Survival Benefit and Cost Savings From Compliance With a Simplified 3-Hour Sepsis Bundle in a Series of Prospective, Multisite, Observational Cohorts

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Objectives: To determine mortality and costs associated with adherence to an aggressive, 3-hour sepsis bundle versus noncompliance with greater than or equal to one bundle element for severe sepsis and septic shock patients.

Design: Prospective, multisite, observational study following three sequential, independent cohorts, from a single U.S. health system, through their hospitalization.

Setting: Cohort 1: five tertiary and six community hospitals. Cohort 2: single tertiary, academic medical center. Cohort 3: five tertiary and four community hospitals.

Patients: Consecutive sample of all severe sepsis and septic shock patients (defined: infection, ≥ 2 systemic inflammatory response syndrome, and hypoperfusive organ dysfunction) identified by a quality initiative. The exposure was full 3-hour bundle compliance. Bundle elements are as follows: 1) blood cultures before antibiotics; 2) parenteral antibiotics administered less than or equal to 180 minutes from greater than or equal to two systemic inflammatory response syndrome "and" lactate ordered, or less than or equal to 60 minutes from "time-zero," whichever occurs earlier; 3) lactate result available less than or equal to 90 minutes postorder; and 4) 30 mL/kg IV crystalloid bolus initiated less than or equal to 30 minutes from "time-zero." Main outcomes were in-hospital mortality (all cohorts) and total direct costs (cohorts 2 and 3).

Measurements and Main Results: Cohort 1: 5,819 total patients; 1,050 (18.0%) bundle compliant. Mortality: 604 (22.6%) versus 834 (26.5%); CI, 0.9–7.1%; adjusted odds ratio, 0.72; CI, 0.61–0.86; *p* value is less than 0.001. Cohort 2: 1,697 total patients; 739 (43.5%) bundle compliant. Mortality: 99 (13.4%) versus 171 (17.8%), CI, 1.0–7.9%; adjusted odds ratio, 0.60; CI, 0.44–0.80; *p* value is equal to 0.001. Mean costs: $14,845 versus $20,056; CI, –$4,798 to –5,624; adjusted β, –$2,851; CI, –$4,880 to –822; *p* value is equal to 0.006. Cohort 3: 7,239 total patients; 2,115 (29.2%) bundle compliant. Mortality: 383 (18.1%) versus 1,078 (21.0%); CI, 0.9–4.9%; adjusted odds ratio, 0.84; CI, 0.73–0.96; *p* value is equal to 0.013. Mean costs: $17,885 versus $22,108; CI, –$2,783 to –5,663; adjusted β, –$1,423; CI, –$2,574 to –272; *p* value is equal to 0.015.

Conclusions: In three independent cohorts, 3-hour bundle compliance was associated with improved survival and cost savings. (*Crit Care Med* 2016; XX:00–00)

Key Words: costs and cost analysis; multiple organ failure; sepsis; septic shock; systemic inflammatory response

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Sepsis is a leading cause of death and healthcare spending globally (1, 2). U.S. prevalence alone conservatively exceeds 1,000,000 cases per year in patients greater than or equal to 65, accounting for approximately 350,000 deaths (3). In 2011, sepsis accounted for $20 billion in payer costs (4).

Despite substantial effort, advances in understanding and managing sepsis have been modest. For years, best-practice discourse focused on "early goal-directed therapy", based on a 6-hour septic shock bundle that espoused optimizing central venous pressure (CVP) and oxygenation with inotropes and blood transfusion, adjusted based on rigorous hemodynamic monitoring (5). Three recent multisite randomized trials all failed to demonstrate mortality benefits from EGDT versus "usual care" (6–8). However, although standard-of-care has changed over ensuing years prohibiting direct comparisons, both study and control arm patients in all three recent trials, and in the trial by Rivers et al (5), received early antibiotics and empiric IV fluid resuscitation with average times less than 3 hours. Several studies investigating bundle "compliance," of which early IV fluid and antibiotic administration is a component, report association between full compliance and better outcomes (9–13). This raises the question as to whether the original benefit of EGDT lied not in invasive, resource-intensive, hemodynamic monitoring, but earlier sepsis identification and intervention. The impact of full compliance with a 3-hour bundle alone in a population where there was no requirement to apply a 6-hour bundle has not been investigated.

Recently, a joint Society for Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) Task Force recommended changes to definitions of septic disease and identification measures, focusing on sepsis-induced organ dysfunction and diagnostic criteria (14–16). The literature and recommendations reflect ambiguity in both defining sepsis and executing evidence-based management. Despite this, consensus remains on the importance of early intervention with IV fluids and antibiotics.

Reliable timely parenteral antibiotics and fluid administration for severe sepsis and septic shock (SS/SS) is the accepted standard in randomized trials, but often not achieved in community settings. We began a quality improvement (QI) project based upon the hypothesis that reliably implementing an aggressive 3-hour sepsis treatment bundle for every patient, every time, in a large multihospital health system would improve outcomes. The adopted bundle emphasizes early recognition with a focus on "time-zero" entry points followed by aggressive, time-sensitive collection of blood cultures, ordering and return of lactate levels, and administration of fluids and antibiotics within 180 minutes. Importantly, this approach obligates only rapid delivery of simple interventions with a focus on preventing further organ injury, and has no reliance on physiologic endpoints. It leaves all management beyond 3 hours to physician discretion.

We hypothesize that time-dependent adherence to all elements of a 3-hour sepsis bundle, without reliance on specific physiologic goals, may be sufficient to improve in-hospital mortality while reducing spending for providers and payers alike in this high-incidence, high-acuity population. We conducted a series of sequential, prospective, observational cohort studies with the objective of determining mortality and costs associated with 3-hour bundle compliance.

METHODS

Overall Study Design

Northwell Health began a broad-ranging sepsis care QI project in 2009 and adopted a defined algorithm and 3-hour bundle in 2010 to screen and treat sepsis patients (17). To measure bundle compliance and outcomes, data for all consecutive sepsis patients with (new, sepsis-related) organ dysfunction (defined in **Table 1**)—"severe sepsis" at the time of study design—or septic shock (SS/SS) were prospectively captured throughout their hospital stay in an internally managed QI database. We developed three sequential observational cohort studies (**Fig. 1**) and abstracted relevant data from the QI database into distinct research registries for all analysis. These studies follow similar but independent SS/SS cohorts through their hospitalization with increasingly rigorous methodology. We used sequential cohorts to address limitations of preceding analyses, and reasoned concordant findings would demonstrate reproducibility.

From our initial cohort, we produced a proof-of-concept analysis testing the association of bundle compliance with in-hospital mortality, versus noncompliance with greater than or equal to one bundle element, over a 1-year period in 11 urban, tertiary, and community hospitals in the Northwell Health system (700,000 emergency department [ED] visits per year). After concluding the first study period, we expanded QI data collection to conduct more rigorous analysis and begin assessing utilization and financial outcomes in a second cohort drawn from a single tertiary-care center (90,000 ED visits per year). Finally, we again broadened data collection to prospectively capture data on factors limiting our first two analyses. We then conducted a third study across nine tertiary and community hospitals across the health system (475,000 ED visits per year) to determine if findings held in the better-defined, multisite cohort. To maintain independence, we drew each cohort from nonoverlapping time periods: no patient encounter is included in more than one cohort. We detail methodology common to all three analyses below, before discussing individual cohorts.

Sepsis Algorithm and Bundle

All SS/SS patients met eligibility for algorithm care (**eFig. 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/C281). We defined SS/SS as infection and two or more systemic inflammatory response syndrome (SIRS) criteria (20) and lactate greater than or equal to 2.2 mmol/L or acute sepsis-related organ dysfunction (defined in Table 1). While more inclusive than SCCM guidelines at the time, this is consistent with the 2.0 mmol/L lactate cut-off in both Sepsis-3 and Centers for Medicare and Medicaid Services' definitions (14, 21). "Time-zero" was the laboratory result or vital sign measurement time

TABLE 1. Organ Dysfunction "Time-Zero" Criteria for 3-Hour Bundle Application and Study Inclusion

Organ Dysfunction Criteria[a]	Definition
Hyperlactemia	Serum lactate ≥ 2.2 mmol/L
Hypotension	Systolic blood pressure < 90 mm Hg or a mean arterial pressure < 65 mm Hg
Acute kidney injury[b]	Serum creatinine > 2.0 mg/dL in the absence of chronic kidney disease or 50% increase from known baseline
Thrombocytopenia	Platelet count < 150,000 cells/μm^3
Coagulopathy[c]	International normalized ratio > 1.5, activated partial thromboplastin time > 30 s, or partial thromboplastin time > 60 s, not otherwise explained by medical history
Elevated bilirubin	Serum bilirubin > 2.0 mg/dL in the absence of preexisting liver failure
Acute altered mental status	New altered mentation unrelated to the patient's prior medical history
Compromised oxygenation[d]	New increased O_2 requirement to maintain arterial oxygen saturation > 90% or a Pao_2/Fio_2 ratio < 300
≥ 2 "Super-SIRS" criteria at triage	Locally developed consensus criteria, where meeting ≥ 2 criteria at triage was a "time-zero" entry point for 3-hr bundle care. "Super-SIRS" criteria were as follows: 1) Heart rate ≥ 120 2) Respiratory rate ≥ 24 3) Systolic blood pressure < 90 mm Hg or mean arterial pressure < 65 mm Hg 4) Temperature ≥ 38.0°C (101.0°F) or ≤ 36.0°C (96.8°F) 5) Acutely altered mental status

SIRS = systemic inflammatory response syndrome.

[a]These seven "time-zero" triggers were used as 3-hr bundle entry points as well as study inclusion criteria. The intention was for all patients with a suspected infection who met ≥ 2 systemic inflammatory response syndrome (SIRS) criteria and "any" one of these criteria to receive care fully adherent to all 3-hr bundle elements. All patients included in this study had a source of infection, met at least two SIRS criteria, and met at least one of the above organ dysfunction criteria.

[b]Adapted from Kidney Disease: Improving Global Outcomes criteria for defining acute kidney injury (18).

[c]Adapted from the 2001 International Sepsis Definitions Conference (Sepsis-2) report (19).

[d]Adapted from the 2001 International Sepsis Definitions Conference (Sepsis-2) report (19).

first causing the patient to meet inclusion criteria. To expedite algorithm inclusion, we employed locally developed consensus criteria, nicknamed "Super-SIRS," at triage (Table 1) as an additional time-zero entry point. These criteria display overlap with Sepsis-3 recommendations, particularly pertaining to tachypnea and altered mentation (altered mental status [AMS]) triggers (14). The intention was to provide bundle compliant care to all eligible patients, which requires the following:

1. Blood cultures drawn before antibiotic administration.
2. Source-directed, broad-spectrum, parenteral antibiotics administered within 180 minutes of sepsis identification (≥ 2 SIRS and lactate ordered) or 60 minutes of time-zero (≥ 2 SIRS and available laboratory results or vital signs indicating hypoperfusion or organ dysfunction), whichever occurs earlier.
3. Lactate result available within 90 minutes of order (ordered upon recognition of infection with SIRS).
4. 30 mL/kg IV crystalloid bolus initiated within 30 minutes of time-zero.

The 3-hour bundle does not obligate central line placement or monitoring of CVPs, central venous oxygenation, or mixed venous oxygenation. Importantly, care beyond 3 hours was not protocolized and at physician discretion.

QI Initiative and Database Abstraction Process

eMethods 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/C280) details the underlying QI initiative, data collection process, and data fields captured.

Selection and Treatment of Study Subjects and Data

We abstracted relevant data from the prospective QI database into distinct, international review board–approved, research databases for each cohort. Subjects were all SS/SS patients in the QI database over the given study period (eFig. 1, Supplemental Digital Content 2, http://links.lww.com/CCM/C281). The exposure was 3-hour bundle compliance: whether all bundle elements were accomplished. To control for denominator expansion from improved recognition and Hawthorne effect, we did not include encounters before 2012, that is, 2 years after implementing the QI initiative.

For cohorts 2 and 3, we assessed financial measures using data obtained from the detailed accounting database maintained by the Northwell Health system. Financial methods and data-field definitions are detailed in **eMethods 2** (Supplemental Digital Content 1, http://links.lww.com/CCM/C280).

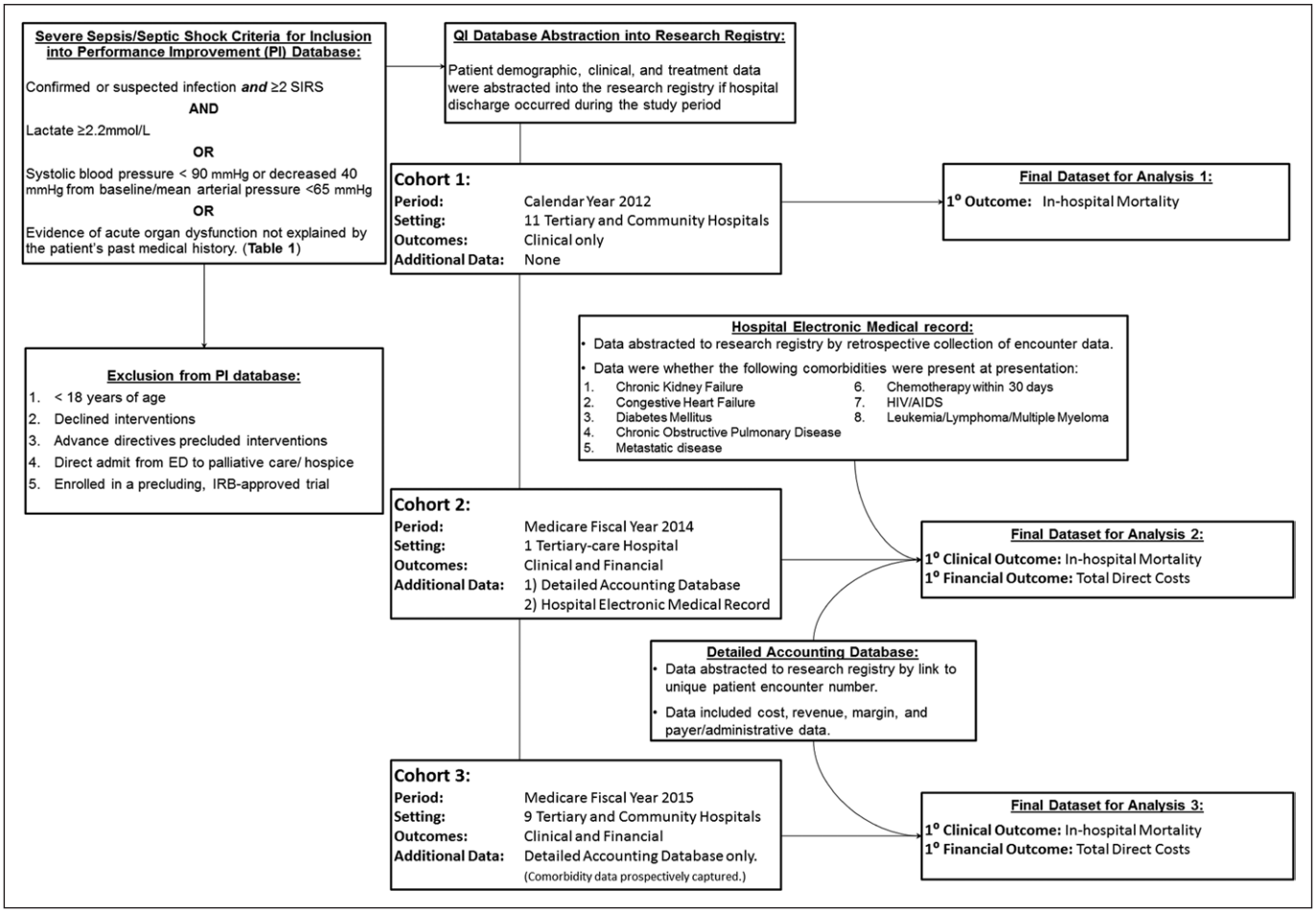

Figure 1. Schematic of investigational design. ED = emergency department, IRB = international review board, QI = quality Improvement, SIRS = systemic inflammatory response syndrome.

Outcomes

The primary clinical outcome was in-hospital mortality. In cohorts 2 and 3, the primary financial outcome was total direct cost (TDC) (secondary outcomes are described in **eMethods 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/C280).

Statistical Analyses

We performed analyses using SAS version 9.3 (SAS Institute, Cary, NC). There were no missing data for data fields used, and no loss-to-follow-up. We report continuous variables as means (SDS) or medians (interquartile ranges) and categoric variables as proportions. We report 95% CIs for outcome measures. In an effort not to present misleading data, we do not report *p* values for descriptive and outcome variables in univariate comparisons of exposure groups.

For all regression models, we employed forward selection, entering variables as covariates in the model for *p* value greater than 0.25, retaining them for *p* value less than 0.05. Bundle compliance was then entered and retained in the model regardless of significance. Model terms' main effects were considered significant for *p* value less than 0.05. We attempt to provide a measure of each model's internal validity. To do so, we assessed final logistic models' goodness-of-fit with Hosmer-Lemeshow test: the null hypothesis that the model adequately fit the data was accepted for *p* value greater than 0.05. We used adjusted r^2 to assess fit for final linear models (statistical methods for secondary outcomes are described in **eMethods 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/C280).

Cohort 1–Initial, System-Wide, Proof-of-Concept Analysis

Cohort 1 subjects were all SS/SS patients in the QI database admitted to any of the 11 participating hospitals during 2012. No QI database patients were excluded. We did not prospectively collect subjects' comorbidity data.

Cohort 2–Single-Site, Detailed Clinical-Financial Analysis

Cohort 2 comprised all SS/SS patients in the QI database treated at a single tertiary-care center, discharged during medicare fiscal year (MFY) 2014. No QI database patients were excluded. We extracted financial data from the accounting database and comorbidity data from the hospital's electronic medical record (Fig. 1). All data fields assessed from both datasets were available for all subjects. We autopopulated financial data using

unique identifiers. A single abstractor, blinded to subjects' compliance status, retrospectively collected comorbidity data.

Cohort 3–Multisite, Detailed Clinical-Financial Analysis

Cohort 3 subjects were all SS/SS QI database patients discharged during MFY 2015 and treated at a facility whose financial data were available in the accounting database. We included comorbidity data as a prospectively collected QI data field prior to this study period. Added data fields were severe sepsis versus septic shock diagnosis, infection site (e.g., respiratory), whether infections had nosocomial etiology, and need for mechanical ventilation. When extracting financial data, we excluded two community hospitals because data were unavailable. Of the nine hospitals with available financial data, no data fields had missing data for any encounters. No patients from this subset were excluded. Additionally, we analyzed the primary mortality outcome of the two subsets of the cohort: CHF and chronic renal failure (CRF) patients.

RESULTS

Cohort 1

There were 5,819 SS/SS patients in the 2012 cohort; 1,050 (18.0%) received bundle compliant care. **Tables 2** and **3** list subject characteristics. A higher proportion of compliant subjects presented with hypotension and had higher initial lactate; fewer had central catheters placed or received central hemodynamic monitoring. Groups demonstrated no other substantial differences. Expanded subject characteristics are reported in **eTable 1** (Supplemental Digital Content 3, http://links.lww.com/CCM/C282). The compliant group had 224 mortalities (21.3%) versus 1,213 (25.4%) in the noncompliant group (CI, 1.3–6.9%). In multivariable regression, bundle compliance was associated with significantly reduced mortality (odds ratio [OR], 0.72; 0.61–0.86; $p < 0.001$) (model covariables are described in **Table 4**).

Cohort 2

In the MFY 2014 cohort, 739 (43.5%) of 1,697 subjects received compliant care. Tables 2 and 3 summarize subject characteristics. Proportionally, more compliant subjects presented with thrombocytopenia or met Super-SIRS criteria; fewer had congestive heart failure (CHF), CRF, and presented with AMS or compromised oxygenation. There were no other substantial group differences. Less than 3% of both groups received central catheters or central hemodynamic monitoring. The compliant group experienced 99 mortalities (13.4%) versus 171 (17.8%) noncompliant mortalities (CI, 1.0–7.9%); mean TDC were $14,845 versus $20,056 (CI, –$4,798 to –5,624).

Table 4 summarizes adjusted outcomes and model covariables. As observed in cohort 1, multiple regression showed compliance in cohort 2 was associated with significantly lower mortality (OR, 0.65; CI, 0.49–0.87; $p = 0.004$) and lower TDC (β, –$2,851; CI, –$4,880 to –822; $p = 0.006$; $r^2 = 0.45$).

Cohort 3

The MFY 2015 cohort followed 7,239 SS/SS subjects. A total of 2,115 subjects (29.2%) received compliant care. (Subject characteristics are described in Tables 2 and 3). A total of 5,727 (79.1%) were tertiary facility patients. Compliant subjects presented with higher lactate. They had lower frequency of CHF, CRF, comorbid metastatic disease, central line placement, and central hemodynamic monitoring. The compliant group had 383 mortalities (18.1%) versus the noncompliant group's 1,078 (21.0%) (CI, 0.9–4.9%). TDC averaged $17,885 for compliance versus $22,108 for noncompliance (CI, $2,783–5,663).

We report adjusted outcomes and model covariables in Table 4. In multivariable regression, compliance in cohort 3 was again associated with significantly lower in-hospital mortality (OR, 0.84; CI, 0.73–0.96, $p = 0.013$) and TDC (β, –$1,423; CI, –$2,574 to –272; $p = 0.015$; $r^2 = 0.49$).

Subpopulations

For CHF patients, there were 56 compliant-group mortalities (23.6%) versus 234 noncompliant mortalities (29.0%). For CRF, we observed 43 compliant-group deaths (30.5%) versus 162 noncompliant deaths (27.9%). Adjusted ORs are provided in Table 4.

DISCUSSION

In three independent, prospective cohorts of nearly 15,000 SS/SS patients, compliance with a 3-hour sepsis bundle, not reliant on physiologic endpoints but with aggressive timelines, was reproducibly associated with lower in-hospital mortality after adjusting for potential confounders. When assessed in cohorts 2 and 3 (> 7,500 patients), compliance was also associated with substantial cost savings.

In interpreting our results, it is crucial to consider the immediate global burden of sepsis. Our results suggest implementing and adhering to a 3-hour bundle that does not require central access or complex physiologic monitoring could translate to meaningful survival benefit. Bundle compliance was also associated with cost savings, making cost-effectiveness analysis unnecessary. A conservative estimate of 1,000,000 cases per year (3, 22), and our most conservative observed adjusted TDC difference ($1,571 per patient), implies potential aggregate cost savings exceeding $1.5 billion per year in the United States, aligning improved clinical outcomes with improved financial performance.

An important consideration in interpreting these results is that bundle compliance is not defined "all-or-none," but rather "all-or-some." Noncompliant group patients may receive care that includes a majority, or even totality of bundle elements, just not in adherence to our aggressive time goals—for example, fluid resuscitation beginning 35 minutes after time-zero. The aggressiveness of some bundle elements could then partially explain this investigation's low overall mortality, particularly in cohort 2, which was conducted at a high-compliance site. The intent was to give all patients fully compliant bundle care. Although lack of a control population prohibits such an analysis, it is highly likely that the majority of patients received

TABLE 2. Baseline and Presentation Characteristics

	Cohort 1 (Calendar Year 2012)			Cohort 2 (Medicare Fiscal Year 2014)			Cohort 3 (Medicare Fiscal Year 2015)		
Baseline Characteristics	**All Subjects**	**Bundle Compliant**	**Noncompli-ant**	**All Subjects**	**Bundle Compliant**	**Noncom-pliant**	**All Subjects**	**Bundle Compliant**	**Noncom-pliant**
n	5,819	1,050	4,769	1,697	739	958	7,239	2,115	5,124
Tertiary-care center, *n* (%)	3,931 (67.6)	638 (60.1)	3,293 (69.1)	1,697 (100)	739 (100)	958 (100)	5,727 (79.1)	1,472 (69.6)	4,255 (74.3)
Age, yr (IQR)	76 (54–98)	77 (55–99)	75 (52–98)	75 (62–85)	75 (63–85)	75 (62–85)	74 (61–84)	75 (62–85)	73 (61–84)
Male sex, *n* (%)	33,032 (52.1)	527 (50.2)	2,505 (52.5)	909 (53.6)	418 (56.6)	491 (52.3)	3,687 (51.0)	1,124 (53.2)	2,563 (50.0)
Body mass index (SD)	–	–	–	27.0 (8.1)	26.7 (7.7)	27.2 (8.4)	27.4 (7.8)	27.0 (6.7)	27.6 (7.8)
Primary payer class, *n* (%)	–	–	–						
Medicare	–	–	–	1,226 (72.3)	526 (71.2)	700 (73.1)	4,519 (62.4)	1,339 (63.3)	3,180 (62.1)
Medicaid	–	–	–	141 (8.3)	60 (8.1)	81 (8.5)	466 (6.5)	125 (5.9)	341 (6.7)
Commercial I	–	–	–	182 (10.7)	92 (12.5)	90 (9.4)	1,712 (23.8)	490 (23.3)	1,222 (24.0)
Commercial II (high reimbursing)	–	–	–	128 (7.5)	52 (7.0)	76 (7.9)	581 (8.1)	172 (8.2)	409 (8.0)
Comorbidities at presentation, *n* (%)[a]									
Chronic renal failure	–	–	–	179 (10.6)	64 (8.7)	115 (12.0)	722 (10.0)	141 (6.7)	581 (11.3)
Congestive heart failure	–	–	–	256 (15.1)	98 (13.3)	158 (16.5)	1,045 (14.4)	237 (11.2)	808 (15.8)
Chronic obstructive pulmonary disease	–	–	–	245 (14.4)	101 (13.7)	144 (15.0)	502 (6.9)	135 (6.4)	367 (7.2)
Diabetes	–	–	–	553 (32.6)	230 (31.1)	323 (33.7)	2,324 (32.1)	645 (30.5)	1,679 (32.8)
Metastatic disease	–	–	–	97 (5.7)	51 (6.9)	46 (4.8)	1,944 (26.9)	487 (23.0)	1,457 (28.4)
Chemotherapy within 30 d	–	–	–	170 (10.0)	82 (11.1)	88 (9.2)	–	–	–
Immune modifying medications				–	–	–	445 (6.1)	138 (6.5)	307 (6.0)
HIV positive	–	–	–	12 (0.7)	7 (1.0)	5 (0.5)	75 (1.0)	20 (0.9)	55 (1.1)
Leukemia, lymphoma, multiple myeloma	–	–	–	105 (6.2)	50 (6.8)	55 (5.7)	275 (3.8)	73 (3.5)	202 (3.9)
Liver failure	–	–	–	–	–	–	117 (1.6)	37 (1.7)	80 (1.6)
Organ transplant	–	–	–	–	–	–	74 (1.0)	16 (0.8)	58 (1.1)

(*Continued*)

TABLE 2. (*Continued*). Baseline and Presentation Characteristics

Baseline Characteristics	Cohort 1 (Calendar Year 2012)			Cohort 2 (Medicare Fiscal Year 2014)			Cohort 3 (Medicare Fiscal Year 2015)		
	All Subjects	Bundle Compliant	Noncompliant	All Subjects	Bundle Compliant	Noncompliant	All Subjects	Bundle Compliant	Noncompliant
Presentation acuity									
Initial lactate, mmol/L (SD)	3.6 (2.9)	3.6 (2.8)	3.6 (3.0)	2.8 (2.1)	2.9 (2.2)	2.7 (2.0)	3.2 (2.5)	3.3 (2.5)	3.2 (2.5)
Hyperlactemia (≥ 2.2 mmol/L), *n* (%)	3,400 (64.1)	694 (68.4)	2,706 (63.0)	1,051 (61.9)	468 (63.3)	583 (60.8)	4,741 (65.5)	1,498 (70.8)	3,243 (63.3)
Hyperlactemia (≥ 4.0 mmol/L), *n* (%)	1,560 (26.8)	332 (31.6)	1,228 (25.7)	263 (15.5)	122 (16.5)	141 (14.7)	4,169 (57.6)	1,324 (62.6)	2,845 (55.5)
Systolic blood pressure < 90 or mean arterial pressure < 65 mm Hg	2,477 (42.6)	506 (48.2)	1,971 (41.3)	241 (14.2)	108 (14.6)	133 (13.9)	2,405 (33.2)	701 (33.1)	1,704 (33.3)
Acute kidney injury[b]	1,641 (28.2)	266 (25.3)	1,375 (28.8)	375 (22.1)	150 (20.3)	225 (23.5)	1,512 (20.9)	440 (20.8)	1,072 (20.9)
Coagulopathy[c]	941 (16.2)	149 (14.2)	792 (16.6)	323 (19.0)	153 (20.7)	170 (17.8)	443 (6.1)	139 (6.6)	304 (5.9)
Thrombocytopenia[d]	435 (7.5)	68 (6.5)	367 (7.7)	245 (14.4)	125 (16.9)	120 (12.6)	808 (11.2)	225 (10.6)	583 (11.4)
Total bilirubin > 2.0 mg/dL	361 (6.2)	57 (5.4)	304 (6.4)	100 (5.9)	46 (6.2)	54 (5.6)	419 (5.8)	121 (5.7)	298 (5.8)
Acutely altered mental status	933 (16.0)	154 (14.7)	779 (16.3)	150 (8.8)	47 (6.4)	103 (10.8)	1,721 (23.8)	449 (21.2)	1,272 (24.8)
Hypoxemia[e]	1,030 (17.7)	136 (13.0)	894 (18.7)	46 (2.7)	5 (0.7)	43 (4.5)	1,536 (21.2)	403 (19.1)	1,133 (22.1)
Super-systemic inflammatory response syndrome criteria at triage, *n* (%)	2,248 (38.6)	435 (41.4)	1,813 (38.0)	329 (19.4)	195 (26.4)	134 (14.0)	2,162 (30.3)	656 (31.1)	1,506 (29.9)
Septic shock, *n* (%)[e]	–	–	–	–	–	–	1,199 (16.6)	368 (17.4)	831 (16.2)

IQR = interquartile range.

[a]Comorbidities reflect status at time-zero, and would not reflect conditions that developed subsequently during hospital stay.

[b]Acute kidney injury defined as creatinine > 2.0 or 50% increase from a known baseline.

[c]Coagulopathy defined as an international normalized ratio > 1.5 or a partial thromboplastin time > 60 s.

[d]Thrombocytopenia is defined as "platelets < 150,000 cells/μm3".

[e]Hypoxemia defined as Pao_2/Fio_2 < 300 or an increased o_2 requirement to maintain arterial oxygen saturation > 90%.

[f]Septic shock defined as a lactate ≥ 4.0 mmol or hypotension refractory to IV fluid resuscitation.

Dashes signify that this field was not collected or not applicable for the indicated cohort.

some benefit from the attempt to reach full bundle compliance 100% of the time (17). Some of the comparatively low mortality is likely also attributable to the broad SS/SS inclusion criteria. However, our definitions exhibit substantial concordance with Sepsis-3, and we may see lower mortality in future literature utilizing these criteria. Despite low overall mortality and broad noncompliance definition, substantial mortality benefits were observed in compliant groups. This suggests adherence to this 3-hour bundle is sufficient to improve clinical outcomes for SS/SS patients without reliance on invasive monitoring or complex physiologic endpoints.

We note with interest the bundle compliance's accentuated associated mortality benefit for CHF patients and nonsignificant mortality association for CRF patients that trended in the direction of harm. Considering clinical concern for aggressive fluid administration for these patients (evidenced by their propensity for noncompliant care), further investigation in these populations is warranted.

Several potential limitations impact our investigation. First, compliant groups had lower frequency of some comorbidities and organ dysfunction criteria (e.g., CRF and AMS). They conversely had higher lactate and hypotension frequency,

TABLE 3. Treatment and Postdischarge Characteristics

Baseline Characteristics	Cohort 1 (Calendar Year 2012)			Cohort 2 (Medicare Fiscal Year 2014)			Cohort 3 (Medicare Fiscal Year 2015)		
	All Subjects	Bundle Compliant	Noncompliant	All Subjects	Bundle Compliant	Noncompliant	All Subjects	Bundle Compliant	Noncompliant
n	5,819	1,050	4,769	1,697	739	958	7,239	2,115	5,124
3-hr bundle interventions[a]									
Fluid bolus initiated in < 30 min, *n* (%)[b]	1,923 (55.6)	1,050 (100)	873 (36.2)	1,088 (64.1)	739 (100.0)	349 (36.4)	3,723 (51.4)	2,115 (100.0)	1,608 (31.4)
Time to fluid bolus initiation, median (IQR)[b]	25 (−33 to 83)	4.5 (−32 to 41)	48 (−11 to 107)	0 (0–32)	0 (0–7)	34 (0–73)	12 (−38 to 61)	0 (−48 to 10)	42 (−20 to 120)
Lactate order to result time < 90 min, *n* (%)	4,592 (87.5)	1,050 (100)	3,542 (84.4)	1,648 (97.1)	739 (100.0)	909 (94.9)	5,913 (81.7)	2,115 (100.0)	3,798 (74.1)
Lactate order to result time, median (IQR)	40 (−12 to 92)	34 (−8 to 76)	44 (−20 to 108)	24 (14–38)	25 (15–38)	22 (14–37)	40 (24–64.5)	38 (24–54)	43 (24–75.5)
Blood cultures drawn before antibiotics, *n* (%)	4,477 (93.4)	1,050 (100.0)	3,427 (91.5)	24 (14–38)	25 (15–38)	22 (14–.37)	5,119 (70.7)	2,115 (100.0)	3,004 (58.6)
IV antibiotics in < 180 min, *n* (%)	4,294 (73.8)	1,050 (100.0)	3,244 (68.0)	1,456 (85.8)	739 (100.0)	717 (74.8)	5,480 (75.7)	2,115 (100.0)	3,004 (58.6)
Time to antibiotic administration, median (IQR)	67 (−24 to 158)	38 (−19 to 95)	87 (−10 to 184)	46 (5–104)	32 (1–73)	66 (20–172)	57 (5–132)	29 (−4 to 66)	85 (20–208)
Critical care interventions									
Central line inserted, *n* (%)	1,758 (30.2)	277 (26.4)	1,481 (31.1)	30 (1.8)	10 (1.4)	20 (2.1)	1,208 (16.7)	307 (14.5)	901 (17.6)
Central venous pressure monitoring, *n* (%)	920 (15.8)	133 (12.7)	787 (16.5)	11 (2.1)	0 (0)	3 (0.9)	362 (5.0)	67 (3.2)	295 (5.8)
$ScvO_2$ or SvO_2 monitoring, *n* (%)[c]	292 (5.0)	48 (4.6)	244 (5.1)	3 (0.6)	1 (0.6)	10 (3.0)	30 (0.4)	8 (0.4)	22 (0.4)
Composite hemodynamic monitoring, *n* (%)[d]	1,104 (19.0)	164 (15.6)	940 (19.7)	13 (0.8)	1 (0.001)	12 (1.3)	392 (5.4)	75 (3.5)	317 (6.2)
Unadjusted primary outcomes									
In-hospital mortality, *n* (%)	1,437 (24.7)	224 (21.3)	1,213 (25.4)	270 (15.9)	99 (13.4)	171 (17.8)	1,461 (20.2)	383 (18.1) (CI, 1.3%)	1,078 (21.0) (CI, 1.1%)
Total direct cost, mean (95% CI)	–	–	–	$17,787 (SD, $18,205)	$14,845 (CI, $1,608)	$20,056 (CI, $2,021)	$20,874 (SD, 20,882)	$17,885 (CI, $1,135)	$22,108 (CI, $888)
Total direct cost, median (IQR)	–	–	–	$9,654 ($5,439–19,087)	$9,263 ($5,245–15,936)	$10,250 ($5,560–20,621)	$11,066 (5,307–23,274)	$10,066 (4,912–20,027)	$11,543 (5,468–24,487)

(*Continued*)

TABLE 3. (*Continued*). Treatment and Postdischarge Characteristics

Baseline Characteristics	Cohort 1 (Calendar Year 2012)			Cohort 2 (Medicare Fiscal Year 2014)			Cohort 3 (Medicare Fiscal Year 2015)		
	All Subjects	Bundle Compliant	Noncompliant	All Subjects	Bundle Compliant	Noncompliant	All Subjects	Bundle Compliant	Noncompliant
Unadjusted secondary outcomes									
ICU admission, *n* (%)	2,250 (38.7)	455 (43.3)	1,795 (37.6)	495 (29.2)	189 (25.6)	306 (31.9)	3,330 (46.0)	898 (42.5) (CI, 2.1%)	2,432 (47.5) (CI, 1.4%)
ICU LOS (ICU admitted only), d (95% CI)[e]	–	–	–	–	–	–	6 (5.7–6.3)	5 (4.5–5.5)	6 (5.6–6.4)
Vasopressors required, *n* (%)	1,370 (25.6)	240 (24.3)	1,130 (25.8)	68 (4.0)	27 (3.7)	41 (4.3)	1,528 (21.7)	378 (18.1) (CI, 1.7%)	1,150 (23.2) (CI, 1.2%)
Mechanical ventilation Required, *n* (%)	–	–	–	–	–	–	2,097 (29.0)	502 (23.7) (CI, 1.8%)	1,595 (31.1) (CI, 1.3%)
Hospital LOS, d (95% CI)[e]	–	–	–	68 (4.0)	27 (3.7)	41 (4.3)	9 (8.8–9.2)	8 (7.7–8.3)	9 (8.8–9.2)
Adjusted net revenue, mean (95% CI)	–	–	–	$25,233 (SD, $19,301)	$23,120 (CI, $1,646)	$26,864 (CI, $2,117)	$31,270 (SD, 32,762)	$28,367 (CI, $1,803)	$32,469 (CI, $1,175)
Adjusted net revenue, median (IQR)	–	–	–	$16,662 ($11,011–26,585)	$16,592 ($11,183–22,876)	$16,730 ($10,901–28,625)	$16,875 (14,147–35,234)	$16,390 (13,804–30,649)	$17,209 (14,333–37,622)
Contribution margin, mean (95% CI)	–	–	–	$7,141 (SD, $9,794)	$7,991 (CI, $1,382)	$6,487 (CI, $1,288)	$6,613 (SD, 3,319)	$7,760 (CI, $1,371)	$6,139 (CI, $920)
Contribution margin, median (IQR)	–	–	–	$5,201 ($436–11,065)	$5,878 ($859–11,723)	$4,627 (–$387 to 10,143)	$5,273 (–1,397 to 11,516)	$5,228 (–646 to 11,736)	$5,293 (–1,718 to 11,436)

IQR = interquartile range, LOS = length of stay.

[a]All times are in minutes, and reflect the time elapsed from time-zero unless otherwise indicated.

[b]All crystalloid was 0.9% normal saline solution administered at a volume ≥ 30 mL/kg.

[c]Defined as measurement of either central venous oxygenation ($ScvO_2$) or mixed venous (i.e., pulmonary arterial) oxygenation (SvO_2).

[d]Composite hemodynamic monitoring defined as measurement of either central venous pressure or ScvO2 or SvO_2.

[e]Length of stay (LOS) values computed using Kaplan-Meier curve assessment with log-rank test, censored for mortality. We report median LOS in days with 95% CIs of the medians.

Dashes signify that this field was not collected or not applicable for the indicated cohort.

suggesting observed data endogeneity. This is intuitive; sicker patients are more easily identified and subsequently may be more likely to receive appropriate initial care. Since these patients may also be more likely to expire, observed benefits of bundle compliance may even be understated. We attempted to control for these discrepancies with multivariable regression.

Second, nonexperimental findings cannot show causality. However, this investigation assessed prospectively captured observational clinical data of SS/SS encounters in three independent cohorts, each with increasing methodologic rigor and addressing the limitations of preceding analysis. Financial data were not obtained from estimation methods, (e.g., cost-to-charge ratios) but instead from a detailed accounting database utilizing complex encounter-level data. Considering this design, data integrity, and reproducibility of findings, our investigation likely reflects the true practice environment and may have greater external validity than a more rigorously controlled randomized trial.

Third, we used inclusion criteria that do not completely align with either Sepsis-2 or Sepsis-3 consensus definitions (14, 19). Our "severe sepsis" inclusion criteria include additional organ dysfunction indicators, lower lactate, and higher platelet count as "time-zero" triggers compared with Sepsis-2. While there is overlap between our criteria and Sepsis-3 (e.g., altered mentation and tachypnea), concordance is not 100%, limiting generalizability of our population to a population fitting new definitions. Additionally, we cannot determine how many patients meeting Sepsis-3 definitions were excluded because data collection did not capture patients who did not meet our study's criteria. This could potentially reduce the degree to which our work may be compared to both prior and future investigations.

TABLE 4. Adjusted Outcomes From Multivariate Regression Analyses

Outcome	Regression Type	Model Fit	Model Output	Effect Size	95% CI	*p*
Cohort 1 (2012)[a]						
Primary outcome						
Mortality	Logistic	$X^2 = 2.5$; $p = 0.96$	OR	0.74	0.62–0.89	0.001
Secondary outcomes						
ICU admission	Logistic	$X^2 = 37.2$; $p < 0.001$	OR	1.24	1.07–1.43	0.004
Vasopressors required	Logistic	$X^2 = 25.0$; $p = 0.002$	OR	0.83	0.69–0.94	0.043
Cohort 2 (MFY 2014)[b,c]						
Primary outcomes						
Mortality	Logistic	$X^2 = 2.2$; $p = 0.98$	OR	0.65	0.49–0.87	0.004
Total direct cost	Linear	Adjusted $r^2 = 0.45$	β	−$2,851	−$4,880 to −822	0.006
Secondary outcomes						
ICU admission	Logistic	$X^2 = 14.7$; $p = 0.07$	OR	0.68	0.52–0.87	0.002
Hospital LOS[d,e]	Cox	N/A	HR^{-1}	0.88	0.79–0.98	0.022
Adjusted net revenue	Linear	Adjusted $r^2 = 0.30$	β	−$2,545	−$4,950 to −141	0.038
Contribution margin	Linear	Adjusted $r^2 = 0.18$	β	$1,418	−$303 to 3,139	0.106
Cohort 3 (MFY 2015)[f,g]						
Primary outcomes						
60-d in-hospital mortality	Logistic	$X^2 = 3.4$; $p = 0.91$	OR	0.84	0.73–0.97	0.019
Total direct cost	Linear	Adjusted $r^2 = 0.47$	β	−$1,571	−$2,746 to −397	0.009
Secondary outcomes						
ICU admission	Logistic	$X^2 = 21.9$; $p = 0.005$	OR	0.85	0.76–0.95	0.003
Mechanical ventilation	Logistic	$X^2 = 7.8$; $p = 0.45$	OR	0.73	0.64–0.83	0.000
Vasopressors required	Logistic	$X^2 = 7.8$; $p = 0.45$	OR	0.75	0.65–0.86	0.000
Hospital LOS[d,e]	Cox	N/A	HR^{-1}	0.94	0.89–0.99	0.033
Adjusted net revenue	Linear	Adjusted $r^2 = 0.27$	β	−$2,315	−$4,183 to −448	0.015
Contribution margin	Linear	Adjusted $r^2 = 0.10$	β	$934	−$698 to 2,566	0.262

(*Continued*)

TABLE 4. (*Continued*). Adjusted Outcomes From Multivariate Regression Analyses

Outcome	Regression Type	Model Fit	Model Output	Effect Size	95% CI	*p*
Subanalyses[h]						
Heart failure						
60-d in-hospital mortality	Logistic	$X^2 = 8.9$; $p = 0.35$	OR	0.67	0.47–0.95	0.026
Chronic renal failure						
60-d in-hospital mortality	Logistic	$X^2 = 11.4$; $p = 0.18$	OR	1.27	0.83–1.94	0.269

HR = hazard ratio, LOS = length of stay, MFY = medicare fiscal year, N/A = not applicable, OR = odds ratio.

[a]All outcomes from cohort 1 were tested in logistic regression models adjusted for the following variables: age, initial lactate, hypotension, two or more "Super-systemic inflammatory response syndrome (SIRS) criteria" at triage, acute kidney injury, compromised oxygenation, thrombocytopenia, coagulopathy, and altered mental status. The mortality model also adjusted for central line placement, and central venous pressure (CVP)/central venous oxygenation ($Scvo_2$)/mixed venous oxygenation (Svo_2) monitoring. Hosmer-Lemeshow tests assessed goodness-of-fit, where the null hypothesis that the model fit the data was accepted for $p > 0.05$.

[b]Logistic regression models from cohort 2 adjusted for age, congestive heart failure, chronic obstructive pulmonary disease, chronic renal failure, two or more "Super-SIRS criteria" at triage, initial lactate, hypotension, acute kidney injury, thrombocytopenia, altered mental status, and compromised oxygenation. Models did not adjust for central line placement or hemodynamic monitoring (CVP, $Scvo_2$, or Svo_2) because a prohibitively low number of subjects received these interventions. Model fit was assessed using Hosmer-Lemeshow test, where the null hypothesis that the model fit the data was accepted for $p > 0.05$.

[c]Linear regression models from cohort 2 adjusted for age, tertiary versus community site, payer class, congestive heart failure, chronic obstructive pulmonary disease, chronic renal failure, metastatic disease, nosocomial infection, initial lactate, hypotension, coagulopathy, altered mental status, surgical diagnosis-related group (DRG) product line, and case mix index.

[d]Cox model from cohort 2 censored for mortality; adjusted for age, tertiary versus community site, payer class, congestive heart failure, chronic renal failure, nosocomial infection, hypotension, initial lactate, coagulopathy, altered mental status, surgical DRG product line, and case mix index.

[e]The "event" in the Cox model was a live hospital discharge. The hazard ratio (HR) indicates rate of live discharge per unit time in the exposure group over the rate in the referent. The inverse HR (HR^{-1}) is the ratio of time per unit live discharge between groups, that is, the relative length of stay.

[f]Logistic regression models adjusted for age, congestive heart failure, chronic obstructive pulmonary disease, chronic renal failure, nosocomial infection, two or more "Super-SIRS criteria" at triage, initial lactate, hypotension, acute kidney injury, thrombocytopenia, altered mental status, and compromised oxygenation. The mortality model also adjusted for central line placement, and CVP/$Scvo_2$/Svo_2 monitoring. Model fit was assessed using Hosmer-Lemeshow test, where the null hypothesis that the model fit the data was accepted for $p > 0.05$.

[g]Linear regression models adjusted for age, tertiary versus community site, payer class, congestive heart failure, chronic obstructive pulmonary disease, chronic renal failure, metastatic disease, nosocomial infection, initial lactate, hypotension, coagulopathy, altered mental status, surgical DRG product line, and case mix index. The total direct costs (TDC) model also adjusted for central line placement, and CVP/$Scvo_2$/Svo_2 monitoring.

[h]Both subgroup analyses are drawn from cohort 3 and assess the primary mortality outcome. They utilize the same model variables employed in the primary analysis of the entire cohort.

Fourth, observational sepsis literature presents threat of indication bias from unobserved data endogeneity: the intent is to always administer compliant care, implying noncompliant patients may unobservably differ from compliant patients. Pseudorandomization efforts are not well suited to this issue. Propensity score matching does not address unobserved variability. Instrumental variable techniques could attempt to exploit systemic and environmental differences, but an effective instrument is difficult to identify: an environment that is better at effective bundle implementation is likely better at many other things, at which point bundle compliance is no longer the exposure. This typically indicates need for a randomized trial but the overwhelming evidence supporting early intervention renders such an investigation unethical. These issues persist in the literature as a result.

Our investigation spans a dynamic period in the scientific community's understanding and approach. We began data collection before publication of both the multitrial challenge to EGDT's efficacy (6–8) and SCCM/ESICM's recalibrated characterization of sepsis. Although this presents challenges in gauging how our findings fit into the broader sepsis discussion, we believe a few crucial lessons straddle this strategic pivot.

As the SCCM/ESICM task force acknowledged, timely recognition and intervention are essential in sepsis management. Literature consistently suggests best practice in sepsis care is highly time-dependent, particularly for IV fluids and antibiotics (10, 23–26). Protocolized time-to-completion approaches have been validated for other time-sensitive, high-consequence conditions (e.g., cardiac arrest and stroke) (27, 28). It should not be surprising that patients in this study who not only received all appropriate interventions but received them according to explicit, aggressive time goals faired markedly better.

We interpret observed mortality, critical care utilization, and length of stay reductions for compliant subjects as reflective of decreased decompensation risk and drivers of cost savings. Together, this demonstrates 3-hour bundle compliance's association with improved patient outcomes, hospital cost savings, and reduced payer expenditure, suggesting leaner care processes that fit well within the shifting paradigm of healthcare delivery and value-based purchasing.

Our results suggest acknowledging sepsis as a time-dependent, high-consequence emergency warranting highly aggressive management is a clinical imperative. Our bundle accomplishes this, and importantly, several of our bundle elements are more aggressive than current recommendations.

However, as evidenced by our strict compliance definition and observed mortality across both groups, we believe this underlying attitude to be as crucial a driver of survival benefit as any individual bundle component, and arguably the most important inference we draw from this investigation.

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