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J Intensive Care Med 2011 26: 304 originally published online 10 January 2011
DOI: 10.1177/0885066610392499

Journal of Intensive Care Medicine
26(5) 304-313

DOI: 10.1177/0885066610392499
http://jicm.sagepub.com

Resuscitation Bundle Compliance in Severe Sepsis and Septic Shock: Improves Survival, Is Better Late than Never

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Abstract

While clinicians' management of severe sepsis and septic shock has been positively influenced by a number of clinical research studies in the last decade, challenges remain regarding early hemodynamic optimization as envisioned in the Surviving Sepsis Campaign's (SSC) resuscitation bundle (RB). We examined the impact of a hospital-wide continuous quality improvement (CQI) initiative on patients presenting with severe sepsis and septic shock, and the impact of the sepsis RB on patient outcomes when completed beyond the 6-hour recommendation period. The study was an 18-month, prospective cohort study enrolling patients who met the definition of severe sepsis or septic shock. Compliance with the hemodynamic components of the sepsis RB was defined as achieving goal mean arterial pressure (MAP) $\geq$65 mm Hg, central venous pressure (CVP) $\geq$8 mm Hg, and central venous oxygen saturation ($ScvO_2$) $\geq$70%. Compliance was assessed at 6 hours and 18 hours after diagnosis of severe sepsis or septic shock. In all, 498 patients with severe sepsis and/or septic shock were evaluated to determine the upper limit of the range of hours that compliance with the RB would still improve outcomes. Using 18 hours as a marker, *Compliers at 18 hrs* and *Non-Compliers at 18 hrs* were compared. There were 202 patients who had the RB completed in less than or equal to 18 hours. There were 296 patients who did not complete the RB at 18 hours. The *Compliers at 18 hrs* had a significant 10.2% lower hospital mortality 37.1% (22% relative reduction) compared to the *Non-Compliers at 18 hrs* hospital mortality of 47.3% ($P < .03$). When the two groups were adjusted for differences in baseline illness severity, the *Compliers at 18 hrs* had a greater reduction in predicted mortality of 26.8% versus 9.4%, $P < 0.01$.Conclusions: Initiating the sepsis RB for patients with severe sepsis and/or septic shock decreased mortality. A CQI initiative that monitored the implementation in real-time allowed for improvement in compliance and efficacy of the bundle on outcomes. Multiple studies have shown that compliance to the RB within 6 hours lowers hospital mortality. This study uniquely shows that when bundle completion is extended to 18 hours, the mortality reduction remains significant.

Keywords

infection, sepsis, severe sepsis, septic shock, bundles, quality improvement

Background and Introduction

Severe sepsis and septic shock represent significant socioeconomic burden worldwide. There are over 1.2 million cases in the United States, consuming over $50 billion in health care-related costs.[1] Since 1997, sepsis has become the most expensive disease treated within US hospitals. For the hospital in this study, sepsis is responsible for 11.8% of hospital admissions; however, it is responsible for 45% of the hospital deaths and accounts for over $100 million in health care expenditures per year.

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Table 1. Sepsis Resuscitation Bundle

Serum lactate measured.
Blood cultures obtained prior to antibiotic administration.
Broad-spectrum antibiotics administered within 3 hours for ED admissions and 1 hour for non-ED ICU admissions.
In the event of hypotension and/or lactate $\geq$4 mmol/L:
Deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent)
Initiate vasopressor for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) $\geq$65 mmHg
Achieve central venous pressure (CVP) of $\geq$8 mmHg
Achieve central venous oxygen saturation $ScvO_2$ $\geq$70% or a mixed venous oxygen saturation (SvO2) $\geq$65%.

Patients progress from sepsis to severe sepsis regardless of their portal of entry to the hospital. The location and time spent at various locations are associated with unique diagnostic and therapeutic challenges that impact morbidity and mortality.[2] In the United States, the emergency department (ED) represents a portal of entry for over 700 000 cases with waiting times averaging over 5 hours.[3,4] While the ED is a significant portal of entry, an equal number of patients present to intensive care units (ICU) with severe sepsis from inpatient floors, the operating room, and other areas of the hospital. Thus, a comprehensive understanding of the milieu from admission to the ICU is the first step in a successful continuous quality improvement (CQI) initiative.

Survival from acute myocardial infarction, trauma, and stroke has been increased through CQI initiatives that include early identification and implementation of time-sensitive therapies. This CQI initiative comprised a multifaceted strategy that included (1) assessment of the hospital's preexisting sepsis incidence and mortality rate; (2) refinement of methods for early identification of high-risk patients; (3) education to health care providers of the components of the sepsis resuscitation bundle (RB); (4) assessment of compliance with the RB; (5) quantification of health care resource consumption; and (6) assessment of patient outcomes including effects on morbidity and mortality.[5-17]

While many studies in the last decade have improved clinicians' management of severe sepsis and septic shock, an analysis evaluating the impact of these therapies at our institution was lacking.[18] This study examined the impact of a hospital-wide CQI initiative on the mortality of patients with severe sepsis and septic shock. We further examined the effectiveness of hemodynamic optimization as framed in the Surviving Sepsis Campaigns (SSCs) sepsis RB (Table 1) when completed beyond the 6-hour recommendation period.

Materials and Methods

Design and Setting

We initiated an 18-month prospective cohort study of patients with severe sepsis or septic shock. Our primary aim was to develop an institutional CQI initiative to improve compliance with early hemodynamic optimization in septic patients using the RB.[18] The study setting included the ED, medical and surgical ICUs of an urban, academic teaching institution. There are 700 beds in this hospital of which 134 are ICU beds. In addition, the ED manages 98 000 ED visits yearly with an ICU admission rate of 2.5%. The primary outcome analyzed was in-hospital and 28-day mortality during the 18 months of this study.

Eligibility

All patients who were 18 years and older who received care in the ED, medical ICU (MICU), or surgical ICU (SICU) between June 1, 2006, and November 30, 2007, were eligible. We screened patients who presented with (a) suspected infection, (b) $\geq$2 systemic inflammatory response syndrome (SIRS) criteria, (c) lactate level >2 mmol/L or hypotension (systolic blood pressure [SBP]<90, mean arterial pressure [MAP] <65 or an MAP decrease >40 mm Hg from baseline), and (d) $\geq$1 organ failures as described by the Surviving Sepsis Campaign[19] for eligibility. Exclusion criteria included (a) DNR/hospice status at presentation with sepsis, (b) DNR within 6 hours of presentation with sepsis, and (c) early goal-directed therapy (EGDT) started at another acute care facility before transfer to our facility. If a patient had more than 1 episode of sepsis within the same admission, only the data from the initial episode was used for the final analysis.

Protocol Creation, Education, and Implementation

In the spring of 2006, the Henry Ford Hospital (HFH) Sepsis Steering Committee was formed by the Clinical Quality and Safety Department to develop and implement a CQI initiative for severe sepsis and septic shock. The committee consisted of the Administration, Nursing, Pharmacy and Medical Directors of the ICUs, ED, and inpatient medical/surgical floors. The committee used the sepsis RB derived from the Surviving Sepsis Campaign.[19] Minor adjustments were made to accommodate the unique needs of the each particular medical or SICU environment. This group met monthly to review the data and to discuss improvement strategies. The data that were collected prospectively as the initiative progressed are the data analyzed in this study.

This initiative was conducted without adding more clinical staff to execute the treatment protocol. The Sepsis Coordinator was a full-time equivalent position and was responsible for data collection and analysis. She was not involved in any direct medical management, rather coordinated the education about practice guidelines and provided performance feedback. Implementation of the treatment protocol was achieved mainly by ongoing education and direction of the nursing, support and physician staffs. Additional tools were developed which included pharmacy order sets, algorithm pocket cards, badge cards, and a dedicated sepsis phone-line to the pharmacy. Nursing education began during the year prior to the initiation of data collection. This education was enhanced with

lunch-and-learn sessions at the beginning of this study. Physician education was conducted via clinical teaching, Grand Round presentations, and monthly unit orientations for the house staff.

Interventions and Data Collection

Patients were screened daily using the electronic medical record and during daily rounds in each practice unit by the Sepsis Coordinator. The locations of the initial presentation included our ED, affiliated suburban EDs, inpatient general practice units (GPU), MICU, and SICU. Serum lactate levels, antibiotics and vasopressor administration were scanned to select patients who may have been eligible for the RB. Each chart was then reviewed in real-time during weekday hours and retrospectively during nights and weekends to determine if all sepsis RB elements (Table 1) were completed and within what time from sepsis presentation.

Demographics, vital signs, laboratory data, and medical interventions were collected. Baseline ("time zero") and 24-hour severity-of-illness scores were calculated, including the Acute Physiologic and Chronic Health Evaluation Score II (APACHE II) and Sequential Organ Failure Assessment score (SOFA) score. Participants presenting to any ED with severe sepsis or septic shock had their time zero calculated as the time of triage in the ED. Participants presenting to the suburban EDs were enrolled as the location of sepsis origin. This process could be used because all patient data can be accessed via a coordinated electronic medical record. In addition, all ICU admissions were to our facility. For all others enrolled, time zero was defaulted to admission time to the ICU. Transfers from other acute care facilities were excluded given the unknown time of initial sepsis presentation.

Patient Groups

The *Early Compliers at 6 hrs* consisted of eligible patients who received all 6 RB elements within 6 hours (Table 2). The *Non-Compliers* consisted of eligible patients who never met all of the RB elements including a goal MAP $\geq$65 mm Hg, goal central venous pressure (CVP) $\geq$8 mm Hg, or goal $ScvO_2$ $\geq$70% at any time since presentation (Table 2). The *Delayed Compliers after 6 hrs* consisted of patients who received all 6 RB elements but took greater than 6 hours from diagnosis, "time zero" (Table 2). When examined at incremental time points, we determined that the RB had a significant effect on mortality up to 18 hours from presentation. Using this timeline, the *Compliers at 18 hrs* and *Non-Compliers at 18 hrs* were then compared based on this demarcation (Table 2).

Outcomes

The primary outcome was to determine in-hospital and 28-day mortality following the implementation of the sepsis bundle. Our secondary outcome was to examine the effect of varying degrees of completion and delays in sepsis bundle compliance on hospital mortality, length of stay, duration of mechanical ventilation, and hospital disposition.

Table 2. Study Group Definitions for Figure 1 and 2

Figure 1		
Sepsis non-Shock	n = 218	MAP $\geq$65 and lactate <4 (after initial fluid challenge)
Septic shock	n = 498	MAP <65 and/or lactate $\geq$4 (after initial fluid challenge)
Early compliers at 6 hrs	n = 64	All resuscitation bundle elements completed within 6 hours.
Delayed compliers after 6 hrs	n = 273	All resuscitation bundle element completed any time after 6 hours.
Non-Compliers	n = 161	Never completed all resuscitation bundle element at any point in time.
Figure 2		
Compliers at 18 hrs	n = 202	All resuscitation bundle elements completed within 18 hours.
Non-Compliers at 18 hrs	n = 296	All resuscitation bundle elements completed after 18 hours or never completed all resuscitation bundle elements.

Statistical Methods

The Student 2-sample *t*-test, Wilcoxon rank sum test, and chi square test were employed to compare demographic, baseline clinical data, and organ dysfunction scores between the various sepsis RB study groups is listed in Table 2. Multivariate analysis was done to control for confounding factors. Kaplan-Meier probability of survival with 95% confidence intervals described the relative risk of survival within 1 year from admission. For patients with no encounter found on computerized charts, the last known date alive was determined by reviewing computer charting for death summaries and the state death registry.

Results

Of the 716 patients screened, 218 did not meet criteria for severe sepsis or septic shock after the initial fluid bolus was delivered (Figure 1). The hospital mortality of this group of sepsis nonshock patients was 19.7%. The remaining 498 patients who met criteria for severe sepsis or septic shock had an overall mortality of 43.4% compared to the sepsis nonshock group ($P < .01$; Figure 1). We then analyzed the severe sepsis and septic shock group for compliance with the RB elements (Figure 1). The *Early Compliers at 6 hrs* consisted of 64 patients (12.9%), the *Delayed Compliers after 6 hrs* consisted

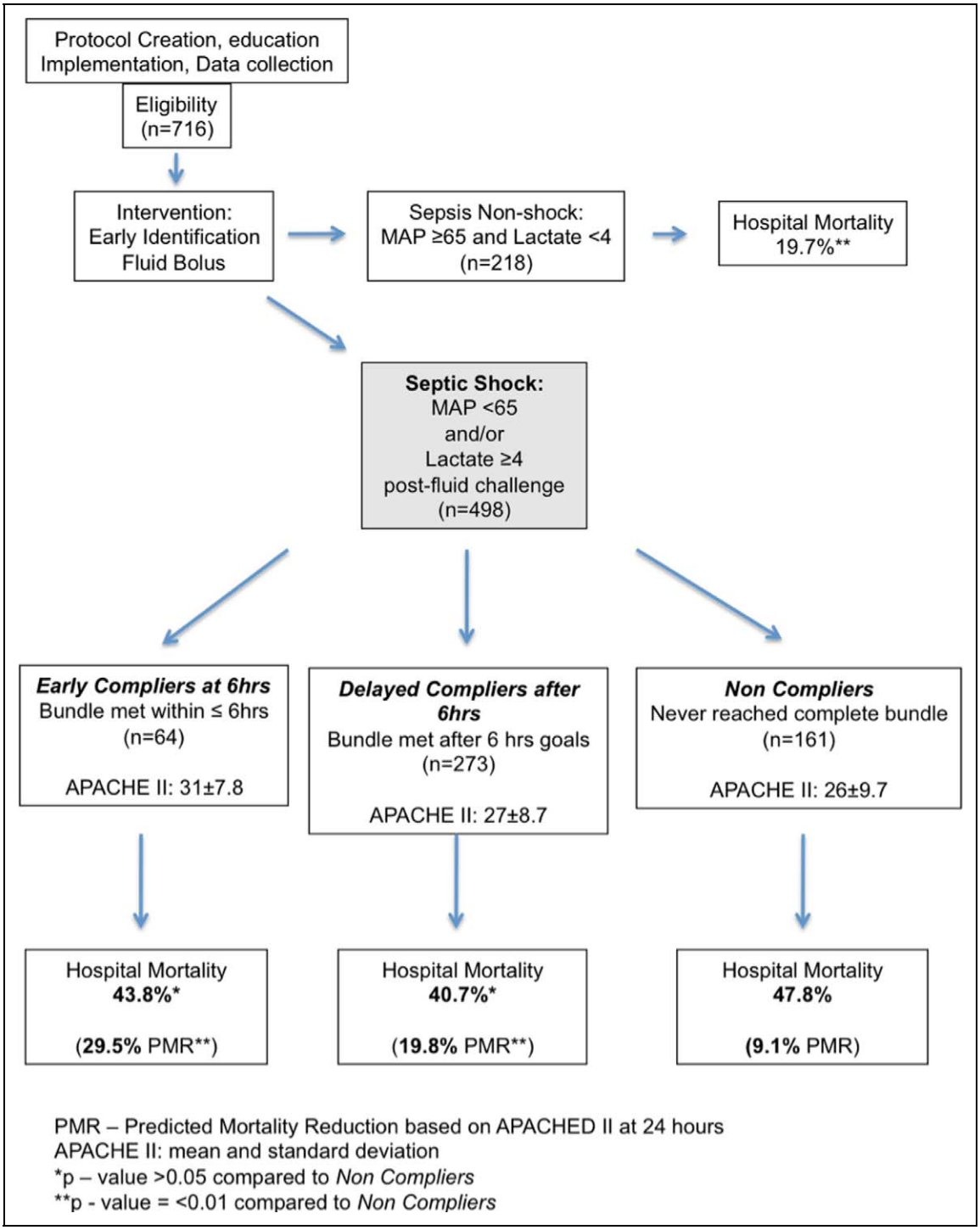

Figure 1. Study overview.

of 273 (54.8%) patients. The *Non-Compliers* consisted of 161 patients, 32.3% of the 498 eligible patients (Figure 1). There was no statistically significant difference in age, sex, race, baseline vital signs, and laboratories between these groups (Table 3). The *Early Compliers at 6 hrs* had a significantly higher 24-hour APACHE II score of 31 $\pm$ 7.8 compared to the *Delayed Compliers after 6 hrs and Non-Compliers* of 27 $\pm$ 8.7 and 26 $\pm$ 9.7, respectively ($P < .01$; Table 4). The in-hospital mortality was not statistically significant between the 3 groups (Figure 1; Table 5). The higher baseline illness severity derived from 24-hour APACHE II in the *Early Complier at 6 hrs* had a predicted mortality of 73.3% significantly higher than the *Delayed Complier after 6 hrs* and the *Non-Compliers* ($P < .01$; Table 4). Considering the increased severity of illness observed in the *Early Compliers at 6 hrs,* the reduction in predicted mortality in the *Early Compliers at 6 hrs* was 29.5%

Table 3. Demographics and Baseline Characteristics of the Patients[a,b]

Variable	*Early Compliers at 6 hrs*[a] Mean % (±SD)	*Delayed Compliers After 6 hrs*[a] Mean % (± SD)	*Non-Compliers* Mean % (± SD)
Sex (male)	56	60	47
Race (Black)	73	66	68
Age (years)	64 (±18.2)	65 (±15.2)	63 (±15.7)
Weight (kg)	87.3 (±33.6)	86.2 (±31)	84.5 (±31.2)
Temp (°C)	37.2 (±1.9)	36.9 (±1.7)	37 (±1.3)
HR (beats/min)	116 (±26)	108 (±24)	107 (±25)
RR (resp/min)	27 (±11)	25 (±9)	25 (±8)
MAP (mm Hg)	76 (±23)	74 (±20)	76 (±22)
Lactate (mmol/L)	4.94 (±3.43)	4.86 (±3.93)	4.86 (±3.43)
Arterial pH	7.34 (±0.12)	7.33 (±0.14)	7.34 (±0.12)
A-aD02 (mm Hg)	403 (±179)	398 (±178)	352 (±187)
PaO_2	135 (±101)	132 (±96)	116 (±71)
PaO_2/FiO_2	266 (±171)	299 (±209)	306 (±222)
Na+ (meq/L)	136.6 (±6.1)	139 (±7.6)	138.1 (±6.1)
K+ (meq/L)	4.3 (±1.1)	4.2 (±1.1)	4.2 (±1.2)
Creatinine (mg/dL)	2.8 (±2.1)	2.77 (±2.5)	2.8 (±2.2)
WBC	15 (±11.9)	15.9 (±12.8)	16.3 (±15.1)
Hct	31.7 (±7.3)	31.6 (±7.4)	31.2 (±6.7)
Platelet	245 (±150.2)	226 (±132)	244 (±210)
Bilirubin	1.6 (±1.6)	2.7 (±2.7)	1.9 (±2)

[a] $P > .05$ compared to *Non-Compliers* for all variables.
[b] Patient characteristics of hemodynamic variables and laboratories are values first available upon presentation to intensive care unit or emergency department. Proportions are presented as percentages (number of patients).

Table 4. Illness Severity Characteristics of all Patients With Septic Shock[a]

	Early Compliers at 6 hrs	*Delayed Compliers After 6 hrs*	*Non-Compliers*
APACHE II			
Baseline	23 (±7.5)[b]	20.4 (±7.8)	19 (±7.7)
24 hour	31 (±7.8)[b]	27 (±8.7)	26 (±9.7)
Predicted Mortality	73.3%[b]	56.9%	60.5%
SOFA—24hr	10.5 (±3.8)[b]	9.9 (±4.9)[b]	8.3 (±4.4)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, sequential organ failure assessment score.
[a] Predicted mortality based on APACHE II score at 24 hours. Values are mean ± SD.
[b] $P < .01$ compared to *Non-Compliers*.

compared to 19.8% and 9.1% in the *Delayed Compliers after 6 hrs* and *Non-Compliers*, respectively ($P < .01$; Table 5).

We then reexamined the 498 severe sepsis and septic shock patients in the study population by increments of 6 hours to determine the upper limit of time that the RB would positively affect outcomes. There were significant reductions in mortality for RB compliance up to 18 hours ($P = .03$; Figure 2). There was no significant improvement in mortality after 18 hours even when the RB was completed. Using 18 hours as a demarcating point, there were 202 patients (40.6%) who had the RB completed in ≤18 hours (*Compliers at 18 hrs*; Figure 2). There were 296 patients (59.4%) who either completed the RB after 18 hours (135) or never completed the RB (161), this comprised the *Non-Compliers at 18 hrs* (Figure 2).

Table 5. Mortality of all Patients With Septic Shock[a]

	Early Compliers at 6 hrs	*Delayed Compliers after 6 hrs*	*Non-Compliers*
Hospital mortality	43.8%[b]	40.7%[b]	47.8%
28-day mortality	40.6%[b]	38.1%[b]	44.1%
Absolute PMR	29.5%[c]	19.8%[c]	9.1%

[a] Predicted mortality derived from the Acute Physiologic and Chronic Health Evaluation Score II (APACHE II) at 24 hours. Absolute predicted mortality reduction (PMR): difference in predicted mortality minus hospital mortality.
[b] $P > .05$ compared to *Non-Compliers*.
[c] $P < .01$ compared to *Non-Compliers*.

There was no statistically significant difference in age, sex, race, baseline vital signs, and laboratories between the *Compliers at 18 hrs* and *Non-Compliers at 18 hrs* (Table 6). The *Compliers at 18 hrs* had a significantly lower hospital mortality of 10.2% compared to *the Non-Compliers at 18 hrs* ($P = .03$; Figure 2; Table 10). When the 2 groups were adjusted for differences in baseline illness severity, 24-hour APACHE II, the *Compliers at 18 hrs* had a greater reduction in predicted mortality of 26.8% versus 9.4%, $P < .01$ (Table 8 and 10).

Sources of infection and the presence of bacteremia and/or fungemia were equally distributed at 33% between the 2 groups ($P > .05$). The *Compliers at 18 hrs* received significantly more fluid at 0 to 6 hours ($P = .04$), 7 to 24 hours, and during the 0- to 24-hour period ($P < .01$; Table 9). There was no statistically significant difference in vasopressor or transfusion therapy between the 2 groups during the first 24 hours (Table 9).

All patients regardless of RB compliance received comparable surgical source control, stress ulcer prophylaxis, deep-venous thrombosis prophylaxis, glycemic control, and low-tidal volume ventilatory support (Table 9). Both groups had similar endotracheal intubation rates and need for mechanical ventilation. Compliance with the SSCs maintenance bundle[20] that includes application of protective lung strategies, consideration for low-dose steroids, glycemic control, and use of recombinant activated protein C was similar in both groups (Table 9).

Reaching a goal CVP ≥ 8 mm Hg within 18 hours was obtained in the 100% of *Compliers at 18 hrs* (53% met within 6 hours) versus 49% in the *Non-Compliers at 18 hrs* (21% met within 6 hours; Table 9). Compliance with goal MAP ≥65 mm Hg was 100% of *Compliers at 18 hrs* versus 88% in *Non-Compliers at 18 hrs. G*oal $ScvO_2$ ≥70% within 18 hours was obtained in the 100% of *Compliers at 18 hrs* (55% in 6 hours) versus 53% in *Non-Compliers at 18 hrs* (22% within 6 hours; Table 9).

Figure 3 illustrates the bundle compliance of *Compliers at 18 hrs* during our study period. The percentage of *Compliers at 18 hrs* was 30.4% in the first quarter with the nadir being 28.3% in the 2nd quarter. The percentage of *Compliers*

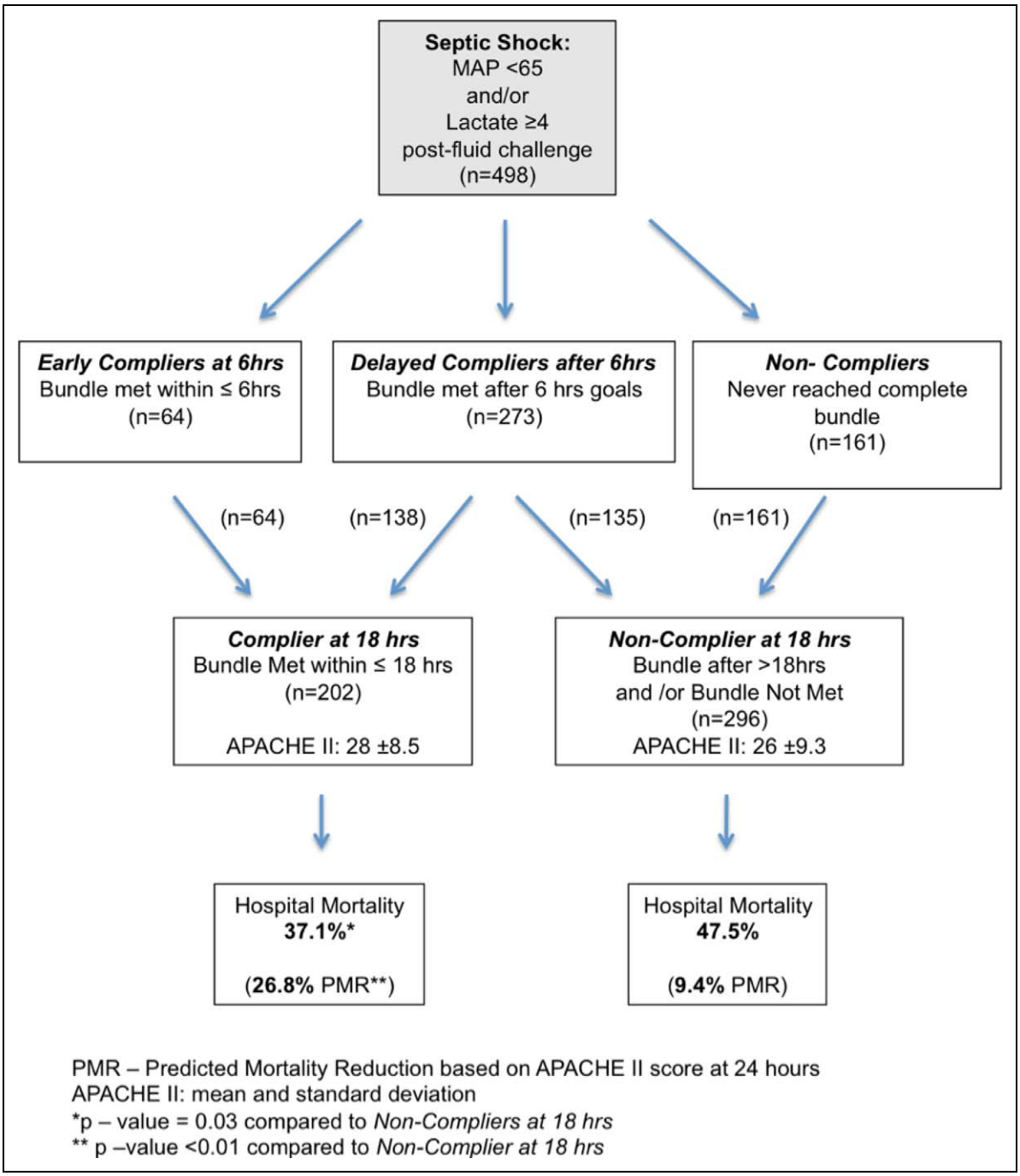

Figure 2. Study overview.

at 18 hrs increased for each subsequent quarter peaking at 63% during the last quarter of the study (Figure 3). Analysis of *Non-Compliers at 18 hrs* showed improvement in compliance with the number of RB elements completed each quarter even though not all 6 RB elements were met. During the first quarter of the study, 4 RB elements or less were completed in 35% of patients while 5 or more elements were completed in 65% of patients. By the last quarter of the study, 100% of patients had at least 5 or 6 elements completed when combining the set of *Compliers at 18 hrs* and *Non-Compliers at 18 hrs*.

We analyzed the individual sepsis RB elements by institutional location of severe sepsis presentation. Over half of the patients presented from the ED (52%) and the remainder originated in the ICU and inpatient GPU (medical-surgical floors; Table 7). The percentage compliance with RB elements depended upon the location of initial presentation and time of assessment with compliance. Achieving the goal of broad-spectrum antibiotic delivery within 3 hours for all locations had the lowest compliance in the ED (57.5%) and the highest compliance in the ICU (88.1%). With the other 5 sepsis RB

Table 6. Demographics and Baseline Characteristics of *Compliers at 18 hrs* compared to *Non-Compliers at 18hrs*[a]

Variable	*Compliers at 18 hrs* Mean % (±SD)	*Non-Compliers at 18 hrs* Mean % (±SD)
Sex (male)	53	53
Race (Black)	71	65
Age (years)	65	63
Weight (kg)	85.4 (±31.1)	86.1 (±31.6)
Temp (°C)	37.0 (±1.9)	37.0 (±1.4)
HR (beats/min)	112 (±26)[b]	106 (±24)[b]
RR (resp/min)	26 (±11)[c]	25 (±8)[c]
MAP (mm Hg)	76 (±21)	74 (±21)
Lactate (mmol/L)	5.02 (±4.02)	4.76 (±3.48)
Arterial pH	7.34 (±0.14)	7.33 (±0.13)
A-aD02 (mm Hg)	406 (±182)	373 (±180)
PaO_2 (mm Hg)	134 (±100)	122 (±80)
PaO_2/FiO_2	304 (±190)	291 (±220)
Na + (mEq/L)	138.2 (±7.1)	138.5 (±7.0)
K+ (mEq/L)	4.2 (±1.1)	4.2 (±1)
Creatinine (mg/dL)	2.8 (±2)	2.8 (±2.6)
WBC	15.9 (±13.9)	15.9 (±13.1)
Hct	31.9 (±7.3)	31.1 (±7.1)
Platelet	234 (±139)	234 (±179)
Bilirubin	2 (±2)	2.4 (±2)

[a] Patient characteristics of hemodynamic variables and laboratories are values first available upon presentation. Proportions are presented as percentages (number of patients)
[b] P = .02 compared to *Non-Compliers at 18 hrs.*
[c] P = .04 compared to *Non-Compliers at 18 hrs.*

elements completed and extending the time to antibiotic from 3 hours to 18 hours, the overall bundle compliance increased from 71% to 98%, with the hospital mortality remaining the same at 37%. The ED had the highest compliance for goal CVP ≥8 mm Hg of 70.5% at 18 hours and $ScvO_2$ ≥70% within 18 hours at 75.6% compared to the ICU, GPU, and suburban ED. The most common missing element in the ICU was goal $ScvO_2$ ≥70% within 18 hours at 52.5% compliance. The GPU reached 57.5% compliance and 59.4% compliance for goal CVP ≥8 mm Hg and $ScvO_2$ ≥70% within 18 hours, respectively. The Suburban ED had the lowest compliance for $ScvO_2$ ≥70% within 18 hours at 45%. Kaplan Meier survival curve predicted a significantly higher probability of survival in *Compliers at 18 hrs* compared to *Non-Compliers at 18 hrs* up to 1 year from hospital admission (Figure 4; $P < .05$).

Table 7. Origin of Presentation

	Compliers at 18 hrs	*Non-Compliers at 18 hrs*
ED	61%[a]	44%
ICU	17%[a]	28%
GPU	19%	23%
Suburban ED	3%	5%

Abbreviations: ED, emergency department; ICU, intensive care unit; GPU, general practitioner unit.
[a] P < .01 compared to *Non-Compliers at 18 hrs.*

Discussion

This study supports previous studies that initiation of an institutional CQI effort leads to increased RB compliance and decreased mortality among patients with severe sepsis or septic shock even with completion beyond 6 hours.[21] This study was further generalized to all critically ill patients such as immunosuppressed and those with metastatic disease. As a result, the patients in this study had a higher mean APACHE II score and higher predicted hospital mortality compared to the original EGDT study group.[13] Correcting for severity of illness with

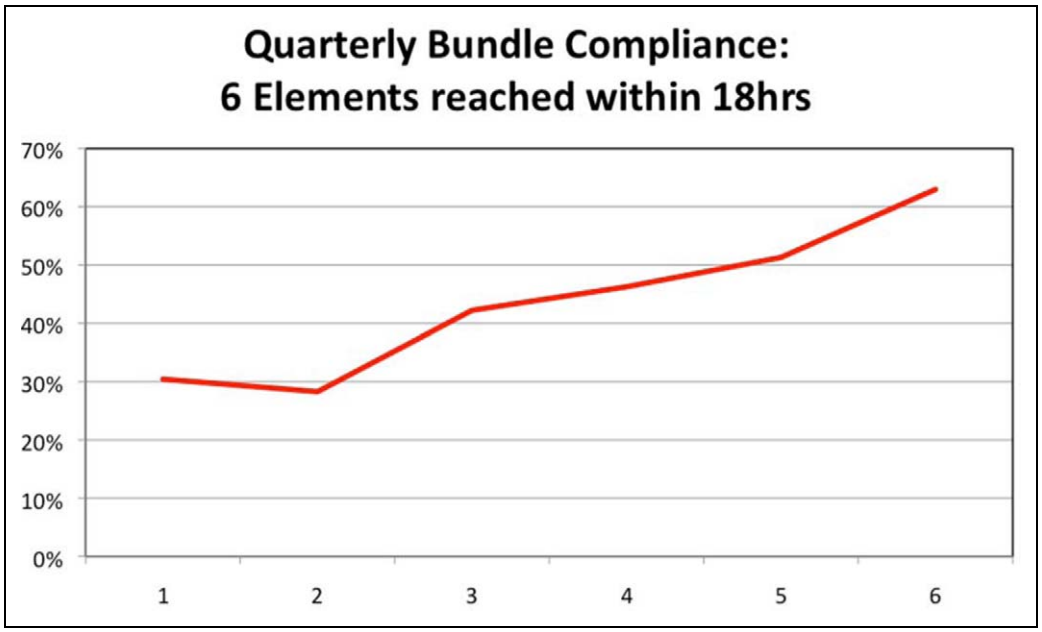

Figure 3. *Compliers at 18 hrs* compliance over 6-quarter period. Increase compliance in *Compliers at 18 hrs* over 6 quarters.

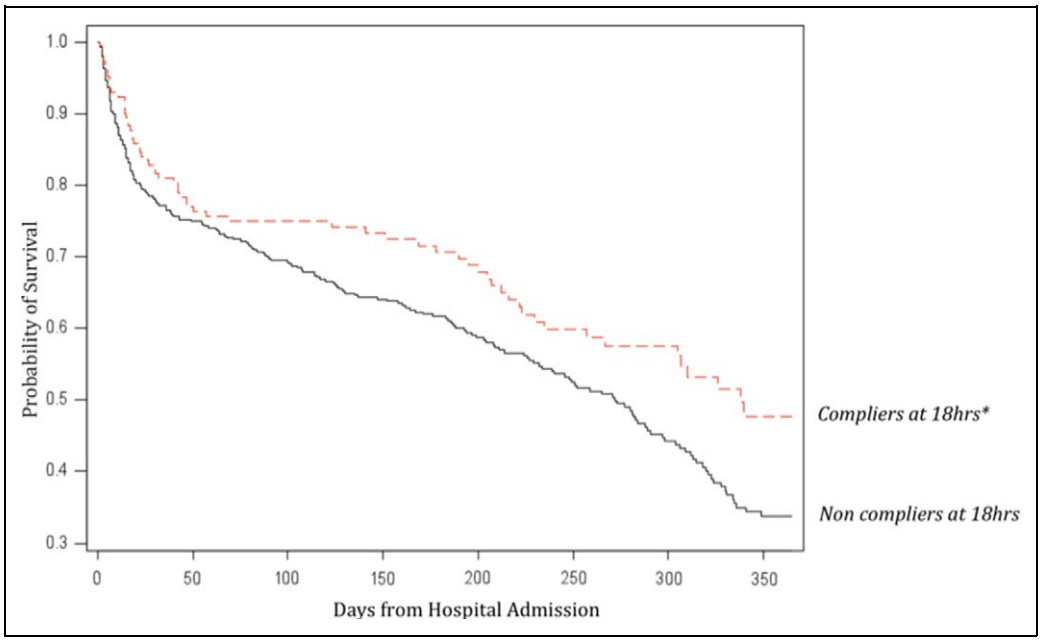

Figure 4. Kaplan Meier probability of survival for *Compliers at 18 hrs* from admission to 1 year compared to *Non-Compliers at 18 hrs*. Increase in probability of survival after 1 year from presentation. * $P < .05$

Table 8. Severity of Illness Characteristics of *Compliers at 18 hrs* compared to *Non-Compliers at 18 hrs*[a]

	Compliers at 18 hrs[b]	*Non Compliers at 18 hrs*
APACHE II		
Baseline	21 (±7.8)	20 (±7.8)
24 hour	28 (±8.5)	26 (±9.3)
Predicted mortality	63.9%	56.9%
SOFA—24 hour	9.9 (±4.5)	9.2 (±4.9)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, sequential organ failure assessment score.
[a] Predicted mortality based on APACHE II at 24 hours. Values are means ±SD.
[b] *P* value >.05 compared to *Non-Compliers at 18 hrs*.

24-hour APACHE II, *Early Compliers at 6 hrs* had a 3-fold reduction of predicted hospital mortality compared to *Non-Compliers*.

The presence of infection and frequency of bacteremia was 33%, consistent with previous sepsis trials.[13] This finding confirms antibiotic therapy as one cornerstone in early sepsis resuscitation.[22] The time for antibiotic administration recommended by the Surviving Sepsis Campaign 2004 is within 3 hours of presentation to the ED and within 1 hour of presentation to the ICU. Inspite of these recommendations, there was no significant difference in our mortality when antibiotics were given within 3 hours compared to within 18 hours. As shown by the EGDT therapy study, early aggressive volume therapy is associated with increased survival and less vasopressor use.[13] Consistent with these findings, the *Compliers at 18 hrs* on average received 7.7 L of crystalloid in the first 24 hours, almost 2 L more than the *Non Compliers at 18 hrs*. The occurrence of vasopressor at presentation and 24 hours were not significantly different between *Compliers at 18 hrs* and *Non-Compliers at 18 hrs*.

Our CQI initiative goal was to increase compliance with the sepsis RB over the 18-month period, with the assistance of a Sepsis Coordinator. We were able to show improvement to over 60% in *Compliers at 18 hrs*. For *Early Compliers at 6 hrs*, our improvement was only 12% over 18 months. When evaluating the number of individual RB elements completed, during the 1st quarter, 65% had 5 or more bundle elements completed compared to the last quarter with 100% having 5 or more bundle elements completed. Further studies are needed to evaluate for an association between the number of bundle elements completed and hospital mortality. This CQI initiative was established and evaluated at an urban academic teaching institution. RB compliance was strictly dependent on timely documentation of all 6 sepsis RB elements documented as met or not.

Conclusion

In our institution, the CQI initiative for the sepsis RB decreased mortality. More importantly, we found significant benefit even when complete RB compliance was achieved as late as 18 hours from time of presentation. The assistance of an institutional Sepsis Coordinator allowed the continuous monitoring of compliance, and as a result, improved compliance with all elements of the sepsis RB. With the high prevalence of sepsis patients coming from the ED, institutional efforts and resources should be directed toward this portal of entry to further improve outcomes.

Acknowledgments

We would like to acknowledge the clerical, nursing and support personnel in the emergency department, general practice units, and the

Table 9. Interventions in 1st 24 hours for *Compliers at 18 hrs* and *Non-Compliers at 18 hrs*[a]

Variable	*Compliers at 18 hrs*	*Non-Compliers at 18 hrs*
Inclusion		
MAP < 65 mmHg (initial)	73%	74%
SBP < 90 mmHg (initial)	65%	61%
Lactate $\geq$ 4 mmol/L (initial)	56%	53%
Resuscitation		
Crystalloid volume 0-6 hours (L)	2.85 ($\pm$ 1.8)[b]	2.33 ($\pm$ 2.0)
Crystalloid volume 7-24 hours (L)	4.82 ($\pm$ 3.9)[c]	3.63 ($\pm$ 2.6)
Crystalloid volume first 24 hours (L)	7.70 ($\pm$ 4.5)[c]	5.96 ($\pm$ 3.7)
Vasopressor upon presentation	12%	14%
Vasopressor first 24 hours	64%	57%
Intubated	58%	52%
RB Elements—6 hours		
Antibiotics given within 3 hours	71%	72%
MAP $\geq$65 mmHg post resuscitation	100%[c]	88%
CVP $\geq$8 mmHg goal within 6 hours	53%[c]	21%
$ScvO_2$ $\geq$70% goal in 6 hours	55%[c]	22%
RB Elements—18 hours		
Antibiotics given within 18 hours	100%[b]	98%
CVP $\geq$8 mm Hg obtained within 18 hours	100%[c]	49%
$ScvO_2$ $\geq$70% obtained within 18 hours	100%[c]	53%
Maintenance RB Elements		
Steroid stim test	38%	31%
Steroids given	29%	25%
Appropriate for Drotecogin alfa	3.5%	1.7%
Drotecogin alfa given	3.5%	1.4%
glucose between 90 and 150 mg/dl	12.4%	10.8%
Median IPP<30 (those intubated)	85%	79%

Abbreviations: CVP, central venous pressure; $ScvO_2$, central venous oxygen saturation; MAP, mean arterial pressure; SBP, systolic blood pressure; IPP, inspired plateau pressure.

[a] Values are means $\pm$ SD. Patient characteristics of hemodynamic variables and laboratories are values first available upon presentation. Proportions are presented as percentages (number of patients)

[b] P = .04 compared to *Non-Compliers at 18 hrs.*

[c] P < .01 compared to *Non-Compliers at 18 hrs.*

Table 10. Outcomes[a]

	Compliers at 18 hrs	*Non-Compliers at 18 hrs*
Hospital mortality	37.1%[b]	47.3%
28-day mortality	35.6%[b]	43.6%
Absolute PMR	26.8%[c]	9.4%

[a] Predicted mortality derived from the Acute Physiology and Chronic Health Evaluation II (APACHE II) at 24 hours. Predicted mortality reduction (PMR): difference in predicted mortality minus hospital mortality.

[b] *P* = .03 compared to *Non-Compliers* at 18 hrs

[c] *P* < .01 compared to *Non-Compliers* at 18 hrs

medical and surgical intensive care units at Henry Ford Hospital and thank those involved in the Sepsis Steering Committee, Dr David Amponsah, Dr Ronny Otero, Dr Audwin J. Garcia, Joyce Farrer, Dr Razaq Badamosi, and Dr Michael Eichenhorn. Also, we would like to thank Dr Emanuel Rivers for his time and assistance in this institutional CQI initiative.

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