Antibiotic Delays and Feasibility of a 1-Hour-From-Triage Antibiotic Requirement: Analysis of an Emergency Department Sepsis Quality Improvement Database

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Study objective: We identify factors associated with delayed emergency department (ED) antibiotics and determine feasibility of a 1-hour-from-triage antibiotic requirement in sepsis.

Methods: We studied all ED adult septic patients in accordance with Centers for Medicare & Medicaid Services Severe Sepsis and Septic Shock National Quality Measures in 2 consecutive 12-month intervals. During the second interval, a quality improvement intervention was conducted: a sepsis screening protocol plus case-specific feedback to clinicians. Data were abstracted retrospectively through electronic query and chart review. Primary outcomes were antibiotic delay greater than 3 hours from documented onset of hypoperfusion (per Centers for Medicare & Medicaid Services Severe Sepsis and Septic Shock National Quality Measures) and antibiotic delay greater than 1 hour from triage (per 2018 Surviving Sepsis Campaign recommendations).

Results: We identified 297 and 357 septic patients before and during the quality improvement intervention, respectively. Before and during quality improvement intervention, antibiotic delay in accordance with Centers for Medicare & Medicaid Services measures occurred in 30% and 21% of cases (−9% [95% confidence interval −16% to −2%]); and in accordance with 2018 Surviving Sepsis Campaign recommendations, 85% and 71% (−14% [95% confidence interval −20% to −8%]). Four factors were independently associated with both definitions of antibiotic delay: vague (ie, nonexplicitly infectious) presenting symptoms, triage location to nonacute areas, care before the quality improvement intervention, and lower Sequential [Sepsis-related] Organ Failure Assessment scores. Most patients did not receive antibiotics within 1 hour of triage, with the exception of a small subset post–quality improvement intervention who presented with explicit infectious symptoms and triage hypotension.

Conclusion: The quality improvement intervention significantly reduced antibiotic delays, yet most septic patients did not receive antibiotics within 1 hour of triage. Compliance with the 2018 Surviving Sepsis Campaign would require a wholesale alteration in the management of ED patients with either vague symptoms or absence of triage hypotension. [Ann Emerg Med. 2020;75:93-99.]

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INTRODUCTION

Background

Early antibiotic administration for patients with sepsis has been a focus of recent consensus recommendations and national quality measures, driven by investigations demonstrating an association between increased mortality and each additional hour of delay in antibiotic administration,[1-3] although a meta-analysis[4] showed no benefit of antibiotic administration within 3 hours of triage or 1 hour of shock onset. Despite uncertainty about the clinical value of timely antibiotics, the Centers for Medicare & Medicaid Services (CMS) currently requires hospitals to publicly report the proportion of patients who receive a sepsis treatment bundle that includes administration of broad-spectrum antibiotics within 3 hours from the time of onset of new organ dysfunction in patients with systemic inflammatory response syndrome and documented infection.[5] Moreover, the 2018 update of the Surviving Sepsis Campaign recommendations advised even earlier administration of antibiotics as a new standard of care for sepsis patients; namely, that antibiotics should be administered within 1 hour from triage.[6] This

Editor's Capsule Summary

What is already known on this topic

Despite a lack of evidence, recent recommendations suggest a 1-hour-from-triage requirement for antibiotic administration in patients with sepsis.

What question this study addressed

The study addressed the feasibility of complying with a 1-hour-from-triage requirement both before and after a quality improvement intervention and factors associated with a delay in antibiotic administration.

What this study adds to our knowledge

In this single emergency department (ED) retrospective time series study of 654 septic patients, only a fraction of patients were treated with antibiotics within 1 hour from triage, and quality improvement interventions did not significantly change this fraction.

How this is relevant to clinical practice

In this ED, a 1-hour-from-triage requirement for antibiotic administration in patients with sepsis is not obtainable in the majority of patients, even with quality improvement interventions aimed at achieving the goal.

recommendation was controversial, and the Infectious Diseases Society of America did not endorse the 2018 Surviving Sepsis Campaign in part because of their concern that the 1-hour guideline would encourage inappropriate administration of broad-spectrum antibiotics.[7]

In the current analysis, we examined emergency department (ED) patient data collected before and during a sepsis quality improvement initiative. Our goal was to identify factors associated with antibiotic delay, validate the quality improvement initiative, and identify the patient population whose antibiotic administration time would need to be further shortened to comply with the 2018 Surviving Sepsis Campaign recommendations.

MATERIALS AND METHODS

Study Design, Setting, and Selection of Participants

This was a retrospective cohort analysis approved by the institutional review board. We studied all adult ED patients (≥18 years) from April 1, 2014, to March 31, 2016, who met criteria adapted from the current CMS Severe Sepsis and Septic Shock (SEP-1) definition[5] for septic shock: a final hospital *International Classification of Diseases, 10th Revision* diagnosis code for sepsis; either confirmed source of infection or high suspicion for infection documented in the admission note; and development of persistent hypotension (systolic blood pressure <90 mm Hg on at least 2 measurements), or elevated lactate level greater than or equal to 4.0 mmol/L, or use of vasopressor medication in the ED. We excluded patients receiving comfort measures only, who were unlikely to receive aggressive management, and also those transferred from an outside facility and already treated for infection before arrival.

Interventions

Precisely halfway through the analysis interval, our ED initiated a sepsis care quality improvement intervention. The intervention involved a sepsis screening protocol plus timely, case-specific performance feedback e-mailed to physicians, midlevel providers, and nurses involved in treating the septic patient. The protocol was communicated to all clinical staff through e-mail, flyers, and departmental presentations, with *de minimus* communication activities before the formal start of the quality improvement intervention. The Shock Precautions on Triage (SPoT) Sepsis rule was the basis for sepsis screening. It is positive when a patient has mild vital sign abnormalities (pulse rate >systolic blood pressure or systolic blood pressure <100 mm Hg) and a clinical concern for infection (explicit symptoms of infection, or vague symptoms in a patient with major comorbidities, or any patient in extremis). In a previous report (data from before the current analysis interval), we found that the SPoT Sepsis rule was significantly more sensitive than the quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) score for adult patients with sepsis in our ED, and it had similar specificity.[8]

Data Collection and Processing

Data were sourced from the hospital electronic medical record. Laboratory results, vital signs, patient locations, demographics, and hospital outcome were downloaded electronically. For each parameter in our research database, at least 20 cases were randomly reviewed and compared with the source (ie, the hospital's electronic medical record) to confirm perfect agreement, including relevant time stamps, thus ensuring that we had accurately extracted and processed electronic data.

Blinded to encounter date and outcome, 2 trained chart reviewers independently reviewed clinical notes (triage note, as well as nursing and providers' initial assessments) and completed a standardized data entry form[9] for presenting symptoms, documentation of difficult intravenous access or need for ultrasonographically guided access, medications, and other ED treatments. The reviewers also verified whether active infection was

documented in the hospital admission note. For every subject, the codings of the 2 reviewers were compared, and any disagreements were resolved by majority vote in a review session that included a third (physician) reviewer. Presenting symptoms were then labeled as explicit versus vague according to an objective categorization schema described by Filbin et al.[10] Explicit symptoms included fever, chills, or rigors; cough with productive sputum; dysuria; reported skin redness or concern for soft tissue infection; referral for specific infection diagnosis; or measured temperature greater than or equal to 100.4°F (38.0°C) at triage. Symptoms were defined as vague if they did not include any of the explicit symptoms. Cohen's κ was computed for reviewer-coded parameters.

The primary outcome was proportion of patients with delayed antibiotics. The CMS definition of delay was greater than 3 hours until documented appropriate antibiotic administration from the first onset of hypoperfusion (ie, systolic blood pressure <90 mm Hg or lactate level ≥2.0 mmol/L, occurring at triage or anytime in the ED thereafter, which are the CMS-specified organ dysfunction elements linked to perfusion[5]). The 2018 Surviving Sepsis Campaign definition of delay was documented appropriate antibiotics greater than 1 hour after triage. Appropriate broad-spectrum antibiotics for sepsis were explicitly determined in accordance with CMS measures.[5] Secondary outcomes were times to antibiotics and the rates of ICU admission and hospital mortality.

Primary Data Analysis

Descriptive statistics were calculated for patient cohorts before and during the quality improvement intervention. For comparing outcomes, we used the χ^2 test for proportions and Wilcoxon rank sum test for continuous variables. We also performed multivariable analysis to identify independent factors associated with antibiotic delay by both CMS and 2018 Surviving Sepsis Campaign definitions. We included 15 prespecified candidate parameters in 2 multivariable logistic regression models (one for each specified outcome). Variables were selected to include those with univariate significance with either outcome, those with plausible theoretic association with antibiotic delays, and variables standardly included in sepsis models.

RESULTS

A total of 654 patients were enrolled, 297 preintervention and 357 during the quality improvement intervention. For independent adjudication of presence of ED infection or not, Cohen's κ was 0.72. For other adjudicated parameters (eg, difficult intravenous access and individual symptoms that determined vague versus explicit classification), Cohen's κ ranged from 0.71 to 0.90.

Patient characteristics were generally similar between cohorts, including demographics, baseline comorbidities, presenting symptoms, infection source, and illness severity parameters (Table 1). More than half of the patients screened positive for sepsis at triage by the SPoT Sepsis rule, although a minority did not. Less than half of the patients had a positive triage qSOFA score (≥2) or triage hypotension.

Rates of antibiotic delay were significantly reduced pre– versus post–quality improvement (Table 2): 30% versus 21% of cases (–9% [95% confidence interval {CI} –16% to –2%]) according to CMS measures, and 85% versus 71% (–14% [95% CI –20% to –8%]) according to the 2018 Surviving Sepsis Campaign recommendation. There was no difference in clinical outcomes between cohorts.

Vague presenting symptoms and triage location to nonacute areas were independently associated with antibiotic delay for both CMS and 2018 Surviving Sepsis Campaign definitions of delay, as was receiving care before the quality improvement intervention and lower SOFA score (Table 3). For the 2018 Surviving Sepsis Campaign definition, triage to nonacute areas had the largest odds ratio for delay. Of patients with triage hypotension, 95% were triaged to the acute area, indicating likely collinearity between these parameters. Table 3 reports effect size and 95% CI for all covariates included in both models.

LIMITATIONS

First, our findings arose from a single center. Second, in accordance with SEP-1, sepsis diagnosis was based in part on billing codes, which often depend on the subjective diagnostic judgment of clinicians and billing staff, and may even be biased by financial incentives. Third, the pre- and postintervention cohorts were enrolled at different times, so the observed reduction in antibiotic delays during the quality improvement intervention may be due to other factors or secular trends that we did not account for. Fourth, "appropriate" antibiotic was based on CMS measures, whereas clinical effectiveness was not evaluated. Fifth, findings could be biased by systematic documentation errors or omissions (eg, inaccurate times for antibiotic administration), and metrics of process care based solely on ED documentation are relatively crude. Also, we may have missed some information in the documentation, although having every subject chart independently reviewed by 2 reviewers provided mitigation. Sixth, we used a basic multivariable analysis

Table 1. Patient characteristics.

Demographics	Preintervention, n=297	Intervention, n=357
Age, median (IQR), y	65 (53–77)	66 (54–77)
Men, No. (%)	174 (58.6)	213 (59.7)
Race, No. (%)		
Non-Hispanic white	236 (79.5)	280 (78.4)
Non-Hispanic black	20 (6.7)	16 (4.5)
Hispanic	10 (3.4)	9 (2.5)
Asian	12 (4.0)	20 (5.6)
Unknown	19 (6.4)	32 (9.0)
Charlson score, median (IQR)	3.0 (1.0–4.0)	2.0 (1.0–4.0)
Triage characteristics		
Explicit symptoms of infection on presentation, No. (%)	189 (63.6)	220 (61.6)
Hypotension at triage (SBP <90 mm Hg), No. (%)	56 (18.9)	93 (26.1)
qSOFA score ≥2 at triage, No. (%)	84 (28)	94 (26)
Positive "SPoT Sepsis" screen result* at triage, No. (%)	183 (62)	207 (58)
Active ED patient census at triage, median (IQR)	73 (57–88)	85 (71–103)
Characteristics of infection		
Documented infectious source,† No. (%)		
Respiratory	73 (24.6)	96 (26.9)
Abdominal	70 (23.6)	76 (21.3)
Urinary	51 (17.2)	74 (20.7)
Wound/soft tissue/skin	19 (6.4)	21 (5.9)
Unclear	83 (27.9)	86 (24.1)
Other	15 (5.1)	16 (4.5)
Time to initial SBP <90 mm Hg, median (IQR), h	1.3 (0.2-3.6)	1.1 (0.1–4.3)
Initial serum lactate, median (IQR), mmol/L	4.0 (2.1–5.4)	3.5 (2.1–5.0)
High lactate level (>4 mmol/L), No. (%)	143 (48.1)	157 (44.0)
SOFA score, mean (SD)	7.2 (3.6)	6.8 (3.7)
ED management characteristics, No. (%)		
Triage location, "acute care" area	217 (73.1)	275 (77)
Documented intravenous access difficulty	55 (18.5)	87 (24.4)
Sepsis flag set on electronic track board	151 (50.8)	288 (80.7)
Received vasopressors in the ED	145 (48.8)	172 (48.2)
Intubated in the ED	53 (17.8)	59 (16.5)

IQR, Interquartile range; *SBP*, systolic blood pressure.
*SPoT Sepsis screen is positive when a patient has mild vital sign abnormalities (pulse rate >SBP or SBP <100 mm Hg) together with a clinical concern for infection (explicit symptoms of infection, or vague symptoms in a patient with major comorbidities, or any patient in extremis).[7]
†Patients may have greater than one documented source of suspected infection.

methodology; alternative approaches are possible and could yield alternative findings.

DISCUSSION

We conducted a retrospective analysis to identify factors associated with antibiotic delay in ED patients with sepsis. For the CMS definition of delay, we found 4 independent clinical predictors: vague presenting symptoms, triage to nonacute areas of the ED, pre–quality improvement intervention period, and lower SOFA score. As for the 2018 Surviving Sepsis Campaign definition, we found that most septic patients had antibiotic delays greater than 1 hour from triage, except for a small subgroup with frank hypotension at triage and explicit symptoms who were treated after the start of the ED quality improvement intervention.

Table 2. Study outcomes.

Primary and Secondary Outcomes	Preintervention, n=297	Intervention, n=357	Δ Absolute (95% CI)
Primary outcomes: pre- vs intervention cohorts (and subgroups)			
Antibiotic delay >3 h from hypoperfusion,* % (n)	30 (90/297)	21 (76/357)	−9 (−16 to −2)
Subgroup: explicit presenting symptoms and triage SBP <90 mm Hg, % (n)	17 (5/30)	14 (7/51)	−2.9 (−19 to 13)
Subgroup: all others, % (n)	32 (85/267)	23 (69/306)	−9 (−17 to −2)
Antibiotic delay >1 h from triage, % (n)	85 (252/297)	71 (253/357)	−14 (−20 to −8)
Subgroup: explicit presenting symptoms and triage SBP <90 mm Hg, % (n)	70 (21/30)	39 (20/51)	−31 (−52 to −10)
Subgroup: all others, % (n)	86 (231/267)	76 (233/306)	−10 (−17 to −4)
Secondary outcomes: pre- vs intervention cohorts			
Time to appropriate antibiotic from hypoperfusion, median (IQR), h	1.6 [0.5 to 3.0]	0.8 [0.2 to 1.9]	−0.6 (−0.9 to −0.4)
Time to appropriate antibiotic from triage, median (IQR), h	2.5 [1.3 to 4.2]	1.7 [0.8 to 3.4]	−0.6 (−0.9 to −0.3)
Appropriate antibiotics never received in ED, % (n)	8 (24/297)	7 (26/357)	−1 (−5 to 3)
Admission to ICU within 48 h, % (n)	72 (213/297)	66 (234/357)	−6 (−13 to 1)
Hospital mortality, % (n)	23 (67/297)	23 (82/357)	0 (−6 to 7)

95% CIs according to Wald asymptotic confidence limits for differences in proportions and according to Hodges-Lehmann estimates for differences in median times.
*Hypoperfusion defined as SBP less than 90 mm Hg or lactate level greater than or equal to 2 mmol/L.

Metrics of ED crowding were not predictive of antibiotic delay, nor was difficult intravenous access, suggesting that timely antibiotic administration depended on diagnostic assessment, rather than strictly operational factors.

A large fraction of septic patients presented with vague symptoms (ie, nonspecific complaints such as lethargy, somnolence, isolated hypotension, or near syncope), and without fever or source-localizing symptoms. This finding that vague symptoms were common in patients with sepsis

Table 3. Multivariable logistic regression analysis for factors associated with antibiotic delays.

Antibiotic Delay Definition: Characteristic	Hypoperfusion* +180 Minutes (CMS Measure), Adjusted Odds Ratio (95% CI)	Triage+60 Minutes (2018 SSC Recommendation), Adjusted Odds Ratio (95% CI)
Pre–quality improvement intervention	1.7 (1.1–2.5)	2.7 (1.7–4.3)
Vague presenting symptoms	3.1 (2.1–4.7)	4.0 (2.5–6.4)
Triage to nonacute area	2.0 (1.3–3.1)	15.9 (5.6–44.7)
SOFA score	0.9 (0.9–1.0)	0.9 (0.9–1.0)
SBP ≥90 mm Hg at triage	0.9 (0.5–1.4)	2.5 (1.6–4.0)
Age	0.9 (0.6–1.3)	1.0 (0.7–1.6)
Male sex	0.9 (0.6–1.3)	0.7 (0.5–1.2)
Race (nonwhite)	0.9 (0.6–1.5)	1.0 (0.6–1.6)
Charlson score	1.0 (0.9–1.0)	1.0 (0.9–1.1)
Chronic liver disease	1.9 (0.9–3.7)	2.3 (0.9–6.0)
Immunosuppression	0.6 (0.4–1.0)	0.7 (0.4–1.2)
ED capacity at triage	1.1 (0.4–2.6)	1.8 (0.7–5.0)
IV access difficulty	1.4 (0.9–2.3)	1.0 (0.6–1.8)
Lactate level ≥4 mmol/L	1.1 (0.7–1.5)	0.9 (0.6–1.4)
Unclear infection source	1.5 (1.0–2.3)	0.9 (0.6–1.5)

SSC, Surviving Sepsis Campaign; *IV*, intravenous.
c Statistic for multivariable models is 0.71 and 0.80 for CMS and 2018 SSC, respectively.
*Hypoperfusion defined as SBP less than 90 mm Hg or lactate level greater than or equal to 2 mmol/L.

is consistent with that in previous cohorts from our hospital,[8] and it should not be assumed that vague symptoms implied benign disease states; previous analysis suggests that mortality is notably high in patients with vague symptoms even when timing of antibiotics is controlled for.[10]

Most septic patients lacked vital sign abnormalities at triage, having neither hypotension nor even a positive qSOFA score (Table 1). The SPoT Sepsis screening rule was positive in a thin majority of cases. Absence of hypotension was not independently associated with delayed antibiotics according to CMS measures, but the majority of patients who did receive antibiotics within 1 hour of triage had frank hypotension at triage (Table 2).

Triage to nonacute areas of the ED was independently associated with delayed antibiotics (Table 3). We speculate that septic patients who were not triaged to acute areas had more subtle presentations, and after they arrived in nonacute areas, there was likely reduced staffing, reduced monitoring, and possibly less alacrity in work flow.

The CMS definition of timely antibiotic administration permits up to 3 hours after recognition of hypoperfusion, which does allow for some degree of additional testing and assessment before antibiotics are due. Before the quality improvement intervention, median time to antibiotics from first time of hypoperfusion was 1.6 hours; after implementation of the quality improvement initiative, it was reduced to 0.8 hours. The SPoT Sepsis rule, around which the quality improvement intervention was designed, was intended to focus clinicians' attention on mild hemodynamic abnormalities, major comorbidities, and vague symptoms. The quality improvement intervention combined staff education (e-mail, flyers, and presentations) and case-specific feedback to attending physicians, midlevel providers, and nurses alike. We speculate that the feedback intervention reduced CMS-defined antibiotic delays through triage decisions, the timeliness with which providers evaluated potentially septic patients and ordered antibiotics, and the timeliness with which nurses administered antibiotics. Our data support the feasibility of compliance with CMS measures.

Our findings (Table 2) suggest that administration of antibiotics to the majority of septic patients within 1 hour of triage would require a wholesale alteration of our current practices for all patients arriving with stable vital signs, vague nonspecific symptoms, or both. Such patients made up the majority of our sepsis population.

Contemplating how to possibly comply with antibiotics within 1 hour of triage raises essential questions. First, how does one screen for sepsis at triage with sensitivity sufficient to identify most cases? We found that most septic patients lacked positive qSOFA scores at triage. The SPoT Sepsis screening rule is more sensitive,[8] but even this rule failed to identify a sizable fraction of septic patients at triage. Second, what operational practices would enable patients with nonspecific triage presentation to receive antibiotics within 1 hour: rapid diagnostic testing by a sepsis team, empirical antibiotics administered without diagnostic data, or both? We note the Infectious Diseases Society of America concerns that the 2018 Surviving Sepsis Campaign could encourage inappropriate administration of broad-spectrum antibiotics.[7] This leads to the third question: what will be the effect on other ED patients if substantial staffing resources are diverted to patients with stable triage vital signs or vague, nonspecific presenting symptoms?

Given that adhering to the 2018 Surviving Sepsis Campaign would require a fundamental change in how our ED treats patients who present with vague symptoms or unremarkable vital signs, whereas the clinical effectiveness of requiring antibiotics within 1 hour of triage is wholly uncertain, it is our opinion that currently the 2018 Surviving Sepsis Campaign recommendations about antibiotic timing are unjustifiable.

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REFERENCES

1. 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.
2. 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.
3. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med*. 2014;42:1749-1755.
4. Sterling SA, Miller WR, Pryor J, et al. The impact of timing of antibiotics on outcomes in severe sepsis and septic shock: a systematic review and meta-analysis. *Crit Care Med*. 2015;43:1907-1915.
5. Centers for Medicare & Medicaid Services (CMS). Sepsis Bundle Project (SEP), national hospital inpatient quality measures. Available at: https://www.qualitynet.org. Accessed February 11, 2018.
6. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign bundle: 2018 update. *Intensive Care Med*. 2018;44:925-928.
7. IDSA Sepsis Task Force. Infectious Diseases Society of America (IDSA) position statement: why IDSA did not endorse the Surviving Sepsis Campaign guidelines. *Clin Infect Dis*. 2018;66:1631-1635.
8. Filbin MR, Thorsen JE, Lynch J, et al. Challenges and opportunities for emergency department sepsis screening at triage. *Sci Rep*. 2018;8:11059.
9. Harris PA, Taylor R, Thielke R, et al. Research Electronic Data Capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377-381.
10. 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.