Effect of Automated Real-Time Feedback on Early-Sepsis Care: A Pragmatic Clinical Trial

Daniel E. Leisman, MD, MSCR[1,2]
Hao Deng, MD, MPH, DrPH(c)[2]
Andy H. Lee, MD, MBA[3,4]
Micah H. Flynn, BA[2]
Hayley Rutkey, BS[2]
Martin S. Copenhaver, PhD[2,5]
Elizabeth A. Gay, MD[1]
Sayon Dutta, MD, MPH[3,4,6]
Dustin S. McEvoy, BS[6]
Lisette N. Dunham, PSH, MSPH[6]
Elizabeth A. Mort, MD, MPH[1]
David J. Lucier, MD, MBA, MPH[1]
Jonathan D. Sonis, MD, MHCM[3,4]
Emily L. Aaronson, MD, MPH[3,4]
Kathryn A. Hibbert, MD[7,8]
Kyan C. Safavi, MD, MBA[2,5]

OBJECTIVES: To determine if a real-time monitoring system with automated clinician alerts improves 3-hour sepsis bundle adherence.

DESIGN: Prospective, pragmatic clinical trial. Allocation alternated every 7 days.

SETTING: Quaternary hospital from December 1, 2020 to November 30, 2021.

PATIENTS: Adult emergency department or inpatients meeting objective sepsis criteria triggered an electronic medical record (EMR)-embedded best practice advisory. Enrollment occurred when clinicians acknowledged the advisory indicating they felt sepsis was likely.

INTERVENTION: Real-time automated EMR monitoring identified suspected sepsis patients with incomplete bundle measures within 1-hour of completion deadlines and generated reminder pages. Clinicians responsible for intervention group patients received reminder pages; no pages were sent for controls. The primary analysis cohort was the subset of enrolled patients at risk of bundle nonadherent care that had reminder pages generated.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was orders for all 3-hour bundle elements within guideline time limits. Secondary outcomes included guideline-adherent delivery of all 3-hour bundle elements, 28-day mortality, antibiotic discontinuation within 48-hours, and pathogen recovery from any culture within 7 days of time-zero. Among 3,269 enrolled patients, 1,377 had reminder pages generated and were included in the primary analysis. There were 670 (48.7%) at-risk patients randomized to paging alerts and 707 (51.3%) to control. Bundle-adherent orders were placed for 198 intervention patients (29.6%) versus 149 (21.1%) controls (difference: 8.5%; 95% CI, 3.9–13.1%; $p = 0.0003$). Bundle-adherent care was delivered for 152 (22.7%) intervention versus 121 (17.1%) control patients (difference: 5.6%; 95% CI, 1.4–9.8%; $p = 0.0095$). Mortality was similar between groups (8.4% vs 8.3%), as were early antibiotic discontinuation (35.1% vs 33.4%) and pan-culture negativity (69.0% vs 68.2%).

CONCLUSIONS: Real-time monitoring and paging alerts significantly increased orders for and delivery of guideline-adherent care for suspected sepsis patients at risk of 3-hour bundle nonadherence. The trial was underpowered to determine whether adherence affected mortality. Despite enrolling patients with clinically suspected sepsis, early antibiotic discontinuation and pan-culture negativity were common, highlighting challenges in identifying appropriate patients for sepsis bundle application.

KEY WORDS: Centers for Medicare and Medicaid Services, U.S.; lactic acid; patient care bundles; sepsis; septic shock

Sepsis is the leading cause of death in U.S. hospitals (1), accounting for 35% of all inpatient deaths at significant financial cost (2, 3). Seminal investigations by Kumar et al (4) and Rivers et al (5) and reported improved sepsis mortality with early identification and treatment. Subsequently, international guidelines were developed that recommend a protocolized approach to initial

DOI: 10.1097/CCM.0000000000006057

KEY POINTS

Question: Do real-time clinician reminder alerts increase adherence to the guideline-recommended sepsis 3-hour care bundle?

Findings: In this prospective, cluster-randomized study that included 1,377 sepsis patients at risk of 3-hour bundle nonadherent care, the proportion of patients with orders for fully adherent care was 29.6% with real-time monitoring and paging alerts versus 21.1% with standard care, a significant difference.

Meaning: Real-time monitoring and clinician alerts can increase 3-hour bundle adherence for sepsis patients.

care (6). This sepsis "bundle" includes obtaining blood cultures, measuring serial blood lactate levels, and administering broad-spectrum antibiotics and intravenous fluids within three-to-six hours of presentation (6). These recommendations were adopted and incorporated into the Centers for Medicare and Medicaid Services SEP-1 bundle (7).

Adherence to early care measures, particularly timely antibiotics, is consistently associated with improved outcomes and decreased costs (8–12). Although later early goal-directed therapy trials failed to confirm a benefit of protocolized versus standard care (13–16), these studies had substantially higher adherence to the 3- and 6-hour bundles than the Rivers trial. Meta-analyses suggest differences in initial care between the trials were quantitatively sufficient to explain their divergent mortality results (17).

Delivery of bundle-adherent care can be challenging. Sepsis often presents with vague or nonspecific symptoms that impede rapid diagnosis, and busy clinical environments can interrupt timely delivery of care (18). Emergency departments (EDs), where initial sepsis care is often administered, achieve adherence to all 3- and 6-hour bundle elements in fewer than half of sepsis cases (8). Bundle compliance is often even lower on inpatient wards (19).

Information technology offers an opportunity to improve early-sepsis care by supporting clinicians with real-time monitoring and automatic alerts if they are at risk of bundle nonadherence. We designed the sepsis care tracking platform (SCTP), a monitoring and notification system. The SCTP begins monitoring a patient's electronic medical record (EMR) when objective signs trigger a best practice advisory (BPA) and the responsible clinician acknowledges they are concerned for possible sepsis. The SCTP then tracks, in real-time, adherence to antibiotic administration, blood culture collection, and lactate measurement metrics automatically sending a reminder page to clinicians when care is at risk of bundle nonadherence.

To test the hypothesis that automated paging reminders would improve 3-hour sepsis bundle compliance, we conducted a prospective, pragmatic trial of paging alerts versus standard care.

METHODS

Design

We conducted a prospective, single-center, pragmatic trial that compared automated paging reminders for initial sepsis bundle measures versus standard care among consecutive ED and ward patients with clinical suspicion and objective signs of sepsis (Registration: NCT05625464). The overall trial design is summarized in **Figure 1**. The study was approved by the Mass General Brigham institutional review board (IRB), which granted a waiver of informed consent (September 29, 2020, protocol 2020P002676). The study was performed in full accordance with the IRB and Helsinki Declaration of 1975. The full protocol is available in **Supplement** (http://links.lww.com/CCM/H422).

Patients

Adult patients were automatically enrolled from December 1, 2020, to November 30, 2021, if they triggered a sepsis best practice advisory (BPA) and the BPA was subsequently accepted by the treatment team indicating clinician suspicion for sepsis. If the clinical team did not accept the BPA, the patient was not enrolled. The BPA was previously developed, implemented, and validated, and was in routine clinical use before the trial (20). Criteria that trigger the BPA are detailed in **Supplemental Methods** and **Tables s1** and **s2** (http://links.lww.com/CCM/H422). We excluded outside hospital transfers and patients who triggered BPAs while already in ICU or perioperative areas.

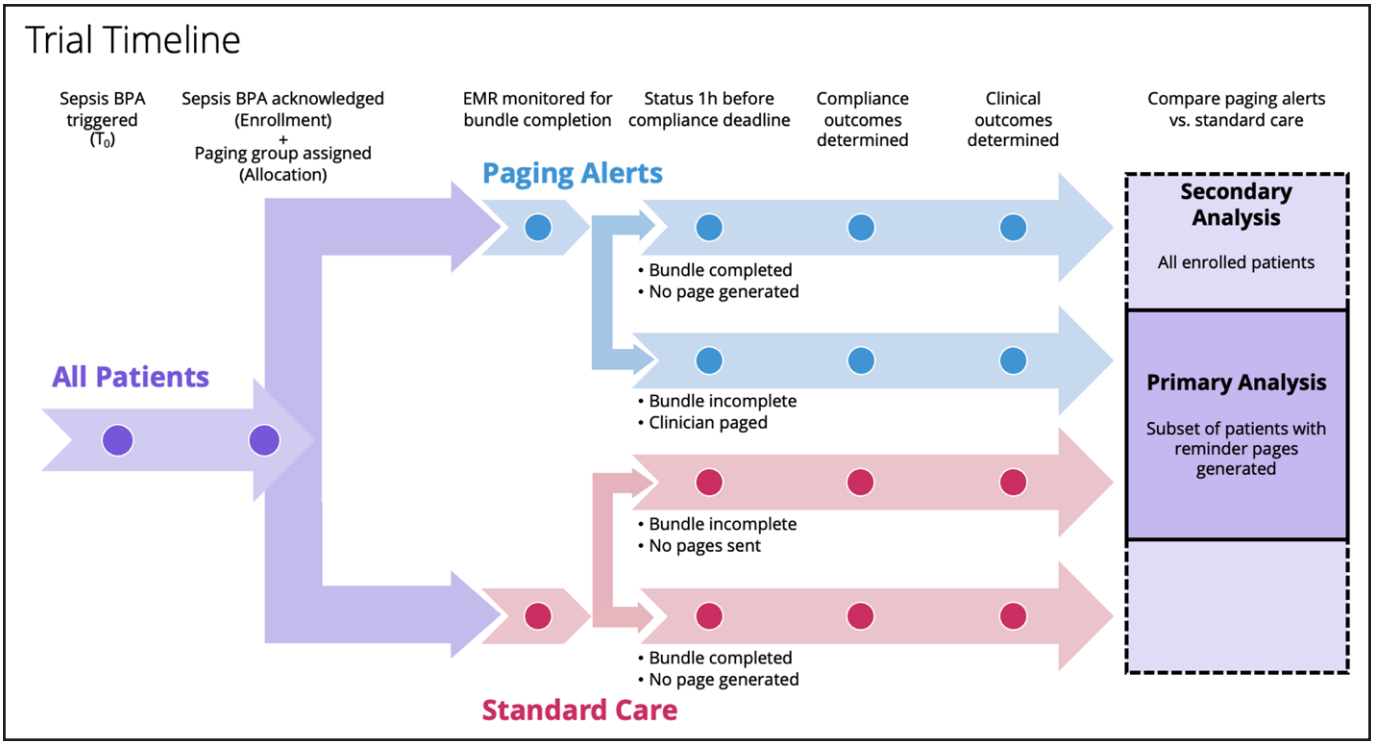

Figure 1. Overall trial design. Schematic representation of the study design and patient flow through the trial. T0 was the time at which a sepsis best practice advisory (BPA) was triggered best on objective criteria in the electronic medical record (EMR). Enrollment occurred automatically at the moment when a clinician acknowledged the BPA by indicating they had clinical suspicion for sepsis. At the time of enrollment, the patient was allocated to either paging alerts or standard care. In both groups, the sepsis care tracking platform continuously monitored the EMR for completion of sepsis bundle elements. If patients had ≥ 1 incomplete bundle element within 1-hour of the compliance deadline, they were considered at-risk of noncompliance and a reminder page was generated. This subset of patients comprised the primary analysis cohort. Pages were sent to patients allocated to the paging alerts group but not to patients in the standard care group. The EMR was then monitored for determination of compliance and clinical outcomes. T0 = time-zero.

Intervention

Technical validation and piloting of the SCTP were performed before the trial period (21). The SCTP-monitored patients were automatically enrolled in real-time if they met inclusion criteria. When a sepsis bundle element was incomplete within 1-hour of the deadline for measure compliance, an alert was automatically generated (**Fig. s1**, http://links.lww.com/CCM/H422). For patients allocated to the intervention, this alert was immediately paged to the responsible clinicians. For patients allocated to the control arm, SCTP monitoring after an accepted BPA alert was concealed and no pages were sent (**Fig. s2**, http://links.lww.com/CCM/H422). Page recipients were the responding clinician (e.g., resident, advanced practitioner) and supervising attending physician (Fig. s2, http://links.lww.com/CCM/H422). Measures eligible for reminder pages were 1) antibiotic initiation, 2) blood cultures collection, 3) initial lactate within 3 hours of time-zero, and 4) repeat lactate result within 6 hours of time-zero if initial lactate was greater than or equal to 2.0 mmol/L. Reminders were not generated for the 30 mL/kg fluid bolus or vasopressor measures. Fluid reminders were not generated because of the greater complexity in capturing these real-time data reliably and because institutional practice is to individualize fluid resuscitation to specific clinical contexts (e.g., severely reduced systolic function). Vasopressor reminders were not implemented because a pilot demonstrated that clinicians did not need reminders for this element and because there were already strong bedside alert mechanisms to trigger rapid intervention for hypotensive patients.

Allocation

Figure 1 summarizes patient flow through the trial. Patients were automatically allocated to standard care or standard care plus paging alerts at the time when

the clinician accepted the sepsis BPA. Logs were kept of all patients eligible for intervention (i.e., had ≥ 1 reminder page generated). Clinicians received pages only for patients assigned to the intervention group. Allocation was assigned by date of time zero. Group assignments alternated between intervention and control every 7 days. This design was adopted to reduce contamination bias, interprovider variation, and maturation bias. Specifically, had patients been individually randomized, clinicians could have simultaneously cared for patients in both study arms, and a reminder page for an intervention patient could prompt care for a control arm patient. Therefore, clustered allocation was selected because we reasoned risk of contamination bias outweighed the risk of systematic differences between alternating weeks over the course of a year.

Investigators were blinded to allocation until analysis completion. For treating clinicians, allocation was unblinded in that they became aware of assignment to paging alerts if they received a reminder page.

Outcomes

We recorded three categories of outcomes: 1) process outcomes, including the primary outcome, which related to clinician orders to initiate sepsis bundle care, 2) care delivery outcomes, reflecting bundle implementation downstream of the orders, and 3) clinical/balancing outcomes, related to patient outcomes and potential adverse effects of bundle adherence.

The primary outcome was overall 3-hour bundle ordering compliance, defined as orders for all 3-hour bundle measures monitored by the SCTP: antibiotics ordered within 180 minutes, blood cultures ordered before antibiotic administration and initial lactate within 180 minutes. We selected ordering (rather than administration) time for the primary outcome because ordering behavior was the direct target of the intervention. Secondary process outcomes were the number of 3-hour bundle elements ordered and specific bundle elements ordered.

For care delivery outcomes, we assessed whether care implementation within the 3-hour window was changed. Specifically, these outcomes reflected antibiotic administration time and collection times for blood cultures and lactate samples.

Clinical outcomes were 28-day mortality, mechanical ventilation or death within 72 hours, ICU admission or death within 72 hours, mechanical ventilation or death during hospitalization, ICU admission or death during hospitalization, and hospital length-of-stay. Balancing outcomes were antibiotic discontinuation within 48 hours and culture negativity (detailed further in Supplemental Methods, http://links.lww.com/CCM/H422), as these could suggest excessive sepsis bundle application. All outcomes reflected time elapsed after time zero.

Statistical Analysis

We report continuous variables as mean (SD) or median (interquartile range), and categorical variables as frequency (percent). Hypothesis tests were two-sided with results considered statistically significant at p value of less than 0.05. We analyzed all data on intention-to-treat basis. The unit-of-analysis was the individual patient. Sample size and interim analyses are detailed in Supplemental Methods (http://links.lww.com/CCM/H422). Analyses were performed in SAS (SAS Institute, Cary, NC).

The primary analysis was performed within the subset of subjects that had a reminder page for a 3-hour bundle measure generated (i.e., ≥ 1 incomplete bundle element at hour 2) because this subset reflected both the population at risk of nonadherence and the population for whom practice could be changed. We compared groups by Chi-square test and by logistic regression adjusted for whether time-zero occurred during the daytime (7 AM–7 PM), whether time-zero occurred in the ED, and days between enrollment and trial initiation. All binary clinical/balancing outcomes were analyzed with multivariable logistic regression adjusting for age, Charlson comorbidity index, initial quick Sepsis Organ Failure Assessment, lactate, creatinine, platelet count, and bilirubin (see Supplemental Methods, http://links.lww.com/CCM/H422). Analyses of continuous, ordinal, and time-to-event outcomes are described in Supplemental Methods (http://links.lww.com/CCM/H422).

Because paging alerts for one patient could potentially lead to spillover by prompting clinicians to act on other patients, sensitivity analyses were performed among the entire cohort of trial patients, including those for whom no alert was generated.

Additionally, we prespecified four subgroup analyses: 1) patients with alerts generated for antibiotics

versus other bundle elements, 2) patients who did versus did not test positive for COVID-19, 3) patients with initial lactate greater than or equal to 4.0 versus 2.1–3.9 versus less than or equal to 2.0 mmol/L, and 4) patients with versus without significant hemodynamic instability within 1-hour of time-zero, defined as systolic, diastolic, or mean arterial pressure less than 90, greater than 50, or less than 65mm Hg, respectively, AND heart rate less than 100 beats per minute.

We also conducted several post hoc sensitivity analyses, outlined in Supplemental Methods (http://links.lww.com/CCM/H422).

RESULTS

Enrollment and Baseline Characteristics

The trial ended as scheduled after 12 months of enrollment. Among 7,830 sepsis BPA alerts triggered, 3,828 (48.9%) were acknowledged as "sepsis possible" whereas 2,728 (34.8%) were dismissed as "sepsis unlikely" and 1,274 (16.3%) were unacknowledged (**Fig. 2**). After trial exclusion criteria, there were n = 3,269 unique patients enrolled, with n = 1,639 (50.1%) allocated to paging alerts and n = 1,630 (49.9%) to standard care (Fig. 2). Six-hundred seventy (40.9%) paging alert encounters had an alert generated versus 707 (43.4%) for standard care. All 670 paging alert patients had alerts paged as allocated, whereas 702 (99.3%) standard care patients with alerts generated received no page as allocated. Five (0.7%) standard care patients wrongly received pages.

The 1,377 patients in the primary analysis cohort were 44.5% female with median age of 64 years (interquartile range [IQR]: 50–76) and initial lactate 2.4 mmol/L (IQR: 1.9–3.2). Chronic heart failure, chronic kidney disease, and cirrhosis diagnoses were carried by 312 (22.7%), 321 (23.3%), and 65 (4.7%) patients, respectively. Most presentations occurred in the ED (1,334 [96.9%]). These features were similar between paging alerts and standard care groups (**Table 1**).

Process and Care Delivery Endpoints

Among at-risk patients who had a page generated, full 3-hour bundle ordering compliance was achieved in 198/670 (29.6%) paging alert versus 149 of 707 (21.1%) standard care patients (difference: 8.5% [95% CI, 3.9–13.1%], p = 0.0003) (**Table 2**; and **Table s3**, http://links.lww.com/CCM/H422). In multivariable logistic regression, paging alerts remained associated with significantly higher overall 3-hour bundle compliance (aOR: 1.56 [1.22–1.99], p = 0.0004).

Paging alert patients had significantly higher compliance with orders for antibiotics (41.9% vs 34.2%, difference: 7.7% [2.6–12.8%], p = 0.0032) and blood cultures (65.8% vs 60.5%, difference: 5.3% [0.2–10.4%], p = 0.0423), but not initial lactate measurement (88.1% vs 85.9%, difference: 2.2% [–1.4 to 5.8%], p = 0.23). Paging alerts were associated with significantly higher odds of compliance with more total bundle element orders (aOR: 1.38 [1.14–1.68], p = 0.0012).

When bundle compliance was assessed using time of care delivery, results were consistent with ordering compliance (Table 2; and Table s3, http://links.lww.com/CCM/H422). Paging alert patients again had higher overall 3-hour bundle compliance (22.7% vs 17.1%, difference: 5.6% [1.4–9.8%], p = 0.0095), as well higher antibiotic administration and blood culture collection compliance. The paging alert group had higher odds of receiving more bundle elements in compliant fashion (aOR: 1.29 [1.06–1.58], p = 0.0105). There was no difference between groups for initial or repeat lactate compliance.

Clinical and Balancing Endpoints

There was no difference in 28-day mortality between paging alerts (8.4%) and standard care (8.4%) (difference: 0% [–2.9 to 2.9%], p = 0.99) (Table 2). In the alerts group, 106 (15.8%) patients were admitted to the ICU or died within 72 hours versus 93 (13.1%) standard care patients (difference: 2.7% [–1.1 to 6.4%], p = 0.16). Mechanical ventilation or death occurred within 72 hours for 73 (10.9%) and 60 (8.5%) paging alert and standard care patients, respectively (difference: 2.4% [–0.7 to 5.5%], p = 0.13). Hospital length-of-stay was similar between groups (**Table s4**, http://links.lww.com/CCM/H422).

Blood cultures were positive in 78 (11.6%) and 75 (10.6%) paging alert and standard care patients, respectively (difference: 1.0% [–2.3 to 4.4%], p = 0.54) (Table 2). Similar numbers of patients between groups had a likely bacterial pathogen recovered from nonblood cultures (24.8% vs 25.5%, difference: –0.7% [–5.3 to 3.9%], p = 0.77) or from

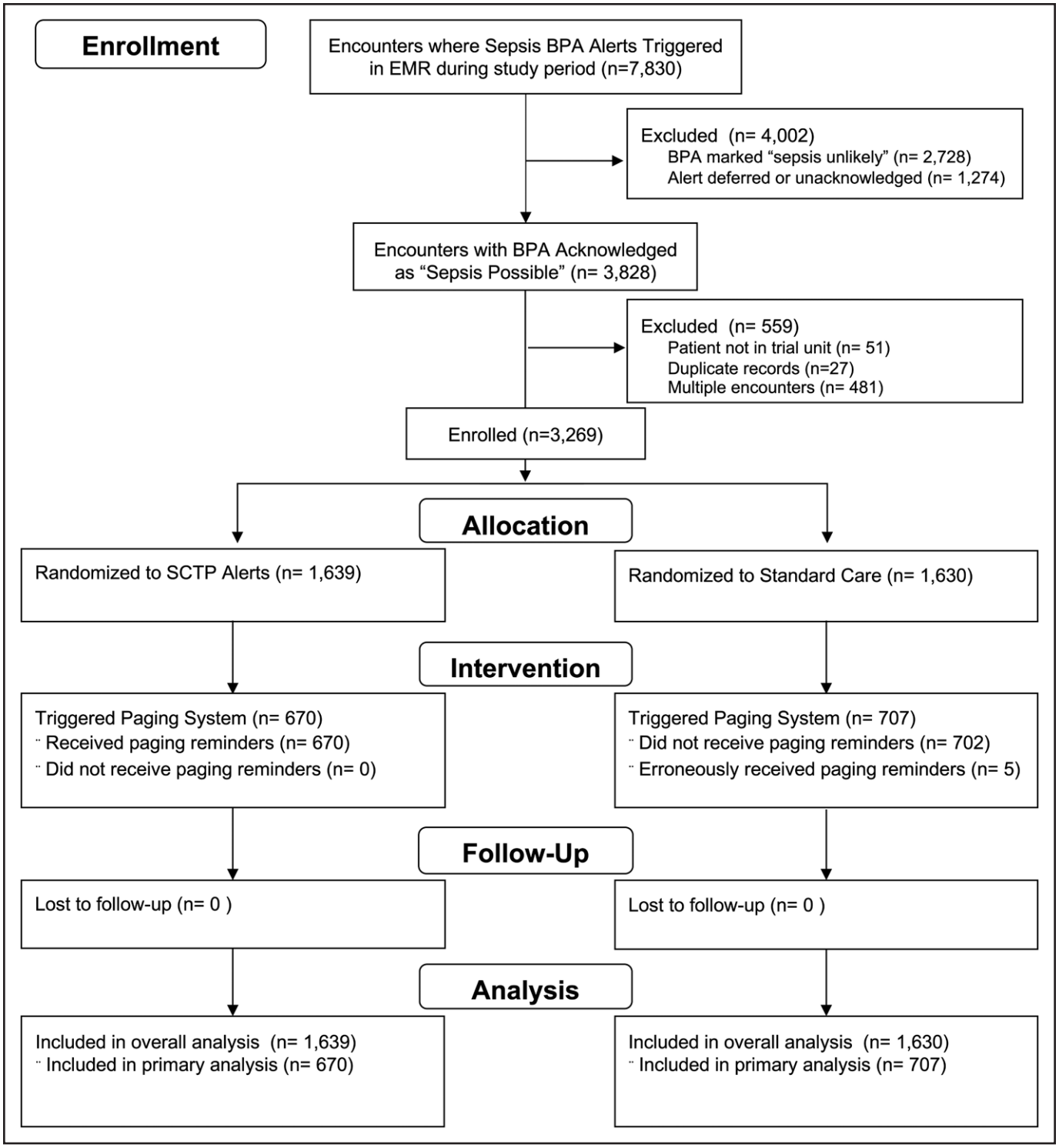

Figure 2. Consort diagram for trial enrollment, allocation, and analysis. BPA = best practice advisory, EMR = electronic medical record, SCTP = sepsis care tracking platform.

any culture (31.0% vs 31.8%, difference: –0.8% [–5.7 to 4.1%], $p = 0.76$). Antibiotic discontinuation occurred by hour 48 in 235 (35.1%) paging alert and 236 (33.4%) standard care patients (difference: 1.7% [–3.3 to 6.7%]).

Prespecified Subgroup Analyses

Prespecified subgroup analyses are shown in **Figure 3**. We did not detect any statistically significant heterogeneity of treatment effect for paging alerts.

TABLE 1.
Demographics and Baseline Characteristics in Primary Analysis Cohort

Outcome	All Patients	Paging Alerts	Standard Care
Primary Analysis Cohort	***n* = 1,377**	***n* = 670**	***n* = 707**
Page generated	1,377 (100%)	670 (100%)	707 (100%)
Page sent	675 (49.0%)	670 (100%)	5 (0.7%)
Age (yr)—median (IQR)	64 (50,76)	64 (50, 76)	65 (51, 76)
Female	613 (44.5%)	292 (43.6%)	321 (45.4%)
Emergency department at T0	1,334 (96.9%)	652 (97.3%)	682 (96.5%)
Daytime hours at T0	864 (62.7%)	429 (64.0%)	435 (61.5%)
Active COVID-19	31 (2.3%)	11 (1.6%)	20 (2.8%)
Heart rate—median (IQR)	95 (80, 112)	98 (82, 114)	93 (79, 110)
Respiratory rate—median (IQR)	20 (18, 22)	20 (18, 22)	20 (18, 22)
Systolic BP (mm Hg)—median (IQR)	117 (104, 134)	117 (104, 134)	117 (104, 134)
Diastolic BP (mm Hg)—median (IQR)	62 (53, 75)	62 (53, 74)	62 (53, 76)
Altered mental status	612 (44.4%)	306 (45.7%)	306 (43.3%)
Hemodynamic instability	411 (29.9%)	210 (31.3%)	201 (28.4%)
Quick Sepsis Organ Failure Assessment ≥ 2	274 (19.9%)	146 (21.8%)	128 (18.1%)
Initial lactate (mmol/L)—median (IQR)	2.4 (1.9, 3.2)	2.4 (1.9, 3.2)	2.4 (1.8, 3.1)
≤ 2.0 mmol/L	438 (31.8%)	202 (30.2%)	236 (33.4%)
2.1–3.9 mmol/L	757 (55.0%)	378 (56.4%)	379 (53.6%)
≥ 4.0 mmol/L	182 (13.2%)	90 (13.4%)	92 (13.0%)
Initial creatinine (mg/dL)—median (IQR)	1.1 (0.8, 1.7)	1.2 (0.9, 1.7)	1.1 (0.8, 1.7)
Initial platelets (cells/nL)—median (IQR)	205 (147, 246)	206 (150, 263)	203 (144, 269)
Initial bilirubin (mg/dL)—median (IQR)	0.6 (0.4, 1.0)	0.6 (0.4, 1.0)	0.6 (0.4, 1.0)
Charlson comorbidity index—median (IQR)	2 (0, 4)	2 (0, 4)	2 (0, 4)
Myocardial infarction	148 (10.7%)	75 (11.2%)	73 (10.3%)
Congestive heart failure	312 (22.7%)	155 (23.1%)	157 (22.2%)
Peripheral vascular disease	138 (10.0%)	66 (9.9%)	72 (10.2%)
Cerebrovascular disease or Transient ischemic attack	96 (7.0%)	52 (7.8%)	44 (6.2%)
Dementia	90 (6.5%)	49 (7.3%)	41 (5.8%)
Chronic pulmonary disease	285 (20.7%)	139 (20.7%)	146 (20.7%)
Connective tissue disease	50 (3.6%)	24 (3.6%)	26 (3.7%)
Peptic ulcer disease	30 (2.2%)	18 (2.7%)	12 (1.7%)
Mild liver disease	174 (12.6%)	85 (12.7%)	89 (12.6%)
Moderate or severe liver disease	65 (4.7%)	33 (4.9%)	32 (4.5%)
Moderate or severe renal disease	321 (23.3%)	166 (24.8%)	155 (21.9%)
Diabetes	420 (30.5%)	201 (30.0%)	219 (31.0%)
Leukemia or lymphoma	191 (13.9%)	85 (12.7%)	106 (15.0%)
Hemiplegia	36 (2.6%)	16 (2.4%)	20 (2.8%)
Solid tumor	97 (7.0%)	44 (6.6%)	53 (7.5%)

BP = blood pressure, IQR = interquartile range.

Displays patient characteristics at enrollment. All data are presented as frequency (percent) unless otherwise indicated.

TABLE 2.
Main Outcomes in Primary Analysis Cohort

Outcome	Paging Alerts *n* = 670	Standard Care *n* = 707	Δ, (95% CI), *p*	aOR (95% CI), *p*
Ordering outcomes				
Overall 3-hr bundle orders	198 (29.6%)	149 (21.1%)	8.5% (3.9 to 13.1), $p = 0.0003$	1.56 (1.22 to 1.99), $p = 0.0004$
Antibiotic orders	281 (41.9%)	242 (34.2%)	7.7% (2.6 to 12.8), $p = 0.0032$	1.39 (1.12 to 1.73), $p = 0.0033$
Blood culture orders	441 (65.8%)	428 (60.5%)	5.3% (0.2 to 10.4), $p = 0.0423$	1.25 (1.00 to 1.56), $p = 0.0502$
Minutes to antibiotic orders[a]	359 (314, 411)	432 (381, 489)	−73 (−133 to −0), $p = 0.0487$	−77 (−141 to 1), $p = 0.0528$
Number of bundle elements ordered[b]			1.40 (1.15 to 1.70), $p = 0.0008$	1.38 (1.14 to 1.68), $p = 0.0012$
All 3	198 (29.6%)	149 (21.1%)		
2	266 (39.7%)	304 (43.0%)		
1	186 (27.8%)	222 (31.4%)		
None	20 (3.0%)	32 (4.5%)		
Care delivery outcomes				
Overall 3 hr bundle delivery	152 (22.7)	121 (17.1%)	5.6% (1.4 to 9.8), $p = 0.0095$	1.42 (1.09 to 1.86), $p = 0.0099$
Antibiotic administration	234 (34.9%)	214 (30.3%)	4.7% (−0.3 to 9.6), $p = 0.0653$	1.26 (1.00 to 1.58), $p = 0.0489$
Blood culture collection	432 (64.5%)	417 (59.0%)	5.5% (0.4 to 10.6), $p = 0.0360$	1.26 (1.01 to 1.56), $p = 0.0426$
Minutes to antibiotic administration[a]	405 (362 to 454)	481 (431 to 537)	−76 (−135 to −7), $p = 0.0328$	−76 (−135 to −7), $p = 0.0327$
Number of bundle elements delivered[b]			1.31 (1.07 to 1.59), $p = 0.0075$	1.29 (1.06 to 1.58), $p = 0.0105$
All 3	152 (22.7%)	121 (17.1%)		
2	297 (44.3%)	319 (45.1%)		
1	199 (29.7%)	233 (33.0%)		
None	22 (3.3%)	34 (4.8%)		
Clinical outcomes				
28-d mortality	56 (8.4%)	59 (8.3%)	0.1% (−2.9 to 2.9), $p = 0.99$	0.95 (0.63 to 1.43), $p = 0.79$
MV or death by 72 hr	73 (10.9%)	60 (8.5%)	2.4% (−0.7 to 5.5), $p = 0.13$	1.20 (0.82 to 1.77), $p = 0.35$
MV or death during hospitalization	90 (13.4%)	80 (11.3%)	2.1% (−1.4 to 5.6%), $p = 0.23$	1.15 (0.81 to 1.63), $p = 0.44$
ICU admission or death by 72 hr	106 (15.8%)	93 (13.1%)	2.7% (−1.1 to 6.4), $p = 0.16$	1.15 (0.83 to 1.58), $p = 0.41$
ICU admission or death during hospitalization	158 (23.6%)	140 (19.8%)	3.8 (−0.6 to 8.1), $p = 0.0887$	1.17 (0.88 to 1.54), $p = 0.28$

(*Continued*)

TABLE 2. (*Continued*)
Main Outcomes in Primary Analysis Cohort

Outcome	Paging Alerts	Standard Care		
	n = 670	*n* = 707	Δ, (95% CI), *p*	aOR (95% CI), *p*
Balancing outcomes				
Positive blood culture	78 (11.6%)	75 (10.6%)	1.3% (−2.3 to 4.4), $p = 0.54$	1.08 (0.77 to 1.53), $p = 0.64$
Nonblood culture with likely bacterial pathogen	166 (24.8%)	180 (25.5%)	−0.7% (−5.3 to 3.9), $p = 0.77$	0.97 (0.76 to 1.25), $p = 0.81$
Any positive culture	208 (31.0%)	225 (31.8%)	−0.8% (−5.7 to 4.1), $p = 0.76$	0.96 (0.76 to 1.21), $p = 0.72$
Antibiotics discontinued by 48 hr	235 (35.1%)	236 (33.4%)	1.7% (−3.3 to 6.7), $p = 0.51$	1.07 (0.85 to 1.35), $p = 0.57$

Δ = difference, aOR = adjusted odds ratio, MV = mechanical ventilation, OR = odds ratio.

[a]For time to antibiotics, group columns display the geometric means and corresponding 95% CI. Δ and aOR columns display back-transformed differences and adjusted differences, respectively, in log-minutes from linear regression models, which reflect the difference in geometric means.

[b]Number of elements outcomes reports ORs from unadjusted and multivariable proportional odds models where higher OR indicates higher odds of more bundle elements being compliant. Main outcomes for the primary analysis cohort. The Δ column displays absolute risk differences vs standard care. The aOR column displays odds ratios vs standard care from multivariable models. Ordering and care delivery outcome models adjusted for time-of-day, date of randomization, and emergency department vs inpatient at time-zero. Clinical and balancing outcome models adjusted for age, Charlson comorbidity index, initial lactate, qSOFA, creatinine, bilirubin, and platelets.

Overall Cohort Analysis

Table s5 (http://links.lww.com/CCM/H422) displays the characteristics of the overall cohort. Among all enrolled patients, full 3-hour bundle ordering compliance remained significantly higher for paging alerts (994/1,639 [60.7%]) than standard care (927/1,630 [56.9%]) (difference: 3.8% [0.4–7.2%], $p = 0.0283$) (**Table s6**, http://links.lww.com/CCM/H422). There was no difference in clinical or balancing outcomes between groups in the overall cohort (**Table s7**, http://links.lww.com/CCM/H422).

Sepsis Diagnosis Codes

The prevalence of explicit and implicit sepsis diagnosis codes (listed in **Supplemental Data-1**, http://links.lww.com/CCM/H423) is reported in **Table s8** (http://links.lww.com/CCM/H422). Overall, post hoc sepsis diagnoses did not modify the association of paging alerts with increased 3-hour bundle adherence (**Fig. s3**, http://links.lww.com/CCM/H422). There was no statistically significant effect modification, although numerically, paging alerts appeared to have higher adherence with blood cultures in patients with sepsis diagnoses and higher adherence with antibiotics in patients without sepsis diagnoses.

Post hoc Sensitivity Analyses

Cluster analysis where the week of allocation was the unit of analysis showed similar results to the primary analysis (**Fig. s4**, http://links.lww.com/CCM/H422). Results also remained consistent with the primary analysis in the sensitivity analyses that included additional covariate adjustment (**Table s9**, http://links.lww.com/CCM/H422), that excluded patients with antibiotic orders at or before time-zero (**Table s10**, http://links.lww.com/CCM/H422), that excluded patients with either antibiotic or blood culture orders at or before time-zero (**Table s11**, http://links.lww.com/CCM/H422), and that considered ED arrival as time-zero (**Table s12**, http://links.lww.com/CCM/H422).

Table s13 (http://links.lww.com/CCM/H422) shows differences between intervention group patients with 3-hour bundle adherence versus nonadherence.

DISCUSSION

In this prospective, single-center, pragmatic trial of real-time sepsis care monitoring and alerts for patients at risk of receiving 3-hour bundle nonadherent care, paging

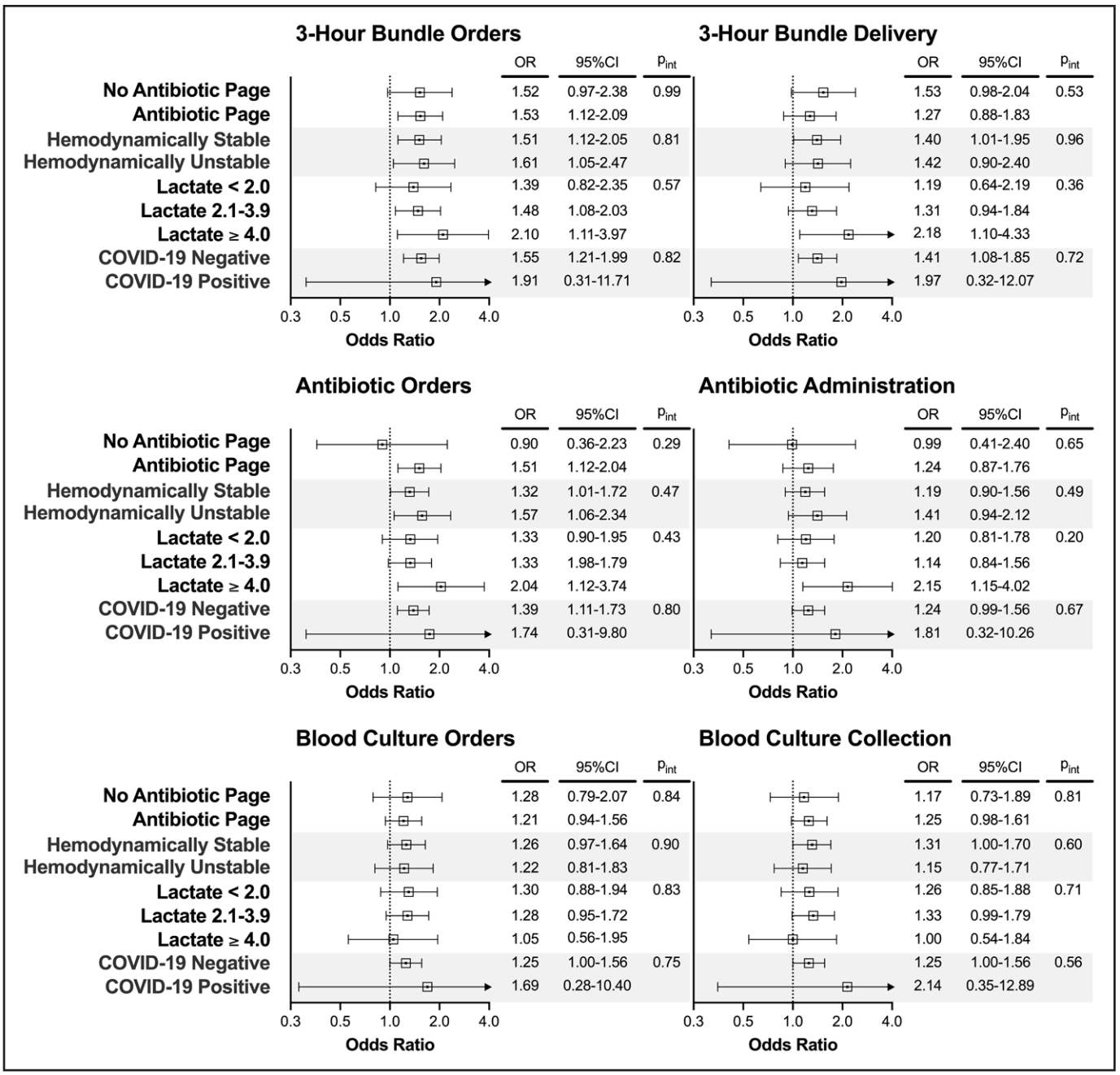

Figure 3. Prespecified subgroup analyses. Displays the odds ratios (OR) within each of the four prespecified subgroup for paging alerts for the indicated outcome within the primary analysis cohort (all patients with a page generated). The *left column* shows results for ordering compliance (primary outcome) and the *right column* shows results for care delivery compliance. The p_{int} shows the *p* value corresponding to the interaction test for heterogeneity of treatment effect. Antibiotic page refers to whether or not a reminder page for specifically antibiotic administration was generated, as pages were not sent to patients in the control arm. No antibiotic page generated therefore reflects patients for whom the generated pages were only for bundle elements other than antibiotics.

reminders significantly increased both orders for and delivery of 3-hour bundle compliant care. This effect was driven primarily by increased adherence to timely antibiotic administration and blood culture collection. These results indicate that real-time monitoring and clinician alerts can improve the timely delivery of early-sepsis care.

Many investigations have developed and evaluated sophisticated automated monitoring platforms to detect patients at risk of having sepsis (22–25), but few have tested automated systems to ensure initial care delivery for patients whom clinicians have already identified as having a high likelihood of sepsis. In addition to

the efficacy demonstrated in this study, characteristics that make paging alerts an attractive intervention to improve early-sepsis bundle compliance include the relative simplicity of deploying the tool within an existing EMR and the ability to update and target the tool to specific bundle elements as evidence evolves.

In this trial, higher bundle compliance among the paging alerts group was driven primarily by early antibiotics and blood cultures—elements with strong supporting evidence. Epidemiological studies and controlled animal experiments report consistent association between delayed antibiotics and worse outcomes (4, 8–10, 17, 26). Failing to obtain blood cultures before antibiotics reduces culture sensitivity by 50% (27). In turn, culture negativity contributes to diagnostic uncertainty and exposure to potential harms associated with inability to narrow or tailor antimicrobial therapy.

Despite significantly increased compliance with paging alerts, nearly 40% of all enrolled patients in the paging arm did not have fully adherent orders for the 3-hour bundle. One possible explanation is that the high frequency of noncompliance reflects failure to deliver appropriate early-sepsis care. This could be consistent with low compliance rates reported in sepsis literature (12, 28, 29). Our results might indicate that while automated alerts may reduce lapses related to cognitive load (e.g., due to high patient-to-staff ratios), other challenges, such as frequent care transitions, also contribute importantly to nonadherence and are less susceptible to mitigation with cognitive aid interventions.

However, while enrollment required clinicians to acknowledge clinical suspicion for sepsis, this reflects only one timepoint early in a patient's course. An alternative explanation for low overall compliance could be that many patients were determined to not have sepsis as more data became available. This explanation is compatible with the high prevalence of early antibiotic discontinuation and pan-culture negativity. Estimates of the trial's true sepsis prevalence varied widely; while only 34% of primary analysis patients had an explicit or implicit sepsis diagnosis code, 88% had either an associated sepsis code or antibiotics continued past hour 48. However, given that all subjects both met objective criteria and had clinical suspicion for sepsis at enrollment, current guidelines would nevertheless recommend that all of these patients receive sepsis bundle care (6). Therefore, our results likely underscore the difficulty in early identification of appropriate patients for sepsis bundle application.

We found no difference in mortality or other clinical outcomes. There are no randomized trials that investigate the effect of 3-hour bundle compliant care on patient outcomes—there is likely insufficient equipoise to conduct such a trial. Although random allocation to paging alerts presents a potentially ideal instrumental variable to assess whether 3-hour bundle compliant care improves these outcomes (30), the present study was underpowered to detect any such difference. These results are therefore exploratory. However, we found that paging alerts did not increase early antibiotic discontinuation or culture negativity, which could indicate that at minimum, the intervention did not increase inappropriate bundle application versus standard care.

We acknowledge several study limitations. First, single-center design may limit generalization. Second, trial enrollment required clinicians to accept a sepsis BPA, indicating they felt the patient either likely or possibly had sepsis. When clinicians dismissed BPAs by selecting "sepsis unlikely," patients were not enrolled. Excluding these patients omitted many patients who likely did not have sepsis but may have also excluded sepsis patients with atypical presentations. The latter patients may be most likely to have bundle nonadherent care and worse outcomes (18). Clinician nonengagement with EMR alerts could have also affected enrollment. However, only 16% of BPA alerts went unacknowledged. Third, we assigned allocation by week of enrollment, rather than by patient-level randomization, to mitigate contamination bias by ensuring clinicians were not simultaneously caring for intervention and control patients. Although systematic differences between alternating weeks over the course of a year seem unlikely, this possibility cannot be excluded. Fourth, paging reminders could potentially spill over to other patients receiving care from the same clinician. Consequently, if paging alerts for one patient increased the probability of bundle completion by the time pages were generated in other patients, then systematic differences could exist between the primary analysis trial groups. However, there was no significant difference in the proportion of patients with pages generated between groups. More importantly, this issue could only arise if the intervention increased bundle compliance.

CONCLUSIONS

A real-time sepsis care monitoring and paging alert system significantly increased both orders for and the delivery of 3-hour adherent care for suspected sepsis patients at risk of receiving 3-hour bundle nonadherent care. However, despite enrolling patients with actively acknowledged clinical suspicion for sepsis, early antibiotic discontinuation and culture negativity were common, highlighting challenges in identifying appropriate patients for sepsis bundle application.

1 Department of Medicine, Massachusetts General Hospital, Boston, MA.

2 Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA.

3 Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA.

4 Department of Emergency Medicine, Harvard Medical School, Boston, MA.

5 Healthcare Systems Engineering, Massachusetts General Hospital, Boston, MA.

6 Mass General Brigham Digital, Mass General Brigham Health System, Sommerville, MA.

7 Division of Pulmonary and Critical Care Medicine, Department of Medicine, Massachusetts General Hospital, Boston, MA.

8 Department of Medicine, Harvard Medical School, Boston, MA.

Drs. Hibbert and Safavi are co-senior authors.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Drs. Leisman and Rutkey's institution received funding from Harvard Medical Institution Incorporated. Dr. Gay's institution received funding from the National Heart, Lung, and Blood Institute (1 R38 HL 150212-01); She received support for article research from the National Institutes of Health. Drs. Mort and Safavi's institutions received funding from CRICO. Dr. Mort disclosed she teaches at Harvard Medical School; she received support for article research from CRICO. Dr. Sonis received funding for being an expert witness for emergency medicine-related medical malpractices cases. Drs. Aaronson and Hibbert received funding from CRICO. Dr. Aaronson received funding from Walmart Health and Wellness. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: dleisman@mgh.harvard.edu

Trial Registration: NCT05625464

REFERENCES

1. Liu V, Escobar GJ, Greene JD, et al: Hospital deaths in patients with sepsis from 2 independent cohorts. *JAMA* 2014; 312:90–92
2. Rhee C, Dantes R, Epstein L, et al; CDC Prevention Epicenter Program: Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. *JAMA* 2017; 318:1241–1249
3. Buchman TG, Simpson SQ, Sciarretta KL, et al: Sepsis among medicare beneficiaries: 1. The burdens of sepsis, 2012-2018. *Crit Care Med* 2020; 48:276–288
4. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589–1596
5. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
6. Evans L, Rhodes A, Alhazzani W, et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021; 49:e1063–e1143
7. Severe Sepsis/Septic Shock: Management bundle. Centers for medicare and medicaid services measures inventory tool, department of health and human services. Available at: https://cmit.cms.gov/CMIT_public/ViewMeasure?MeasureId=5175. Accessed September 17, 2019
8. Seymour CW, Gesten F, Prescott HC, et al: Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med* 2017; 376:2235–2244
9. Liu VX, Fielding-Singh V, Greene JD, et al: The timing of early antibiotics and hospital mortality in sepsis. *Am J Respir Crit Care Med* 2017; 196:856–863
10. Taylor SP, Anderson WE, Beam K, et al: The association between antibiotic delay intervals and hospital mortality among patients treated in the emergency department for suspected sepsis. *Crit Care Med* 2021; 49:741–747
11. Liu VX, Morehouse JW, Marelich GP, et al: Multicenter implementation of a treatment bundle for patients with sepsis and intermediate lactate values. *Am J Respir Crit Care Med* 2016; 193:1264–1270
12. Leisman DE, Doerfler ME, Ward MF, et al: Survival benefit and cost savings from compliance with a simplified 3-hour sepsis bundle in a series of prospective, multisite, observational cohorts. *Crit Care Med* 2017; 45:395–406
13. Mouncey PR, Osborn TM, Power GS, et al; ProMISe Trial Investigators: Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015; 372:1301–1311
14. Peake SL, Delaney A, Bailey M, et al; ARISE Investigators: Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014; 371:1496–1506
15. Yealy DM, Kellum JA, Huang DT, et al; ProCESS Investigators: A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; 370:1683–1693
16. PRISM Investigators; Rowan KM, Angus DC, Bailey M, et al: Early, goal-directed therapy for septic shock—a patient-level meta-analysis. *N Engl J Med* 2017; 376:2223–2234
17. Kalil AC, Johnson DW, Lisco SJ, et al: Early goal-directed therapy for sepsis: A novel solution for discordant survival outcomes in clinical trials. *Crit Care Med* 2017; 45:607–614
18. Filbin MR, Lynch J, Gillingham TD, et al: Presenting symptoms independently predict mortality in septic shock: Importance

of a previously unmeasured confounder. *Crit Care Med* 2018; 46:1592–1599

19. Leisman DE, Angel C, Schneider SM, et al: Sepsis presenting in hospitals versus emergency departments: Demographic, resuscitation, and outcome patterns in a multicenter retrospective cohort. *J Hosp Med* 2019; 14:340–348
20. Dutta S, McEvoy DS, Rubins DM, et al: Clinical decision support improves blood culture collection before intravenous antibiotic administration in the emergency department. *J Am Med Inform Assoc* 2022; 29:1705–1714
21. Lee AH, Aaronson E, Hibbert KA, et al: Design and implementation of a real-time monitoring platform for optimal sepsis care in an emergency department: observational cohort study. *J Med Internet Res* 2021; 23:e26946
22. Henry KE, Hager DN, Pronovost PJ, et al: A targeted real-time early warning score (TREWScore) for septic shock. *Sci Transl Med* 2015; 7:299ra–29122
23. Nemati S, Holder A, Razmi F, et al: An interpretable machine learning model for accurate prediction of sepsis in the ICU. *Crit Care Med* 2018; 46:547–553
24. Wardi G, Carlile M, Holder A, et al: Predicting progression to septic shock in the emergency department using an externally generalizable machine-learning algorithm. *Ann Emerg Med* 2021; 77:395–406
25. Adams R, Henry KE, Sridharan A, et al: Prospective, multi-site study of patient outcomes after implementation of the TREWS machine learning-based early warning system for sepsis. *Nat Med* 2022; 28:1455–1460
26. Kumar A, Haery C, Paladugu B, et al: The duration of hypotension before the initiation of antibiotic treatment is a critical determinant of survival in a murine model of Escherichia coli septic shock: Association with serum lactate and inflammatory cytokine levels. *J Infect Dis* 2006; 193:251–258
27. Cheng MP, Stenstrom R, Paquette K, et al; FABLED Investigators: Blood culture results before and after antimicrobial administration in patients with severe manifestations of sepsis: A diagnostic study. *Ann Intern Med* 2019; 171:547–554
28. Levy MM, Rhodes A, Phillips GS, et al: Surviving sepsis campaign: Association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med* 2015; 43:3–12
29. Rhodes A, Phillips G, Beale R, et al: The surviving sepsis campaign bundles and outcome: Results from the International Multicentre Prevalence Study on Sepsis (the IMPreSS study). *Intensive Care Med* 2015; 41:1620–1628
30. Iwashyna TJ, Kennedy EH: Instrumental variable analyses. Exploiting natural randomness to understand causal mechanisms. *Ann Am Thorac Soc* 2013; 10:255–260