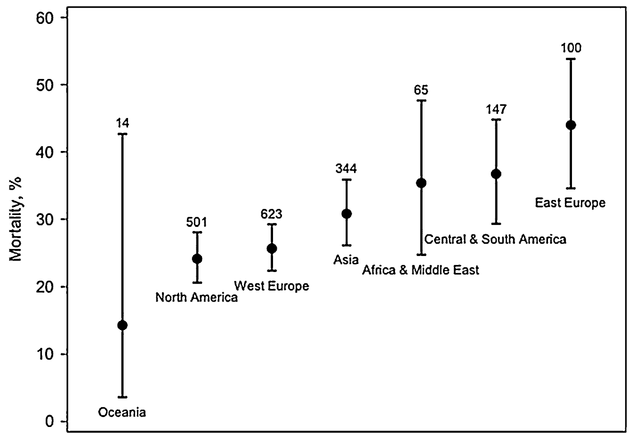

Fig. 1 Estimated mortality and its associated 95 % CI by region where the number represents the observations within each region

diagnosis, origin of sepsis, APACHE II score and country, East Europe and Central/South America remained with higher odds of dying (OR = 2.46 (95 % CI 1.27−4.77), $p = 0.008$ and OR = 2.17 (95 % CI 1.16−4.03), $p = 0.015$), respectively) (Fig. 1). There were no statistical differences found in adjusted mortality rates between North America and Asia, Oceania, West Europe and Africa/Middle East.

Overall compliance with all the 3-h bundle metrics was 19 %. This was associated with lower hospital mortality than non-compliance (20 vs. 31 %, $p < 0.001$). Overall compliance with all the 6-h bundle metrics was 36 %. This was associated with lower hospital mortality than non-compliance (22 vs. 32 %, $p < 0.001$) (Table 2). For patients who had persistent hypotension and/or hyperlactataemia full compliance with the 6-h bundle was reported in 90 (11 %) of patients. The compliance with the 3-h bundle was highest in North America (29 %) and lowest in Central/South America (9.5 %), whereas the compliance with the 6-h bundle was highest in West Europe (41 %) and lowest in Africa/Middle East (26 %) (Table 3). After adjusting the crude mortality differences for ICU admission, sepsis status (severe sepsis or septic shock), location of diagnosis, APACHE II score and country, compliance remained independently associated with improvements in hospital mortality for both the 3-h bundle (OR = 0.64 (95 % CI 0.47−0.87), $p = 0.004$)) and 6-h bundle (OR = 0.71 (95 % CI 0.56−0.90), $p = 0.005$)) (Table 4).

Table 2 Surviving Sepsis Campaign bundle compliance and associated hospital mortality for patients enrolled into the IMPreSS study

Detail	
3-h bundle compliance (all patients, $n = 1794$)	
Measurement of lactate	1002 (55.9)
Obtain blood cultures before administration of antibiotics	883 (49.2)
Administer broad-spectrum intravenous antibiotics	1155 (64.4)
Administer 30 mL/kg crystalloid for hypotension	1017 (56.7)
Full bundle	340 (19.0)
Hospital mortality for 3-h bundle compliance	67/340 (19.7)
Hospital mortality for 3-h bundle non-compliance	443/1454 (30.5)*
6-h bundle compliance (all patients, $n = 1794$)	
Repeat the lactate measurement	1077 (60.0)
Application of vasopressors for hypotension	1479 (82.4)
Measurement of central venous pressure	1209 (67.4)
Measurement of central venous oxygen saturation	1070 (59.6)
Full bundle	637 (35.5)
Hospital mortality for 6-h bundle compliance	143/637 (22.4)
Hospital mortality for 6-h bundle non-compliance	367/1157 (31.7)*
6-h bundle compliance (for only patients with persistent hypotension (MAP <65 mmHg) and/or hyperlactataemia (>4 mmol/L) after volume administration ($n = 824$)	
Repeat the lactate measurement	530 (64.3)
Application of vasopressors for hypotension	544 (66.0)
Measurement of central venous pressure	274 (33.2)
Measurement of central venous oxygen saturation	135 (16.4)
Full bundle	90 (10.9)
Hospital mortality for 6-h bundle compliance	25/90 (27.8)
Hospital mortality for 6-h bundle non-compliance	261/734 (35.6)

All numbers are presented as n (%) unless otherwise stated
* Represents a p value of ≤0.0001 by the Fishers exact test for the mortality of bundle compliance versus non-compliance

Discussion

In this multinational study of severe sepsis and septic shock the hospital mortality rate was 28.4 % and this varied significantly between different geographic regions of the world. Compliance with all of the evidence-based bundle metrics for the treatment of this condition was not high: 19 % for the 3-h bundle and 35.5 % for the 6-h bundle. Patients whose care included compliance with all of these metrics had a 40 % reduction in the odds of dying in hospital with the 3-h bundle and 36 % for the 6-h bundle.

Despite recent reports of reducing mortality rates from septic shock [2, 12] and data from recent randomized controlled trials suggesting the mortality is now quite low [13, 14], we found a hospital mortality rate of 28.4 %. This is consistent with reports from other observational studies [4, 15] that suggest the mortality rate may still be higher than reported from interventional studies [16] that often exclude the highest risk groups of patients, and also more formally structure the delivery of care. We have also found large differences in mortality between different geographic regions. We have previously reported similar findings when comparing Europe to North America where the crude mortality rate was lower in North America, but

Table 3 Surviving Sepsis Campaign bundle compliance and hospital outcome for patients enrolled into the IMPreSS study split by geographic region

Detail	Asia	Oceania	West Europe	East Europe	North America	Central/South America	Africa and Middle East
N	344	14	623	100	501	147	65
3-h bundle compliance							
Measurement of lactate	166 (48.3)	6 (42.9)	376 (60.4)	48 (48.0)	318 (63.5)	64 (43.5)	24 (36.9)
Obtain blood cultures before administration of antibiotics	157 (45.6)	5 (42.9)	284 (45.6)	49 (49.0)	315 (62.9)	58 (39.5)	15 (23.1)
Administer broad-spectrum intravenous antibiotics	229 (66.6)	10 (71.4)	409 (65.7)	74 (74.0)	303 (60.5)	95 (64.6)	35 (53.8)
Administer 30 mL/kg crystalloid	187 (54.4)	11 (78.6)	340 (54.6)	53 (53.0)	312 (62.3)	76 (51.7)	38 (58.5)
Full bundle	50 (14.5)	1 (7.1)	108 (17.3)	14 (14.0)	146 (29.1)	14 (9.5)	7 (10.8)
Hospital mortality for bundle compliance	7 (14.0)	0 (0.0)	19 (17.6)	5 (35.7)	32 (21.9)	4 (28.6)	0 (0.0)
Hospital mortality for bundle non-compliance	99 (33.7)	2 (15.4)	141 (27.4)	39 (45.3)	89 (25.1)	50 (37.6)	23 (39.7)
6-h bundle compliance (all patients, $n = 1794$)							
Repeat the lactate measurement	187 (54.4)	10 (71.4)	434 (69.7)	55 (55.0)	290 (57.9)	74 (50.3)	27 (41.5)
Application of vasopressors for hypotension	308 (89.5)	13 (92.9)	511 (82.0)	89 (89.0)	382 (76.3)	123 (83.7)	53 (81.5)
Measurement of central venous pressure	253 (73.6)	10 (71.4)	427 (68.5)	67 (67.0)	312 (62.3)	99 (67.4)	41 (63.1)
Measurement of central venous oxygen saturation	214 (62.2)	9 (64.3)	377 (60.5)	58 (58.0)	286 (57.1)	89 (60.5)	37 (56.9)
Full bundle	126 (36.6)	7 (50.0)	255 (40.9)	28 (28.0)	163 (32.5)	41 (27.9)	17 (26.2)
Hospital mortality for bundle compliance	34 (27.0)	1 (14.3)	52 (20.4)	13 (46.4)	29 (17.8)	11 (26.8)	3 (17.6)
Hospital mortality for bundle non-compliance	72 (33.0)	1 (14.3)	108 (29.3)	31 (43.1)	92 (27.2)	43 (40.6)	20 (41.7)

All numbers are presented as *n* (%) unless otherwise stated

Table 4 Hospital mortality odds ratios based on general estimating equation (GEE) population-averaged logistic regression models

Detail	Unadjusted hospital mortality odds ratio	95 % CI	*p* value	Adjusted hospital mortality odds ratio	95 % CI	*p* value
Model 1. Hospital mortality by geographic region[a]						
North America (reference)	1.00			1.00		
Asia	1.29	0.80–2.06	0.29	1.22	0.69–2.14	0.49
Oceania	0.52	0.11–2.51	0.41	0.28	0.03–2.67	0.27
West Europe	1.10	0.71–1.70	0.69	0.98	0.58–1.66	0.94
East Europe	2.47	1.41–4.31	0.001	2.46	1.27–4.77	0.008
Central/South America	1.77	1.05–3.00	0.033	2.17	1.16–4.03	0.015
Africa/Middle east	1.69	0.88–3.22	0.11	1.33	0.61–2/86	0.47
Model 2. Hospital mortality by Surviving Sepsis Campaign bundle compliance[b]						
Full 3-h bundle	0.60	0.45–0.80	<0.001	0.64	0.47–0.87	0.004
Full 6-h bundle	0.64	0.52–0.80	<0.001	0.71	0.56–0.90	0.005

[a] Odds ratios are relative to North America and are adjusted for age, ICU admission (yes vs. no), sepsis status (severe vs. shock), location (ED, ward, ICU, OR, unknown), sepsis origin (community, health care, hospital, or ICU acquired), and APACHE II and country as the panel variable

[b] Odds ratios are relative to non-compliance with either the full 3-h or 6-h bundle and are adjusted for ICU admission, sepsis status (severe vs. shock), location (ED, ward, ICU, OR, unknown), and APACHE II. Odds ratios are comparing compliance with non-compliance and country as the panel variable

the difference did not remain after adjusting for baseline confounding influences [17]. In this current study, the differences between West Europe and North America were not significant after adjustments; however, we have been able to document significant differences between North America and Central/South America and Eastern Europe. Other authors have described differences in the provision of intensive care facilitates and treatments between and within continents [18–22], but this study adds to this by extending the findings to a global scale.

The strengths of this study include the defined data set, a web-based data entry portal, a website containing all relevant documents and training manuals and the participation from over 60 countries representing all parts of the globe. We describe a cohort of patients with severe sepsis and septic shock that could be identified in EDs and ICUs in each participating country. We have previously published [7] and extensively marketed [23–25] the evidence-based bundle metrics so they were familiar to all participating sites. We were then able to collect data describing compliance with these metrics and also data describing presentation patterns and severity of these patients, enabling us to correct bundle compliance and outcome metrics for such differences.

Our study has some limitations. Our data set was a compromise between being an exhaustive list describing all facets of a patient with sepsis and being small enough to encourage site participation and data reliability. We enrolled relatively few patients per site on a single study day and for many countries only a few sites participated. This reduces the external generalizability of our data set. This 'point' estimate reduces the external validity as there is likely to be significant variance in both admission numbers of patients presenting to hospital and clinical practice on a day to day basis and also does not compensate for the known seasonal variations in incidence of the condition in the different regions of the world. In addition we only followed our patients up until hospital discharge; therefore, we have little understanding into what happened to the patients following discharge and to where the patients went. This is likely to be very different between countries in the study.

We have limited data describing other quality metrics of the participating institutions. It is possible that the association we have found between bundle compliance and outcome improvement may be nothing more than a surrogate of how well that institution performs. It would be unwise to infer causality from this relationship. Indeed results from several recent large randomized controlled trials [13, 14, 26] have questioned the need for some of the elements that are included in the 6-h bundle. These new data are currently being assimilated into an update of the evidence-based guidelines and the quality improvement metrics will also change to reflect the new data, in particular the emphasis placed on measurement of central venous oxygen saturations as part of the overall protocolized resuscitation strategy.

Our study has confirmed the reports of others that compliance with sepsis improvement metrics are not good, although when performed they are associated with outcome improvements. This study is the first report of compliance with the 2012 SSC bundles [7] and as such adds to the literature supporting this methodology for quality improvement [4, 17, 27–29]. Our study confirms previous reports that the rate of bundle compliance is different between regions [4, 17] and confirms the ability of sites in North America to perform the initial (3-h) resuscitation bundle elements better that other regions, but also suggests that Western Europe has higher compliance with the 6-h elements. In addition we have confirmed the reports that compliance with these tools improves outcome even when taking into account all presenting differences [4, 17, 23, 25, 27, 28].

In conclusion we have observed in a large multinational observational study that compliance with evidence-based bundle metrics designed to improve outcomes from septic shock remains low, varies significantly between different geographical regions and when performed is associated with improvements in outcome.

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Conflicts of interest AR, JDC, DdB, ML, LE and RF have all held leadership positions in the Surviving Sepsis Campaign. No other conflicts of interest have been declared as relevant to this paper.

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