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Physician variation in time to antimicrobial treatment for septic patients presenting to the emergency department

Ithan D. Peltan, MD,MSc^{1,2,3,*}, Kristina H. Mitchell, MD³, Kristina E. Rudd, MD³, Blake A. Mann, MD³, David J. Carlbom, MD³, Catherine L. Hough, MD,MSc³, Thomas D. Rea, MD⁴, and Samuel M. Brown, MD,MS^{1,2}

¹Division of Pulmonary and Critical Care Medicine, Intermountain Medical Center, Salt Lake City, UT

²Division of Pulmonary and Critical Care Medicine, University of Utah School of Medicine, Salt Lake City, UT

³Division of Pulmonary and Critical Care Medicine, University of Washington School of Medicine, Seattle, WA

⁴Department of Medicine, University of Washington School of Medicine, Seattle, WA

Abstract

Objective—Delayed initiation of appropriate antimicrobials is linked to higher sepsis mortality. We investigated inter-physician variation in septic patients' door-to-antimicrobial time.

Design—Retrospective cohort study.

Setting—Emergency department (ED) of an academic medical center.

Subjects—Adult patients treated with antimicrobials in the ED between 2009 and 2015 for fluid-refractory severe sepsis or septic shock. Patients who were transferred, received antimicrobials prior to ED arrival, or were treated by an attending physician who cared for <5 study patients were excluded.

Interventions—None.

Measurements and Methods—We employed multivariable linear regression to evaluate the association between treating attending physician and door-to-antimicrobial time after adjustment for illness severity (APACHE II score), patient age, prehospital or arrival hypotension, admission from a long-term care facility, mode of arrival, weekend or nighttime admission, source of infection, and trainee involvement in care. Among 421 eligible patients, 74% received antimicrobials within three hours of ED arrival. After covariate adjustment, attending physicians'

*Corresponding author: Itthan D. Peltan, MD, MSc, Division of Pulmonary & Critical Care Medicine, Intermountain Medical Center (T5/STICU), 5121 S. Cottonwood St., Salt Lake City, UT 84107, itthan.peltan@utah.edu, Tel: (801) 507-6556.

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(N=40) median door-to-antimicrobial times varied significantly, ranging from 71 to 359 minutes ($p=0.002$). The percentage of each physician's patients whose antimicrobials began within 3 hours of ED arrival ranged from 0% to 100%. Overall, 12% of variability in antimicrobial timing was explained by the attending physician compared to 4% attributable to illness severity as measured by the APACHE II score ($p<0.001$). Some but not all physicians started antimicrobials later for patients who were normotensive on presentation ($p=0.017$) or who had a source of infection other than pneumonia ($p=0.006$). The adjusted odds of in-hospital mortality increased by 20% for each one hour increase in door-to-antimicrobial time ($p=0.046$).

Conclusions—Among patients with severe sepsis or septic shock receiving antimicrobials in the ED, door-to-antimicrobial times varied five-fold among treating physicians. Given the association between antimicrobial delay and mortality, interventions to reduce physician variation in antimicrobial initiation are likely indicated.

Keywords

Sepsis; Antimicrobial timing; Septic shock; Physician variation; Door-to-antibiotic time

INTRODUCTION

Sepsis is an increasingly common and highly morbid syndrome of infection and organ dysfunction (1–4). Sepsis and septic shock kill approximately 20% of the 700,000 patients hospitalized with this diagnosis each year and cost the U.S. medical system \$24.3 billion in 2007 (5, 6). Early identification and aggressive management of sepsis, including prompt administration of appropriate antimicrobials (7, 8), improve patient outcomes (9–11).

Sepsis care quality metrics and guidelines consequently emphasize early antimicrobials. The recent Centers for Medicare and Medicaid sepsis core measure, for instance, mandates antimicrobial initiation within three hours. The Surviving Sepsis Campaign guidelines similarly specified a three-hour ceiling for antimicrobial initiation and, while recommending an even more aggressive one-hour goal, also described a lack of data supporting the feasibility of this target (12). Patient and hospital factors influencing antimicrobial timing include non-typical clinical presentation (13–16), sepsis developing after admission (15), patient sex (17), arrival by ambulance (18, 19), diagnostic testing delays (16, 20), computerized physician order entry (21), teaching hospital status (15), emergency department (ED) crowding (22), and ED boarding (23). Though physicians vary in their management of otherwise-similar patients with sepsis (24, 25), the extent to which physicians' practice patterns influence antimicrobial timing in patients presenting to the ED with sepsis has not been previously investigated.

We therefore evaluated attending physician variation in antimicrobial timing in a cohort of patients with severe sepsis or septic shock treated with antimicrobials in an academic ED and explored whether the presence of hypotension by ED arrival modified physicians' antimicrobial treatment behavior.

MATERIALS AND METHODS

We conducted a retrospective cohort study of adult patients presenting to the ED of a university-operated public hospital in Seattle, WA between June 2009 and February 2015. Patients were included if severe sepsis or septic shock prompted ED attending physicians to activate the hospital's sepsis alert protocol. Criteria for activation of this protocol, which triggers bedside consultation by intensive care clinicians and nurses, included suspected infection plus hypoperfusion (mean arterial pressure <65 mmHg, systolic blood pressure <90 mmHg, and/or lactate >4 mmol/L) despite fluid resuscitation (30 ml/kg of crystalloid). The sepsis alert protocol could also be activated based on ED physician judgment. To ensure patients manifested sufficient evidence of infection during their ED stay to prompt an ED physician to initiate antimicrobials, we excluded patients who did not receive antimicrobials while in the ED (Supplemental Digital Content 1, Table S1, list of eligible antimicrobials). We excluded patients transferred from another acute care hospital or who received antimicrobials prior to hospital arrival. To provide adequate power for evaluation of individual physician prescribing behaviors, we included only patients who received care from an attending physician who treated at least four other eligible patients. Of note, all data collection and primary data analysis occurred prior to development and publication of new consensus criteria for sepsis and septic shock in early 2016 (1). The University of Washington Institutional Review Board approved the study with a waiver of informed consent.

The time from ED registration to antimicrobial initiation, laboratory results, and patient demographics were obtained from the electronic medical record. Antimicrobial administration times were verified by manual abstraction if missing or potentially erroneous (recorded as occurring prior to ED arrival, >90 minutes after sepsis protocol activation, or >6 hours after ED arrival). The Charlson comorbidity index was calculated from discharge diagnoses as previously described (26). Trained nurse and physician abstractors obtained information on comorbidities and patient classification for the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (27), prehospital clinical characteristics and care, and initial ED vital signs and interventions by manual review the electronic medical record and scanned paper documentation. A random sample of records (6%) was reviewed by a second, blinded abstractor, with near-perfect interrater agreement (28) as measured by APACHE II patient classification κ 0.91 (95% CI 0.80–1.00), initial prehospital systolic blood pressure κ 0.87 (95% CI 0.78–0.92), and complete agreement between manually abstracted antimicrobial initiation times. Information on physician training and experience was obtained from publicly-available data.

Hypotension was defined as systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg prior to or at the time of ED arrival. Severe sepsis and septic shock were defined according to then-current consensus criteria (12). Weekend arrivals occurred between midnight on Saturday morning through 11:59 pm Sunday. Nighttime admission was 11 pm to 8 am daily. Long-term care residents included patients admitted from a long-term acute care hospital, skilled nursing facility, or rehabilitation facility.

Bivariate analyses of continuous variables used unpaired t-tests with unequal variance or Mann-Whitney tests as appropriate. Categorical variables were compared using the chi-squared test or Fisher exact test. We employed multivariable linear or logistic regression with Huber-White sandwich estimators to evaluate the association between the primary outcome, time from ED arrival, and individual attending physicians, entered into the model using indicator variables. The model was adjusted for potential confounding and precision variables, which were specified a priori and included off hours admission, hypotension on or prior to ED arrival, source of admission, source of infection, age, APACHE II score, prehospital ambulance care, and involvement of a trainee in the patient's care. We quantified the variation in antimicrobial timing explained by the attending physician and model covariates by comparing the full model's R^2 statistic to the R^2 for models excluding the independent variable of interest. In an exploratory analysis, we evaluated whether the effect on antimicrobial timing of patient comorbidities, initial white blood count (WBC), initial lactate, initial temperature, and each covariate in the primary model varied by physician using a series of models incorporating an interaction term between the covariate and the physician. Non-binary covariates were first dichotomized: age (≤ 60 versus >60 years); severity of illness (APACHE II score ≤ 25 vs >25); comorbidities (Charlson score ≤ 2 versus >2); abnormal WBC ($4-12$ versus <4 or >12 [thousand per deciliter]); abnormal temperature ($36-38^\circ\text{C}$ versus $<36^\circ\text{C}$ or $>38^\circ\text{C}$); lactate (≤ 4 versus >4 mmol/L); and source of infection (pneumonia versus other source). We restricted each analysis to the subset of physicians treating at least 5 patients with and 5 patients without the tested covariate and excluded covariates where ≤ 8 physicians did not meet this criterion. Abnormal WBC, source of admission, trainee involvement, and prehospital ambulance care were thereby excluded from this analysis.

We also evaluated the association between door-to-antimicrobial time and mortality. For this analysis, we used a best subsets leaps-and-bounds algorithm to test all possible combinations of candidate variables for inclusion in a multivariable logistic regression model evaluating predictors of in-hospital mortality (29). Candidate predictors were door-to-antimicrobial time, APACHE II score, Charlson comorbidity score, initial lactate, vasopressor use in the ED, source of admission, source of infection, and hypotension on or prior to ED arrival. We maintained a 10:1 ratio of outcome events to candidate predictors (30). The Akaike information criterion, which balances the improved model fit from predictor inclusion against the increased risk of overfitting, was used to select the final model (31). We evaluated the final model using the Hosmer-Lemeshow goodness-of-fit test, where a p-value <0.1 indicates inadequate fit (32).

We performed several sensitivity analyses. We repeated the primary analysis including only attending physicians treating ≥ 10 eligible patients to assess for decreased physician variation with larger per-physician samples and after excluding the physician with the longest median door-to-antimicrobial time. Next, we tested restricting the cohort to patients with hypotension at or prior to ED arrival or patients who met severe sepsis or septic shock criteria. Third, we tested the effect of redefining the cohort by antimicrobial initiation within 3 hours, 6 hours, or 12 hours of ED arrival rather than antimicrobial initiation in the ED. Fourth, to evaluate the possibility that late sepsis presentations in patients spending more time in the ED drove the observed association, we repeated the primary analysis with

additional adjustment for ED length of stay. Finally, in an exploratory sensitivity analysis, we evaluated whether adjusting for a potential surrogate for delayed sepsis recognition — the door-to-sepsis alert time, dichotomized at its median value (≤ 141 versus >141 minutes) — influenced our findings. As in the primary analysis, subjects were excluded from each of these sensitivity analyses unless treated by an attending physician who cared for at least 4 other patients meeting the analysis inclusion criteria. Analyses were performed using Stata version 14.1 (StataCorp LP, College Station, TX). A p-value <0.05 was considered significant.

RESULTS

Among 421 eligible patients with fluid-refractory severe sepsis or septic shock in the emergency department (Supplemental Digital Content 2, Figure S1, patient enrollment flow diagram), the 313 patients (74%) who received antimicrobials within 180 minutes of ED arrival were sicker, spent less time in the emergency department, and were more likely to receive prehospital care and to have a trainee participate in their care (Table 1). Hospital mortality was 18% (N=78). The 40 attending physicians who cared for 5 or more eligible patients had a mean 10.5 years of experience and cared for a median 10 (interquartile range [IQR] 6–12) patient subjects. Nearly all physicians (94%) were board certified in emergency medicine.

Overall, median time from patient ED arrival to antimicrobial initiation was 118 (IQR 82–185) minutes (Supplemental Digital Content 3, Figure S2, density plot of time to antimicrobials). Individual physicians' unadjusted median time to antimicrobials ranged from 67 to 337 minutes (Supplemental Digital Content 4, Figure S3, subjects' unadjusted time to antimicrobials by attending physician).

After adjustment for demographic and clinical factors, the median time to antimicrobials was 147 (IQR 103–187) minutes (Supplemental Digital Content 3, Figure S2, density plot of time to antimicrobials). By physician, median antimicrobial times ranged from 71 to 359 minutes (Figure 1). Subjects' time to antimicrobial administration varied significantly by attending physician ($p=0.002$), and mean antimicrobial times remained significantly different between physicians in the first vs third or fourth quartiles after adjustment ($p<0.001$ for both comparisons, Table 2). The attending physician accounted for 12% of overall subject-level variability in antimicrobial timing (35% of variability explained by the model overall) compared to 4% attributable to illness severity as measured by the APACHE II score (Table 2). Physicians' years of experience were not associated with physician-level antimicrobial timing ($p=0.66$).

The adjusted percentage of each physician's patients who received antimicrobials within 1, 2, or 3 hours of ED admission is shown in Figure 2. Overall, 6.2% of patients received antimicrobials within 1 hour (physician range 0–33%), 35% within 2 hours (physician range 0–89%), and 71% within 3 hours (physician range 0–100%).

After restricting the analysis to the 21 physicians caring for at least 10 study subjects (N=297 patients), physicians' adjusted median time to antimicrobials ranged from 84 to 222

minutes ($p=0.079$). The remaining sensitivity analyses — which (1) included only patients with hypotension on or before ED arrival; (2) included only patients meeting formal severe sepsis or septic shock criteria; (3) excluded the potential influential outlier physician; (4) adjusted for ED length of stay; (5) redefined the study cohort by antimicrobials initiation within 3, 6, or 12 hours of ED admission; and (6) added door-to-sepsis alert time to the primary model— all yielded results similar to the primary analysis, including significant between-physician variation in door-to-antimicrobial time (Supplemental Digital Content 5, Figure S4, sensitivity analyses of physician variation in door-to-antimicrobial time). Antimicrobial timing variation between physician quartiles was somewhat smaller but still statistically significant after adjustment for door-to-sepsis alert time (data not shown).

The final model for in-hospital mortality included door-to-antimicrobial time, APACHE II score, Charlson comorbidity score, vasopressor use in the ED, initial lactate, and hypotension present at or before ED admission (Supplemental Digital Content 6, Table S2, multivariable logistic regression for in-hospital mortality). The odds of in-hospital death increased by 20% for each one-hour increase in door-to-antimicrobial time (odds ratio 1.20, 95% CI 1.00–1.44, $p=0.046$).

In an exploratory analysis, we evaluated factors associated with physician variation (Supplemental Digital Content 7, Table S3, interaction between door-to-antimicrobial predictors and physician). While adjusted door-to-antimicrobial times were shorter for patients with hypotension present by admission or pneumonia as the source of infection, the absence of hypotension or pneumonia influenced physicians differently ($p=0.017$ and $p=0.006$ for interaction between physician and hypotension status or infection source, respectively). Some physicians treated patients equally quickly regardless of hypotension or source of infection and others provided antimicrobials more slowly to patients without hypotension or pneumonia (Figure 3). The effect on door-to-antimicrobial time of age, illness severity, nighttime or weekend admission, comorbidities, initial temperature, and initial lactate did not vary among physicians.

DISCUSSION

Among patients receiving antimicrobials in the ED for fluid-refractory severe sepsis or septic shock, we identified five-fold variation in adjusted door-to-antimicrobial time dependent on which physician cared for the patient. Physician adherence to federal quality standards and international guidelines for prompt antimicrobial treatment varied between 0% and 100%. Physician practice pattern explained three times more variation in antimicrobial timing than any other predictor. A subset of physicians exhibited slower door-to-antimicrobial times when the patient's initial blood pressure remained normal or the source of infection was not pneumonia. Delayed antimicrobials were associated with higher adjusted mortality.

Unwarranted practice variation between regions and hospitals influences care costs and quality for many disease processes (33, 34). How physician practice patterns create this variation, however, is only beginning to be understood, especially for sepsis. While the top 25% of physicians in our study met 3-hour antimicrobial goals for at least 90% of their

patients, we found that 30% of physicians met these goals for 50% or less of their patients. Our data suggest that, even in an institution where overall door-to-antimicrobial performance compares well with published experience (8, 35, 36), physician practice style is an important determinant of timely antimicrobial initiation. Antimicrobial administration in the ED depends heavily on both cognitive and practical actions by the physician (37). As a prerequisite to prompt antimicrobial initiation, the physician must believe that timely appropriate antimicrobials influence outcomes and must prioritize antimicrobial initiation (38). For each individual patient, the physician then must assign the patient's illness severity and pre-test infection probability, update these assessments as new data becomes available, determine that the product of these appraisals exceeds his or her action threshold for antimicrobial initiation, follow through on the decision to order antimicrobials, and ensure the order is executed in a timely fashion (39). Differing approaches to one or more component processes may explain the variability we observed in antimicrobial timing.

In prior studies, patients with non-typical sepsis presentations exhibited longer door-to-antimicrobial times (13–15). We found, however, that only a subset of physicians initiated antimicrobials more slowly when confronted with an infection other than pneumonia. Physicians also reacted differently to illness severity, with some but not all physicians starting antimicrobials later when the patient presented without hypotension. Adjusting for the interval from ED arrival to sepsis alert activation as a potential surrogate for the timeliness of sepsis recognition non-significantly decreased measured physician variation, likely due to these two variables' collinearity. These findings may suggest that some physicians employ heuristics — cognitive short cuts for decision making based on pattern recognition —for sepsis recognition and prioritization that are less likely to be derailed by non-typical or less severe presentations or that these physicians do a better job of “debiasing” their clinical decisions in these circumstances (40). Previous studies also linked sepsis practice habits to physician characteristics, including training type and sex (24, 25, 41, 42). We found no significant association between antimicrobial initiation patterns and physician experience, but our study was not powered for this analysis. Future studies should investigate further the causes of physician variation in door-to-antimicrobial time.

Strengths of this study include a well-characterized cohort of patients with severe sepsis or septic shock. By restricting our study to patients who received antimicrobials in the ED, we studied physicians' treatment patterns on a level playing field (i.e. for patients with severe sepsis or septic shock evident prior to ED discharge). We also accounted carefully for known and plausible confounding factors.

One limitation of our study was the inability to compare patient's initial antimicrobials against culture results or the final diagnosis. As a result, we could not determine whether “early treatment” physicians more often gave antimicrobials to patients ultimately determined not to have infection or were more likely to select inadequate antimicrobials. These are important considerations, as inadequate antimicrobials worsen outcome and unnecessary antimicrobials may increase antimicrobial resistance or delay accurate diagnosis of non-infectious etiologies (43, 44). These issues should be addressed in future studies. A study of pneumonia triage decisions in the ED, however, did not show a clear association between physicians' hospital admission rates and their likelihood to under- or

over-triage individual patients (45). Since all patients in our study ultimately received antimicrobials for sepsis in the ED, moreover, guidelines and practicality suggest earlier initiation was preferable to late initiation.

Our study has several additional limitations. Most importantly, we were unable to fully characterize the reasons for physician variation in door-to-antimicrobial time. Further research, likely employing mixed methods, will be required to determine whether physician characteristics (such as sex or training type) influence treatment behaviors and to fully understand how some physicians avoid antimicrobial delay when patient presentation is non-typical. We were also unable to investigate how physician variation in processes of care leading up to antimicrobial initiation — such as laboratory ordering or result review — correlated with variations in door-to-antimicrobial time. We cannot exclude residual confounding, but the strength and magnitude of the association between physician and antimicrobial timing suggests any missing confounders would not undo our findings. We could not evaluate physicians' antimicrobial initiation patterns among septic patients for whom the physician did not activate the hospital's sepsis alert protocol. The sensitivity analysis focusing on physicians who saw a greater number of patients did not reach statistical significance but included a small number of physicians and patients. Since sepsis alerts were designed to facilitate sepsis bundle implementation and intensive care transfer for fluid-refractory sepsis rather than initial diagnosis and treatment, door-to-alert time was likely an imperfect surrogate for delayed sepsis recognition. Finally, we used data from a single academic ED and focused on patients with fluid-refractory sepsis and septic shock. The similarities in overall door-to-antimicrobial time distributions reported here compared to other centers (8, 35) and the Surviving Sepsis Campaign (36) do suggest the practice patterns we found are not unique to our ED, but future studies should evaluate our findings' generalizability to differently-organized EDs (including community EDs), other clinical settings (including patients developing sepsis after hospital admission), and to less severely ill patients.

CONCLUSIONS

Door-to-antimicrobial time varied significantly among physicians treating patients presenting to the ED with fluid-refractory severe sepsis or septic shock. Delayed antimicrobial initiation was associated with increased risk-adjusted mortality. Some, but not all, physicians initiated antimicrobials later if patients remained normotensive on ED arrival or did not have pneumonia. If confirmed, these data suggest interventions targeting physician variation in antimicrobial initiation may improve sepsis care and outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016; 315:801–810. [PubMed: 26903338]
2. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001; 29:1303–1310. [PubMed: 11445675]
3. Seymour CW, Rea TD, Kahn JM, et al. Severe sepsis in pre-hospital emergency care: analysis of incidence, care, and outcome. *Am J Respir Crit Care Med*. 2012; 186:1264–1271. [PubMed: 23087028]
4. Gaieski DF, Edwards JM, Kallan MJ, et al. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med*. 2013; 41:1167–1174. [PubMed: 23442987]
5. Lagu T, Rothberg MB, Shieh M-S, et al. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. *Crit Care Med*. 2012; 40:754–761. [PubMed: 21963582]
6. Kaukonen K-M, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA*. 2014; 311:1308–1316. [PubMed: 24638143]
7. 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. [PubMed: 16625125]
8. Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med*. 2010; 38:1045–1053. [PubMed: 20048677]
9. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New Engl J Med*. 2001; 345:1368–1377. [PubMed: 11794169]
10. ProCESS Investigators. Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. *New Engl J Med*. 2014; 370:1683–1693. [PubMed: 24635773]
11. ARISE Investigators, ANZICS Clinical Trials Group. Peake SL, et al. Goal-directed resuscitation for patients with early septic shock. *New Engl J Med*. 2014; 371:1496–1506. [PubMed: 25272316]
12. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013; 41:580–637. [PubMed: 23353941]
13. Waterer GW, Kessler LA, Wunderink RG. Delayed administration of antibiotics and atypical presentation in community-acquired pneumonia. *Chest*. 2006; 130:11–15. [PubMed: 16840376]
14. Talan DA, Zibulewsky J. Relationship of clinical presentation to time to antibiotics for the emergency department management of suspected bacterial meningitis. *Ann Emerg Med*. 1993; 22:1733–1738. [PubMed: 8214865]
15. Amaral ACKB, Fowler RA, Pinto R, et al. Patient and organizational factors associated with delays in antimicrobial therapy for septic shock. *Crit Care Med*. 2016; 44:2145–2153. [PubMed: 27441899]
16. Cullen M, Fogg T, Delaney A. Timing of appropriate antibiotics in patients with septic shock: a retrospective cohort study. *Emerg Med Australas*. 2013; 25:308–315. [PubMed: 23911021]
17. Madsen TE, Napoli AM. The DISPARITY-II study: delays to antibiotic administration in women with severe sepsis or septic shock. *Acad Emerg Med*. 2014; 21:1499–1502. [PubMed: 25424151]
18. Band RA, Gaieski DF, Hylton JH, et al. Arriving by emergency medical services improves time to treatment endpoints for patients with severe sepsis or septic shock. *Acad Emerg Med*. 2011; 18:934–940. [PubMed: 21883637]

19. Studnek JR, Artho MR, Garner CL, et al. The impact of emergency medical services on the ED care of severe sepsis. *Am J Emerg Med*. 2012; 30:51–56. [PubMed: 21030181]
20. Pines JM, Morton MJ, Datner EM, et al. Systematic delays in antibiotic administration in the emergency department for adult patients admitted with pneumonia. *Acad Emerg Med*. 2006; 13:939–945. [PubMed: 16825671]
21. Cartmill RS, Walker JM, Blosky MA, et al. Impact of electronic order management on the timeliness of antibiotic administration in critical care patients. *Int J Med Inform*. 2012; 81:782–791. [PubMed: 22947701]
22. Fee C, Weber EJ, Maak CA, et al. Effect of emergency department crowding on time to antibiotics in patients admitted with community-acquired pneumonia. *Ann Emerg Med*. 2007; 50:501–9–509.e1. [PubMed: 17913300]
23. Sri-On J, Chang Y, Curley DP, et al. Boarding is associated with higher rates of medication delays and adverse events but fewer laboratory-related delays. *Am J Emerg Med*. 2014; 32:1033–1036. [PubMed: 25027202]
24. Mikkelsen ME, Gaieski DF, Goyal M, et al. Factors associated with nonadherence to early goal-directed therapy in the ED. *Chest*. 2010; 138:551–558. [PubMed: 20173053]
25. Djurkovic S, Baracaldo JC, Guerra JA, et al. A survey of clinicians addressing the approach to the management of severe sepsis and septic shock in the United States. *J Crit Care*. 2010; 25:658.e1–658.e6.
26. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005; 43:1130–1139. [PubMed: 16224307]
27. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985; 13:818–829. [PubMed: 3928249]
28. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977; 33:159–174. [PubMed: 843571]
29. Furnival GM, Wilson RW. Regressions by leaps and bounds. *Technometrics*. 1974; 16:499–511.
30. Peduzzi P, Concato J, Kemper E, et al. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996; 49:1373–1379. [PubMed: 8970487]
31. Akaike, H. Information Theory and an Extension of the Maximum Likelihood Principle. In: Parzen, E. Tanabe, K., Kitagawa, G., editors. *Selected Papers of Hirotugu Akaike*. New York: Springer; 1998. p. 199–213.
32. Hosmer, DW., Lemeshow, S. *Applied Logistic Regression*. New York: Wiley; 1989.
33. Wennberg JE. Time to tackle unwarranted variations in practice. *BMJ*. 2011; 342:d1513–d1513.
34. Kahn JM, Angus DC. Reducing the cost of critical care: new challenges, new solutions. *Am J Respir Crit Care Med*. 2006; 174:1167–1168. [PubMed: 17110650]
35. Puskarich MA, Trzeciak S, Shapiro NI, et al. Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. *Crit Care Med*. 2011; 39:2066–2071. [PubMed: 21572327]
36. 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. [PubMed: 24717459]
37. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement *JAMA*. 1999; 282:1458–1465. [PubMed: 10535437]
38. Barlow G, Nathwani D, Myers E, et al. Identifying barriers to the rapid administration of appropriate antibiotics in community-acquired pneumonia. *J Antimicrob Chemother*. 2008; 61:442–451. [PubMed: 18065412]
39. Funk DJ, Kumar A. Antimicrobial therapy for life-threatening infections: speed is life. *Crit Care Clin*. 2011; 27:53–76. [PubMed: 21144986]
40. Croskerry P. From mindless to mindful practice—cognitive bias and clinical decision making. *New Engl J Med*. 2013; 368:2445–2448. [PubMed: 23802513]
41. McIntyre LA, Hébert PC, Fergusson D, et al. A survey of Canadian intensivists' resuscitation practices in early septic shock. *Crit Care*. 2007; 11:R74. [PubMed: 17623059]

42. Reade MC, Huang DT, Bell D, et al. Variability in management of early severe sepsis. *Emerg Med J.* 2010; 27:110–115. [PubMed: 20156862]
43. Kumar A, Ellis P, Arabi Y, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest.* 2009; 136:1237–1248. [PubMed: 19696123]
44. van Zanten ARH. The golden hour of antibiotic administration in severe sepsis: avoid a false start striving for gold. *Crit Care Med.* 2014; 42:1931–1932. [PubMed: 25029127]
45. Dean NC, Jones JP, Aronsky D, et al. Hospital admission decision for patients with community-acquired pneumonia: variability among physicians in an emergency department. *Ann Emerg Med.* 2012; 59:35–41. [PubMed: 21907451]

Figure 1.

Adjusted time from emergency department admission to antimicrobial initiation by physician. The solid horizontal line indicates the physician's adjusted median time to antimicrobials, bars represent the interquartile range, and vertical lines represent the total range. The horizontal dotted line is the adjusted median door-to-antimicrobial time for the overall cohort.

Figure 2.

Adjusted percentage of physicians' patients receiving antimicrobials within 1, 2, or 3 hours of emergency department (ED) arrival. Symbols sizes are proportional to the number of eligible patients seen by each physician.

Figure 3.

Adjusted time from emergency department admission to antimicrobial initiation by physician and presence or absence of (A) hypotension on or prior to emergency department arrival (13 physicians, 209 patients) or (B) pneumonia versus other source of infection (8 physicians, 144 patients). Physicians were rank ordered by the median door-to-antimicrobial time (solid horizontal line) for patients without hypotension or pneumonia, respectively. Bars represent the interquartile range, and vertical lines represent the total range. The horizontal dotted line is the adjusted median door-to-antimicrobial time for the overall cohort. The influence of hypotension ($p=0.017$ for interaction) and pneumonia ($p=0.006$ for interaction) varied significantly by physician.

Table 1

Demographic and clinical characteristics of patient subjects

Patient subject characteristic	Time to antibiotics (N=313)	180 mins	Time to antibiotics >180 mins (N=108)	p
Age	56 (16)		56 (16)	0.70
Female sex	94 (30.0%)		40 (37.0%)	0.18
Non-white race	106 (33.9%)		34 (31.5%)	0.65
Hispanic	34 (10.9%)		8 (7.4%)	0.30
Admit from long-term care facility	81 (25.9%)		17 (15.7%)	0.03
Received prehospital care	257 (82.1%)		72 (66.7%)	<0.001
Infection source				0.04
Pneumonia	115 (36.7%)		24 (22.2%)	
Soft tissue infection	33 (10.5%)		17 (15.7%)	
Intraabdominal	19 (6.1%)		13 (12.0%)	
Urinary tract	49 (15.7%)		22 (20.4%)	
Bacteremia	14 (4.5%)		4 (3.7%)	
Other	2 (0.6%)		1 (0.9%)	
Unknown	81 (25.9%)		27 (25.0%)	
ED admission data				
Mean arterial pressure (mmHg)	77 (64–97)		85 (72.5–101)	0.02
Lactate (mmol/L) ^a	4.6 (2.7–7.8)		3.9 (2.3–5.8)	0.02
White blood count (1000/dL)	16.4 (10.0)		13.5 (7.4)	0.001
ED management data				
Trainee involvement in care	267 (85.3%)		71 (65.7%)	<0.001
Total IV fluid in ED (L)	3.8 (1.6)		3.8 (1.7)	0.81
Vasopressors started in ED	93 (30.2%)		17 (15.7%)	0.003
APACHE II score	26.2 (10.1)		20.4 (9.7)	<0.001
Met severe sepsis/septic shock criteria	289 (92.3%)		97 (89.8%)	0.41
Follow-up lactate >4 mmol/L ^a	48 (46.6%)		144 (48.2%)	0.79
Charlson index	2.5 (2.2)		2.5 (2.2)	0.89
Death before discharge	61 (19.5%)		17 (15.7%)	0.39
ED length of stay (mins)	302 (129)		504 (193)	<0.001
Hospital length of stay (days)	11.2 (15.1)		12.5 (17.5)	0.51

Values reported as mean (SD), N (%) or median (IQR).

Abbreviations: ALS, advanced life support; APACHE II, Acute Physiology and Chronic Health Evaluation II, ED, emergency department

^aOne subject had no lactate results, and 19 subjects did not have a follow-up lactate result

Table 2

Results of multivariable regression evaluating impact of attending physician on antibiotic timing.

Variable	Regression coefficient ^a (95% CI)	Explained variability in time to antibiotics ^b	P value
Overall model		33.9%	<0.001
Overall effect of attending physician		11.7%	0.002
Quartile 1	Reference		—
Quartile 2	16.2 (−2.6, 35.1)		0.091
Quartile 3	42.7 (20.4, 65.0)		<0.001
Quartile 4	85.2 (52.3, 118.2)		<0.001
APACHE II score	−2.7 (−3.8, −1.7)	4.1%	<0.001
ED arrival via EMS	−28.2 (−60.7, 4.3)	0.7%	0.089
Weekend admission	3.96 (−19.0, 26.9)	0.2%	0.74
Nighttime admission	−2.3 (−22.3, 17.6)	0%	0.82
Age	0.4 (−0.3, 1.0)	0.2%	0.25
Hypotension present on or before ED arrival	−37.5 (−58.1, −17.0)	2.1%	<0.001
Admission from care facility ^c	−20.3 (−44.7, 4.1)	0.4%	0.10
Trainee involvement in care	−21.6 (−50.8, 7.6)	0.4%	0.15
Overall effect of infection source		4%	0.031
Pneumonia	Reference		—
Soft tissue	33.0 (0.6, 65.4)		0.046
Intra-abdominal or gastrointestinal	60.3 (13.9, 106.6)		0.011
Urinary tract	41.8 (12.6, 71.1)		0.005
Bloodstream	−1.5 (−70.8, 67.7)		0.99
Other	196.7 (−198.8, 592.1)		0.33
Unknown	27.1 (2.5, 51.8)		0.031

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ED, emergency department; EMS, emergency medical services;

^aUnless specified, value represents expected change in time from emergency department arrival to antibiotics initiation for a one unit change in exposure variable.^bCalculated as the difference between the R² of the full model (0.339) compared to the R² of the model excluding the specified variable^cCompared to baseline admission from home or clinic setting