Improving Timeliness of Antibiotic Administration Using a Provider and Pharmacist Facing Sepsis Early Warning System in the Emergency Department Setting: A Randomized Controlled Quality Improvement Initiative

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OBJECTIVES: Results of pre-post intervention studies of sepsis early warning systems have been mixed, and randomized clinical trials showing efficacy in the emergency department setting are lacking. Additionally, early warning systems can be resource-intensive and may cause unintended consequences such as antibiotic or IV fluid overuse. We assessed the impact of a pharmacist and provider facing sepsis early warning systems on timeliness of antibiotic administration and sepsis-related clinical outcomes in our setting.

DESIGN: A randomized, controlled quality improvement initiative.

SETTING: The main emergency department of an academic, safety-net healthcare system from August to December 2019.

PATIENTS: Adults presenting to the emergency department.

INTERVENTION: Patients were randomized to standard sepsis care or standard care augmented by the display of a sepsis early warning system–triggered flag in the electronic health record combined with electronic health record–based emergency department pharmacist notification.

MEASUREMENTS AND MAIN RESULTS: The primary process measure was time to antibiotic administration from arrival. A total of 598 patients were included in the study over a 5-month period (285 in the intervention group and 313 in the standard care group). Time to antibiotic administration from emergency department arrival was shorter in the augmented care group than that in the standard care group (median, 2.3 hr [interquartile range, 1.4–4.7 hr] vs 3.0 hr [interquartile range, 1.6–5.5 hr]; $p = 0.039$). The hierarchical composite clinical outcome measure of days alive and out of hospital at 28 days was greater in the augmented care group than that in the standard care group (median, 24.1 vs 22.5 d; $p = 0.011$). Rates of fluid resuscitation and antibiotic utilization did not differ.

CONCLUSIONS: In this single-center randomized quality improvement initiative, the display of an electronic health record–based sepsis early warning system–triggered flag combined with electronic health record–based pharmacist notification was associated with shorter time to antibiotic administration without an increase in undesirable or potentially harmful clinical interventions.

KEY WORDS: decision support; early warning system; electronic health record; emergency department; sepsis

Sepsis is a prevalent, costly, and life-threatening condition (1). Data from observational studies suggest that earlier identification and treatment of sepsis may be associated with better clinical outcomes (2–5).

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This association, coupled with the continued development of electronic health record (EHR)–based decision support, has prompted the development and implementation of numerous automated rule–based sepsis screening tools and prediction-based early warning systems (EWSs) (6–8). Several pre-post intervention studies conducted in the emergency department (ED) setting, where most patients with sepsis present, suggest that implementing automated sepsis detection systems could lead to improvements in time to antibiotics, length of stay (LOS), and mortality (9–18). However, the strength of these conclusions is attenuated by the absence of any randomized controlled studies as well as limited data on potentially adverse clinical effects that these systems may cause (6, 19, 20).

In 2019, our healthcare system elected to implement an EHR-embedded, prediction-based, sepsis EWS. The EWS was derived and validated by the EHR vendor (Epic, Verona, WI) and is leveraged by over 100 healthcare systems in the United States. Although the externally validated performance characteristics appeared promising, the interdisciplinary quality improvement team tasked with improving sepsis outcomes for our system raised concerns that the existing evidence did not clarify sufficiently the potential effects of implementing this EWS on our local practices and clinical outcomes. Thus, in the context of existing quality improvement work to improve sepsis care, we elected to deploy the sepsis EWS tool through a randomized quality improvement cycle to evaluate its impact on sepsis-related process measures, clinical outcomes, and balancing measures (unintended consequences) (21).

MATERIALS AND METHODS

Design, Setting, and Participants

This initiative was one component of a broader system-wide quality improvement initiative to improve sepsis care. This component was a randomized controlled quality improvement initiative guided by a multidisciplinary team of clinical and operational stakeholders. The setting was the main ED of a safety-net healthcare system with a level 1 trauma center designation. The ED serves a large and diverse patient population with approximately 100,000 visits annually. Prior to the start of this specific initiative, ED providers managed sepsis without a standardized screening mechanism, but they did have access to a sepsis-specific order panel that included orders for blood work, cultures, imaging studies, and broad-spectrum antibiotics.

Patients 18 years and older presenting to the ED were randomized to standard care for sepsis versus the pathway augmented with the EWS. For the analysis, only patients for whom the sepsis EWS flag was triggered during their ED encounter were included. Patients evaluated primarily for trauma, stroke, cardiac ischemia rule out or acute blood loss were excluded. Patients with "comfort care" code status (i.e., nonaggressive, symptom-focused care), those who eloped or left against medical advice, and those who were transferred to the labor and delivery unit or to a different hospital were also excluded. For eligible patients, only the first ED encounter during the initiative was included.

The protocol was reviewed and codeveloped as a quality improvement initiative with the healthcare system's Quality Institute, leadership in the Division of Emergency Medicine and representatives from the institution's antimicrobial stewardship program as part of a system-wide quality improvement initiative to improve care for sepsis. The healthcare system's Institutional Review Board independently reviewed the protocol for this initiative and determined that the activity did not qualify as research involving human subjects and waived the need for consent accordingly. Key to this decision was the iterative nature of the work, the autonomy of providers to use clinical judgment as to whether to use the information provided by the EWS, and the lack of blinding as to the randomization. If providers chose, they were free to look up the EWS score on any patient (but were only prompted with it in the augmented care group). Additionally, offering augmented care (e.g., additional pharmacists) to all patients was not feasible, and provider-facilitated EWS augmented care has not yet been clearly determined to be better than usual care despite its widespread use.

Model Validation

Epic's "Early Detection of Sepsis Cognitive Computing Model" was developed and validated by the EHR vendor (Epic) (22). The model is based on a logistic regression that leverages several structured EHR variables to predict the likelihood that a patient will develop clinician identified sepsis during their hospitalization. Variables that drive the model include EHR-entered demographic data, vital signs, laboratory results, orders, and comorbidities (**Table S1**, http://links.lww.com/CCM/G671).

The model runs in the background of the EHR, continuously calculating a score for all patients who are in the inpatient or ED setting.

We internally validated the EWS during a 9-month period prior to this initiative by silently activating the system in the background. During that time, there were 33,164 encounters with 23,543 unique patients in the ED setting. At the vendor proposed threshold (equivalent to a calculated probability of sepsis exceeding 5%), the alert fired in 1,644 ED encounters of 1,409 unique patients. The alert fired before antibiotics were administered 54% of the time. We chose to validate the EWS using the Sepsis-3 outcomes of death and/or 3-day ICU stay in patients meeting the definition of suspected infection (culture sampling followed by antibiotic administration within 72 hr or antibiotic administration followed by culture sampling within 24 hr) (18). For these outcomes, the proposed threshold had a sensitivity of 90%, a specificity of 68%, a positive predictive value of 27%, and a negative predictive value of 98%.

Intervention

After internally validating the sepsis EWS, we moved forward with the systems improvement. We used a randomized quality improvement approach with intent to expand the program to all patients if it was found to be clinically beneficial. This approach has been used by others when iteratively evaluating the impact of an intervention that cannot reasonably be deployed without understanding key characteristics in individual clinical settings (23–25).

Patients were randomized either to standard care or standard care augmented by the EWS (i.e., the intervention group) based on the last digit of their unique internal patient identifier (a value unavailable to most providers). The allocation of digits to either group was ascertained at the outset by using a random number generator, with assignments maintained throughout the study. For patients in the intervention group, when a sepsis EWS score crossed over the established threshold, an alert triggered two events: 1) a flag was displayed as an icon change in a column on a widely used ED patient tracking tool ("track board") and 2) a message was sent to an EHR-based messaging pool monitored by the ED pharmacists. Alerts could only fire once. Once an alert fired, the corresponding flag remained on the track board until discharge or transfer. For patients randomized to the standard care group, no visible flags or messages were generated, but a timestamp was silently registered.

Before implementation, ED providers were educated about the EWS model performance and the initiative during routine meetings, through electronic memoranda and the distribution of pamphlets in common workspaces. As part of a broader initiative, a swim lane plot was developed to guide sepsis response team members in their management of any patients with suspected sepsis, regardless of whether an EWS alert was triggered (**Fig. S1**, http://links.lww.com/CCM/G671). Due to the pragmatic nature of the initiative, we did not register or mandate a specific response to an EWS alert. A clinical pharmacist was generally available in the ED 7 days per week from 10 AM to 9 PM. Upon receiving the EHR-based notification, the pharmacist reviewed the chart and "huddled" with the primary ED provider. Pharmacists could then facilitate the timely ordering and collection of appropriate blood work as well as the ordering and administration of appropriate antibiotics and fluid boluses. The pharmacists' support of the initiative was in addition to other responsibilities, including taking part in acute stroke and cardiac arrest responses, trauma management, positive culture callbacks, medication facilitation and reconciliation, antimicrobial stewardship, and trainee precepting.

Measures and Outcomes

Data were extracted directly from discrete data fields in the EHR using a series of automated queries. Severity of illness in the first 24 hours for patients admitted to the inpatient service was ascertained from a modification of the Sequential Organ Failure Assessment score, where the Pao_2-to-Fio_2 ratio was calculated with Spo_2 instead of the Pao_2 (24). The extent of hospital-associated comorbidity was ascertained using the van Walraven modification of the Elixhauser comorbidity measure (26). This and other diagnosis-based measures were based on *International Classification of Diseases,* 10th Revision (ICD-10) diagnosis codes (27).

Time to antibiotics from arrival was the primary process measure evaluated. The primary clinical outcome was the hierarchical composite measure of days alive and out of hospital (DAOH) at 28 days. Both were determined a priori. DAOH sums the days during the

28-day period following presentation, where patients were both alive and not hospitalized. This composite measure reflects LOS in a way that avoids misattributing success to a short duration that may have been driven by early mortality or premature discharges that increase risk of readmission (28). These outcomes were also evaluated in an a priori determined subgroup of patients in whom the sepsis EWS flag was triggered before antibiotics were administered.

Collected balancing measures included frequencies and weight-based volumes of fluid boluses administered in the ED, rates of *Clostridiodes difficile* infection diagnoses (ICD-10 code A04.7 during the encounter), antibiotic utilization (yes or no), and suspected infection by Sepsis-3 criteria (18). Process measures included antibiotic choice by class, clinical antibiotic indication as documented through the computerized ordering interface, and time to antibiotics from arrival.

We conducted several additional post hoc analyses. These included assessments of differences in time from alert to antibiotic ordering and time from ordering to administration between the prospective study groups. We also compared time from arrival to antibiotic administration in the control group to patients in the EWS model validation cohort.

Statistical Analysis

Testing for differences in continuous variables relied on the two-sided Wilcoxon rank-sum test. Differences in proportions were assessed with the Pearson chi-square test. Testing for differences in secondary balancing and process measures was considered exploratory, and no adjustments were made for multiple comparisons. Analyses were conducted using the R software package, Version 3.5.1 (R Core Team, Vienna, Austria) (29).

Initiative Monitoring

Measures and outcome data generated from the EHR were reviewed at biweekly meetings of unblinded stakeholders including representatives from the Quality Institute and Divisions of Clinical Informatics, Infectious Disease, Emergency Medicine and Pharmacy. The committee agreed a priori to stop the randomized controlled initiative when a majority felt that additional iterations of the initiative would not be informative or when the risks of continuing the initiative outweighed the benefits. Throughout the initiative, stakeholders sought to identify opportunities for improvement, unanticipated consequences, and potentially missed opportunities (instances in which the alert fired in either group yet a diagnosis of sepsis was missed or the alert fired in the intervention group and an alternate diagnosis was missed). Courses of the patients who had inhospital deaths were reviewed by 2 committee members blinded to patient allocation. Feedback from providers was also actively encouraged.

The initiative began on August 16, 2019. The study was interrupted during a 2-week period in November of 2019, when an EHR upgrade prevented the messaging of the sepsis EWS alert to the pharmacists. Data from this period were excluded from analyses. Based on the review of data during one of the December 2019 committee meetings, a unanimous decision was made to discontinue the randomized controlled nature of this initiative and to display the EWS-triggered flag in the EHR and allow EHR-based pharmacist notification for all ED patients.

RESULTS

There were 835 ED encounters with a sepsis EWS-triggered alert during our initiative, which extended from August 16, 2019, to December 16, 2019. Two hundred and thirty-seven encounters were excluded (**Fig. 1**). The final cohort consisted of 598 unique encounters by 598 unique patients, 313 of whom were randomized to the standard care group and 285 to the intervention group. The baseline characteristics appeared balanced (**Table 1**).

Patients in the intervention group had a shorter time to antibiotic administration from ED arrival compared with the standard care group (median, 2.3 hr [interquartile range (IQR), 1.4–4.7 hr] vs 3.0 hr [IQR, 1.6–5.5 hr]; $p = 0.039$) (**Fig. 2**). Patients in the intervention group also had a greater number of DAOH compared with the standard care group (median, 24.1 vs 22.5 d; $p = 0.011$) (**Fig. 3**). The differences in time to antibiotics and DAOH were mirrored in the subgroup analysis of patients who received an alert before antibiotics were administered (**Table S2**, http://links.lww.com/CCM/G671). DAOH and time to antibiotics were negatively correlated, with a Pearson correlation coefficient of −0.18 (95% CI, −0.085 to −0.27).

A post hoc analysis revealed that the intervention group had a shorter time from alert to antibiotic

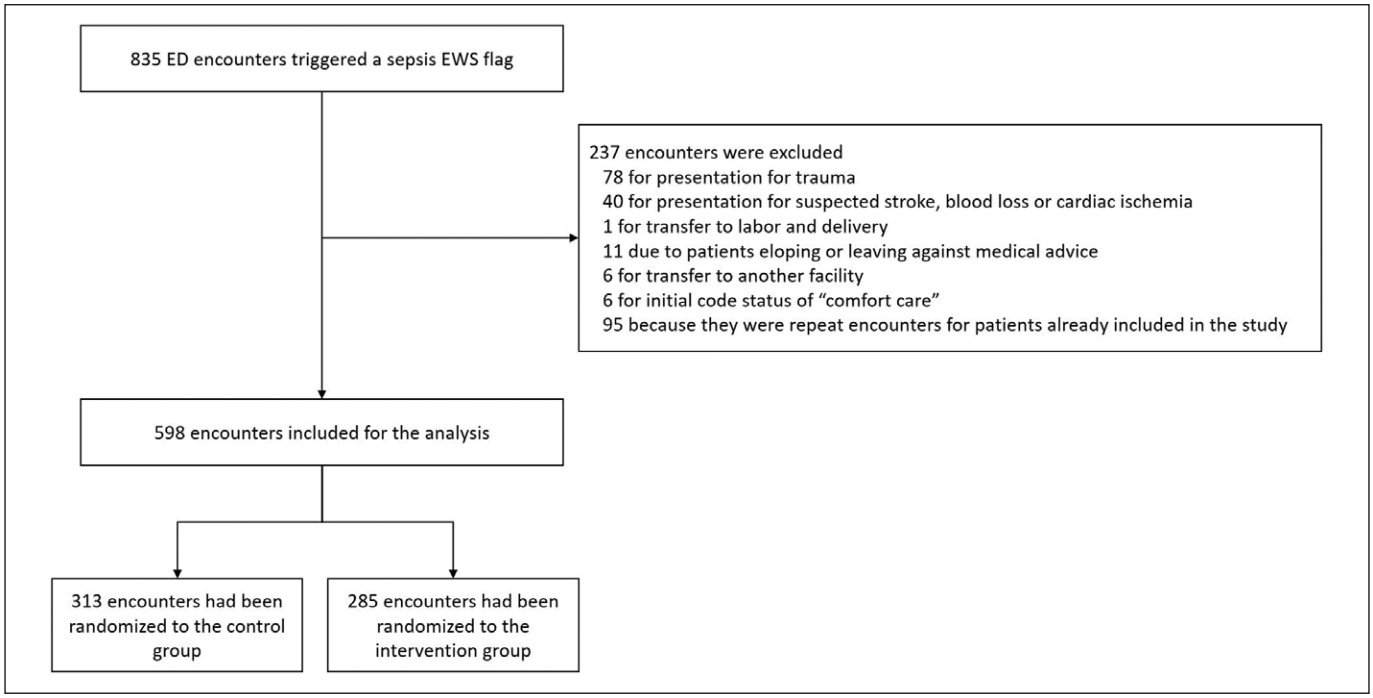

Figure 1. Subject flow diagram. ED = emergency department, EWS = early warning system.

ordering (median, 0.6 hr [IQR, 0.0–2.6 hr] vs 1.4 hr [IQR, 0.2–3.9 hr]; $p = 0.043$) as well as less time from order placement to administration (median, 0.4 hr [IQR, 0.2–0.9 hr] vs 0.7 hr [IQR, 0.3–1.4 hr]; $p = 0.001$) compared with the standard care group. Median time from arrival to antibiotic administration in the standard care group was not significantly different compared to the historical EWS validation cohort (3.0 hr [IQR, 1.6–5.5 hr] vs 2.83 hr [IQR, 1.6–5.6 hr]; $p = 0.85$).

There were no differences in frequency of antibiotic administration, fluid resuscitation, or *C. difficile* infection (**Table 2**). First antibiotic choices by class and user selected indications were not significantly different between the groups (**Tables S3** and **S4**, http://links.lww.com/CCM/G671).

No notable adverse or unanticipated events were elicited during feedback sessions with providers and pharmacists. Chart review of deceased patients revealed no missed opportunities. During meetings occurring throughout the time of the quality initiative, numerous opportunities for ED provider education on the roles of the pharmacist and the EWS arose, but the committee did not identify any need to alter the sepsis EWS's alerting mechanism or pharmacists' roles established at the beginning of the initiative.

Pharmacists estimated that 10% of their clinical effort was spent in adjudicating the sepsis EWS prompts. When pharmacists were asked which component of the sepsis response pathway they felt they impacted, they identified expediting antibiotic preparation and administration as their leading intervention. Providers reported the sepsis flag to be helpful for the initiation of a team-based response to sepsis (Fig. S1, http://links.lww.com/CCM/G671) and were generally appreciative of the assistance offered by the pharmacists.

DISCUSSION

In this single-center prospective randomized quality improvement initiative, the display of a sepsis EWS-triggered flag in the EHR combined with ED pharmacist notification was associated with modest improvements in time to antibiotic administration and a composite sepsis-related clinical outcome with no reported adverse consequences or differences in collected balancing measures.

Our main findings extend those of a number of observational studies, suggesting that timely administration of antibiotic therapy is associated with improved clinical outcomes (2, 3, 17, 30). In a post hoc analysis of the subgroup of patients that had an alert fire before antibiotic administration, both the time from the alert to antibiotic ordering and the time from order placement to delivery were significantly hastened.

TABLE 1.
Patient Characteristics at Baseline

Characteristic	Standard Care ($n = 313$)	Standard Care + Visible Sepsis Early Warning System Alert ($n = 285$)
Age (yr)		
Median (IQR)	62.2 (51.3–71.8)	61.5 (52.6–70.1)
Sex,[a] *n* (%)		
Female	144 (46.0)	146 (51.2)
Male	169 (54.0)	139 (48.8)
Race, *n* (%)		
White	183 (58.5)	150 (52.6)
Black	108 (34.5)	107 (37.5)
American Indian	2 (0.6)	1 (0.4)
Asian	2 (0.6)	2 (0.7)
Unavailable	18 (5.8)	25 (8.8)
Ethnicity, *n* (%)		
Non-Hispanic	279 (89.1)	240 (84.2)
Hispanic	26 (8.3)	37 (13.0)
Unavailable	8 (2.6)	8 (2.8)
Weight (kg)		
Missing, *n* (%)	51 (16.3)	52 (18.2)
Median (IQR)	79.9 (63.4–99.1)	81.6 (64.2–105.6)
Time from admission to alert (hr)		
Median (IQR)	1.2 (0.5–2.2)	1.0 (0.4–2.1)

IQR = interquartile range.
[a]Sex at birth.

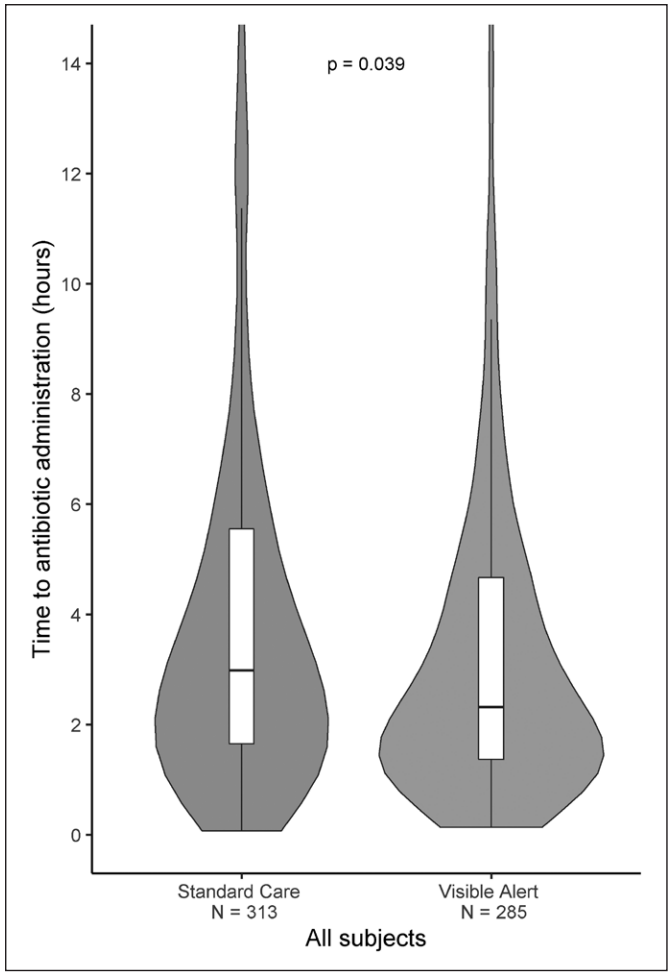

Figure 2. Time to antibiotic administration from arrival in all study subjects. The *shaded violin diagrams* demonstrate the distribution of the data, whereas the *embedded boxplots* highlight sample medians and interquartile ranges. Outliers (values outside 1.5 × the interquartile range from the first and third quartiles) are not demonstrated in the figures but were included in the analysis.

These findings suggest a plausible pathway—namely both earlier recognition and more expedient action—that could conceivably have led to the differences in mortality, LOS, and representation, which were collectively reflected in our composite clinical outcome of DAOH. Although we are unable to directly attribute differences in clinical outcomes to our intervention and its associated process measure, a post hoc analysis of the relationship between DAOH and time to antibiotics supported a negative correlation between the two.

The rather modest impact of our intervention is not surprising. Sepsis care has evolved greatly in the past 20 years, and an emphasis on the importance of early antibiotics is a cornerstone (31, 32). As a result, the additional value of an EWS over current standards of care is likely to be incremental at best. Although our median time to antibiotic administration did not conform with recently suggested standards of door to antibiotic time of one hour, our results nonetheless closely align with others' reported experiences (17, 33–37). Such real-world delays are likely attributable to the fact that many patients who are ultimately diagnosed with sepsis do not manifest overt signs of the condition on arrival as well as the likelihood that patients presenting with milder phenotypes warranted a more measured approach (5, 35). Even within such narrow timeframes, the results of our intervention imply some value for such an approach in settings where there may still be room for improvement.

Much of the published literature regarding the implementation of sepsis alerts in the ED setting is based

Figure 3. Days alive and out of hospital in all study subjects. The *shaded violin diagrams* demonstrate the distribution of the data, whereas the *embedded boxplots* highlight sample medians and interquartile ranges.

on the assessment of the utility of rule-based screening systems through pre-post cohort analyses (9–16). To our knowledge, there is only one randomized controlled trial of the implementation of a prediction-based sepsis EWS that has been published to date (38). In their study, Shimabukuro et al (38) demonstrated significant reductions in both LOS and inpatient mortality in a randomized controlled trial of a machine learning–based sepsis prediction model in the ICU setting. This would make our study the second report of a randomized controlled intervention for a predictive model-based sepsis EWS and the first to be reported in the ED setting. Our findings extend those of Shimabukuro et al (38) and should encourage healthcare systems to continue investigating as well as investing in the implementation of sepsis EWS.

For a sepsis EWS to succeed, it must add value to standard care without unduly increasing provider workloads and alert fatigue (39). In our implementation, alerts were relatively rare and unobtrusive when compared with other EWS, where a pop-up or text-paged alert is typically used (7). Both the pharmacists and providers reported positive experiences with the EWS-supported multidisciplinary interaction. This feedback is consistent with literature that highlights how pharmacists are particularly well-positioned to assist with the response to sepsis (40, 41).

An additional concern with sepsis EWS is that they could conceivably rush ED providers toward empiric therapy and raise the risks of misdiagnoses and antibiotic overuse (42, 43). At least in our experience, rates and relative volumes of fluid resuscitation, the overall frequency of antimicrobial usage, and rates of *C. difficile* diagnoses did not differ between the groups. As a result, the relatively modest improvement in clinical outcomes seen with the intervention weighed favorably against the absence of overt adverse events, signals, or experiences.

The results of our initiative prompted the extension of the EWS to all patients in the ED setting. As EWS-related pharmacist effort was perceived as manageable and otherwise overlapping with their clinical roles, no new pharmacists were hired and no additional resources were requested for the EWS expansion.

Our study has several limitations. First, the generalizability of our study is limited due to our reliance on a single-center experience. However, both the specific sepsis EWS we leveraged and the randomized controlled approach we used to determine its effectiveness are portable and reproducible. Second, although the randomization and track board alerts occurred continuously, pharmacists were not consistently available nor always physically present. A partial exposure to pharmacists likely attenuated their impact on our measured outcomes, but our pragmatic study design did not allow us to account for this. Our study was also underpowered for a meaningful evaluation of the impact of the intervention on more severe septic phenotypes, where earlier antibiotic administration may be most important. In addition, we were unable to confidently rule out the possibility that patients in the standard care group could have received inferior care due to the absence

TABLE 2.
Study Measures and Outcomes

Characteristic	Standard Care ($n = 313$)	Standard Care + Visible Sepsis Early Warning System Alert ($n = 285$)	p[a]
Length of stay (d)			
Median (IQR)	4.0 (1.4–7.0)	3.2 (1.1–6.2)	0.124
Hospital mortality, *n* (%)	25 (8.0)	13 (4.6)	0.086
28-d mortality, *n* (%)	31 (9.9)	17 (6.0)	0.077
Antibiotic utilization, *n* (%)	219 (70.0)	193 (67.7)	0.553
Fluid bolus administration, *n* (%)	203 (64.9)	174 (61.1)	0.336
Volume by weight (mL/kg)			
Median (IQR)	41.0 (22.5–64.2)	39.1 (23.9–62.2)	0.831
Clostridiodes difficile diagnosis, *n* (%)	5 (1.6)	2 (0.7)	0.309
Suspected infection,[b] *n* (%)	169 (54.0)	141 (49.5)	0.269
Admitted to inpatient setting, *n* (%)	254 (81.2)	217 (76.1)	0.135
Admission to ICU, *n* (%)	128 (40.9)	101 (35.4)	0.170
ICU length of stay (d)			
Median (IQR)	3.4 (2.0–6.0)	3.6 (2.0–5.4)	0.937
Day 1 Sequential Organ Failure Assessment score[c]			
Median (IQR)	4.0 (2.0–7.0)	4.0 (2.0–7.0)	0.637
Elixhauser van Walraven comorbidity index			
Median (IQR)	20.0 (13.0–43.0)	22.0 (13.0–43.0)	0.456
28-d representation to emergency department or hospital, *n* (%)	96 (30.7)	70 (24.6)	0.096

IQR = interquartile range.
[a]No adjustments were made for multiple hypothesis testing.
[b]Based on the Sepsis-3 definition.
[c]Sequential Organ Failure Assessment scores were only calculated for patients who were admitted to the inpatient setting.

of an alert, particularly if a provider was unaware of the randomized intervention. However, our reliance on otherwise well-informed pharmacists as drivers of the intervention should have made this unlikely. Supporting this notion is the finding that time to antibiotic administration was not greater in the standard care group when compared to our historical baseline data. Finally, our study was limited by our reliance on a composite clinical outcome measure. DAOH was leveraged because it provides greater statistical power than either LOS or mortality alone. Similar constructs have been leveraged in other disciplines, and reassessing critical care studies through such hierarchal composite end points can expose potentially important differences in outcomes (44–49).

CONCLUSIONS

In this quality improvement initiative, patients presenting to the ED who were randomized to a targeted sepsis EWS notification that was visible to both pharmacists and clinical staff had a significant reduction in time to antibiotic administration and a modestly greater number of days alive and out of hospital (DAOH) compared with those who had the alert hidden from view. The alerts were not seen as burdensome

to ED providers or pharmacists and there were no reported adverse consequences or increases in balancing measures detected. Future studies will be required to determine whether the approach can be generalized to other healthcare systems and settings, particularly in circumstances where pharmacists may not be available to facilitate an EWS response.

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