Emergency Department Crowding Is Associated With Delayed Antibiotics for Sepsis

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Study objective: Barriers to early antibiotic administration for sepsis remain poorly understood. We investigated the association between emergency department (ED) crowding and door-to-antibiotic time in ED sepsis.

Methods: We conducted a retrospective cohort study of ED sepsis patients presenting to 2 community hospitals, a regional referral hospital, and a tertiary teaching hospital. The primary exposure was ED occupancy rate, defined as the ratio of registered ED patients to licensed ED beds. We defined ED overcrowding as an ED occupancy rate greater than or equal to 1. We used multivariable regression to measure the adjusted association between ED crowding and door-to-antibiotic time (elapsed time from ED arrival to first antibiotic initiation). Using Markov multistate models, we also investigated the association between ED crowding and pre-antibiotic care processes.

Results: Among 3,572 eligible sepsis patients, 70% arrived when the ED occupancy rate was greater than or equal to 0.5 and 14% arrived to an overcrowded ED. Median door-to-antibiotic time was 158 minutes (interquartile range 109 to 216 minutes). When the ED was overcrowded, 46% of patients received antibiotics within 3 hours of ED arrival compared with 63% when it was not (difference 14.4%; 95% confidence interval 9.7% to 19.2%). After adjustment, each 10% increase in ED occupancy rate was associated with a 4.0-minute increase (95% confidence interval 2.8 to 5.2 minutes) in door-to-antibiotic time and a decrease in the odds of antibiotic initiation within 3 hours (odds ratio 0.90; 95% confidence interval 0.88 to 0.93). Increasing ED crowding was associated with slower initial patient assessment but not further delays after the initial assessment.

Conclusion: ED crowding was associated with increased sepsis antibiotic delay. Hospitals must devise strategies to optimize sepsis antibiotic administration during periods of ED crowding. [Ann Emerg Med. 2019;73:345-355.]

Please see page 346 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Up to 850,000 adult patients present to US emergency departments (EDs) with sepsis or septic shock each year, representing nearly 1% of all ED visits.[1] Sepsis is fatal for 15% to 20% of patients hospitalized with this syndrome and costs the US health system greater than $24 billion per year.[2] Both preclinical models and large observational analyses suggest that door-to-antibiotic time is a key determinant of sepsis mortality and morbidity.[3-8]

Importance

Government mandates require antibiotic initiation for sepsis within 3 hours.[9,10] International guidelines now recommend antibiotic initiation within 1 hour of ED arrival,[11] a goal achieved for only a fraction of patients.[5] Although some patient-, clinician-, and hospital-level factors associated with antibiotic delay have been identified,[12-14] the mechanisms for antibiotic delay remain unclear.

For patients with myocardial infarction and traumatic injury, conditions in which time to treatment is an important outcome determinant, ED crowding is associated with delays in key care processes.[15,16] Although some evidence suggests sepsis antibiotic delays correlate with increasing ED crowding, these data derive from mainly smaller, single-hospital studies that did not explore the mechanisms of the observed association.[17,18]

Goals of This Investigation

In this multicenter cohort, we sought to determine the association of ED crowding with antibiotic delay among patients presenting to the ED with sepsis. We also sought to identify potential mechanisms linking ED crowding to antibiotic delays.

Editor's Capsule Summary

What is already known on this topic

Emergency department (ED) crowding may impede care of time-critical conditions.

What question this study addressed

Is increased ED crowding associated with delayed administration of antibiotics in sepsis?

What this study adds to our knowledge

In this analysis of 3,572 ED sepsis patients presenting to 1 of 4 hospitals, each 10% increase in ED occupancy was associated with a 4-minute delay in antibiotic administration. ED crowding was associated with slower initial patient assessment but not other ED antibiotic time subsegments.

How this is relevant to clinical practice

ED crowding may interfere with aspects of sepsis care such as timely antibiotic administration. The link between quality standards for sepsis care remains unclear.

MATERIALS AND METHODS

Study Design

We performed a retrospective cohort study of ED sepsis patients. The Intermountain Healthcare institutional review board approved this study with waiver of informed consent.

Setting

We included patients presenting to 1 of 4 EDs belonging to Intermountain Healthcare, a vertically integrated health care system. Study EDs ranged in size from 19 to 57 ED beds, with approximate annual visit volumes ranging from 22,000 to 89,000 (Table E1, available online at http://www.annemergmed.com). EDs belonged to urban and suburban hospitals in and around Salt Lake City, UT, including 1 large Level I trauma and tertiary referral teaching hospital, 1 regional referral hospital, and 2 community hospitals. A single physician practice group provides staffing for all 4 study EDs; physicians' rotation between sites was expected to reduce between-hospital variation in practice patterns.

Approaches to sepsis care were harmonized across the study EDs. Although the EDs did not use sepsis response teams, they used standard sepsis order sets. Clinical decision support for the identification of community-acquired pneumonia was in use during the study period.[19] The EDs allowed nurse-initiated diagnostic testing (but not antibiotic treatment) for specific patient complaints or when all ED beds were occupied. In addition, study hospitals also encouraged and monitored use of a bundled treatment protocol for sepsis patients admitted to the ICU.[20]

Data Collection and Processing

We obtained primary data on patient demographic characteristics, comorbidities, clinical characteristics, treatments, and processes of care, using the Intermountain Healthcare Electronic Data Warehouse, which integrates patient care and hospital operations data from financial, clinical, laboratory, and other departmental databases across the Intermountain system (Figure E1, available online at http://www.annemergmed.com). The Electronic Data Warehouse includes annotated and actively maintained "data marts" devoted to different patient populations and levels of analysis, including data on individual ED patient encounters and unit-level performance statistics organized by time.[21] For cases with missing data or outlying values, trained abstractors performed manual chart review aided by electronic abstraction instruments;[22] these efforts were required for approximately 37% of the cohort.

For this study, we linked individual sepsis patient data with ED operational metrics. Linkages were accomplished deterministically according to the time the patient arrived at the ED (Figure E1, available online at http://www.annemergmed.com). Similarly, we used patients' ED arrival time to link the patient encounter to corresponding nurse and physician staffing counts during the respective period; these data were obtained from the hospital system's human resources department and physician scheduling records maintained by the ED's physician practice group.

We determined antibiotic initiation times from medication administration documentation stored in the Electronic Data Warehouse. In an independent effort for an ICU sepsis registry, trained nurses abstracted antibiotic times for 21% of included subjects; agreement with Electronic Data Warehouse data was excellent (99.2%).

Selection of Participants

Patients presenting to a study ED between July 2013 and September 2015 were eligible for inclusion if they were age 18 years or older, exhibited clinical sepsis while in the ED, and had a hospital discharge diagnosis confirming sepsis. We defined clinical sepsis per the Third International Consensus Definitions for Sepsis and Septic Shock consensus criteria as the combination of confirmed or suspected infection plus new-onset organ failure in the

ED. We defined confirmed or suspected infection by the concurrent administration of antibiotics and collection of body fluid cultures while the patient was in the ED. We defined new-onset organ failure as a Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score greater than or equal to 2 points above baseline.[23,24] Baseline SOFA scores were calculated with data collected before ED arrival, whereas ED SOFA scores were calculated with data collected between ED arrival and hospital admission. Per the Third International Consensus Definitions for Sepsis and Septic Shock criteria[25] and consistent with bedside practice, we assigned SOFA component scores of 0 when data for their calculation were not obtained in the ED. Serum bilirubin level was the most frequently missing value (0.6% of the study cohort). To ensure that further evaluation confirmed ED patients' clinical Third International Consensus Definitions for Sepsis and Septic Shock diagnosis, we used the modified Angus method to identify *International Classification of Diseases, Ninth Revision, Clinical Modification* discharge diagnoses consistent with sepsis.[26,27] We excluded trauma patients and, to ensure independence of analyzed ED encounters, included only the first eligible ED encounter for each patient during the study period.

Exposure and Outcome Measures

The exposure of interest was ED crowding, which we quantified according to a widely accepted 3-component model incorporating input (demand for ED services), throughput (care processes associated with ED evaluation and treatment), and output (ED patient disposition).[28,29] The primary measure of ED crowding was ED occupancy rate, the ratio of registered ED patients (after exclusion of the subject patient) to licensed ED beds. We chose ED crowding because it is readily available, validated, and has been used extensively in ED crowding literature, including studies of sepsis.[17,18,29-31]

Secondary measures of ED crowding included (1) ED overcrowding, defined as an occupancy rate greater than or equal to 1; (2) patient-to-physician ratio; (3) patient-to-nurse ratio; (4) the number of concurrent ED arrivals, defined as the number of patients registering in the ED within 30 minutes before and after the index patient; (5) the number of ED boarders (patients admitted to the hospital but awaiting an inpatient bed); and (6) the Emergency Department Work Index score, an ED crowding scale previously validated in our system that incorporates occupancy metrics adjusted for acuity, boarding, and physician staffing.[29,32,33] We determined ED crowding measures at patient ED arrival.

The primary outcome was door-to-antibiotic time, defined as the time from ED registration until initiation of the first eligible antibiotic in the ED. Eligible agents included intravenous antibiotics, oral vancomycin, and oseltamivir (the full list is shown in Table E2, available online at http://www.annemergmed.com).[5,6,13] Antibiotic initiation within 3 hours of ED arrival was the secondary outcome.

The analysis included factors potentially associated with sepsis care. We defined hypotension as a systolic blood pressure less than 90 mm Hg or mean arterial pressure less than 65 mm Hg on ED arrival. Nighttime and weekend ED arrivals were defined as patients arriving between midnight and 6:59 AM or between midnight Saturday and 11:59 PM on Sunday, respectively. We calculated the Mortality in Emergency Department Sepsis (MEDS) score[34,35] and a weighted comorbidity score based on the Elixhauser Comorbidity Index.[36,37] Trained clinical nurses assigned triage acuity scores during routine clinical care on a standardized 5-point scale.[38] Because few subjects had scores in the lowest acuity category, we pooled the lowest 2 categories when conducting our analyses. We categorized insurance coverage as private, Medicare, Medicaid, or uninsured. We classified patients as married or not, with patients who reported being separated from their spouse classified as being not married.

To model the sequential care processes linking patient arrival to antibiotic initiation, we examined ED operational data, including time from ED arrival until placement in a treatment room, first physician contact, and first laboratory sample collection.

ANALYSIS

Primary Analysis

The primary analysis evaluated the association between door-to-antibiotic time and ED occupancy rate, using multivariable linear regression with robust standard errors. We selected the following adjustment variables for inclusion in the model a priori according to known or plausible association with both the exposure and outcome: hospital, nighttime ED arrival, weekend ED arrival, arrival by ambulance, marital status, type of insurance, illness severity as measured by the MEDS score, triage acuity score, weighted Elixhauser comorbidity score, first systolic blood pressure after ED arrival, Hispanic ethnicity or nonwhite race, sex, and age. We fitted separate models containing these adjustment variables for each secondary metric of ED crowding. Modeling ED occupancy rate quartiles independently (ie, as a nominal rather than an ordinal variable) allowed assessment for a potential nonlinear association between occupancy rate and

antibiotic timing. Secondary analyses investigating the association of ED crowding and antibiotic initiation within 3 hours used multivariable logistic regression with robust standard errors.

Sensitivity Analyses

We tested the robustness of the results in a series of sensitivity analyses: (1) restricting the cohort to patients receiving antibiotics within 6 hours of ED arrival; (2) using a more parsimonious set of adjustment variables (age, sex, MEDS score, nighttime ED arrival, weekend ED arrival, weighted Elixhauser comorbidity score, and hospital); (3) using a generalized linear mixed model to incorporate hospital as a random rather than fixed effect; and (4) replacing linear regression with survival analysis using a Weibull distribution or Cox proportional hazards model. For the Cox model, we continued to measure ED occupancy on the patient's ED arrival as in the primary analysis, but accounted for potential time-dependent effects for variables (ED occupancy rate, mode of arrival to the ED, sex, age, and the pooled acuity score) exhibiting significant deviations from the proportional hazards assumption ($P<.05$ on the proportional hazards test) by incorporating an interaction term between each variable and time.[39,40]

Pre-antibiotic Care Process Analyses

The elapsed time to antibiotic administration encompasses multiple care processes or segments; for example, ED arrival to room placement and room placement to clinician assessment. To test whether these care segments differentially mediated the association between door-to-antibiotic time and ED crowding, we applied Markov multistate model analysis. Markov multistate models are useful when a disease or care process has multiple discrete stages (referred to as "states"), competing endpoints ("absorbing states"), or competing pathways between states. The models allow investigation of the duration of time spent in each state ("sojourn time"), distribution of a population across the different states, or timing of progression from one state to the next.[41-44] Analysis requires the practitioner to prespecify possible transitions, using a Markov chain of ones and zeros.[45] Classic survival analysis, which considers individuals alive until death or censoring, is a special case of multistate models with the simplest possible 2-state model.

We first identified 5 key processes ("states") leading from ED arrival to ED antibiotic initiation (the only absorbing state) and potential transitions between states organized into 2 distinct pathways (Figure 1). We assessed how each transition probability in our multistate model varied as a function of ED crowding while controlling for the set of confounders described previously, modeling time to event with an exponential distribution after confirming that observed and expected prevalence were similar.[45] Formally, at any given time t, a transition probability $p_{ij}(t)$ describes the instantaneous likelihood of transition along available pathways between states I and J; we investigated how $p_{ij}(t)$ varied with ED crowding after adjustment for other influences. First laboratory sample collection time was used as the marker for diagnostic data collection. We excluded from this analysis patients with missing event time data (N=227; 6%) or whose state sequences were implausible or rare (N=21; 0.6%).

We applied multivariable logistic regression to evaluate whether the patient care process pathway was associated with ED occupancy. We also used multivariable linear regression with an indicator variable to determine the association of nurse-initiated diagnostic testing with door-to-antibiotic time. Both analyses incorporated the adjustment variables described previously.

Modifiers of ED Crowding/Antibiotic Timing Association

To investigate whether perceived illness severity or other factors affected the association between ED crowding and door-to-antibiotic time, we performed a preplanned exploratory analysis incorporating an interaction term between potential effect modifiers and the ED occupancy rate in the primary model. Potential effect modifiers, tested one at a time, included hypotension present on ED arrival, triage acuity score, illness severity, arriving to the ED by ambulance, sex, and Hispanic or nonwhite race. We added study site as a post hoc analysis. Pooling high-acuity scores (Canadian

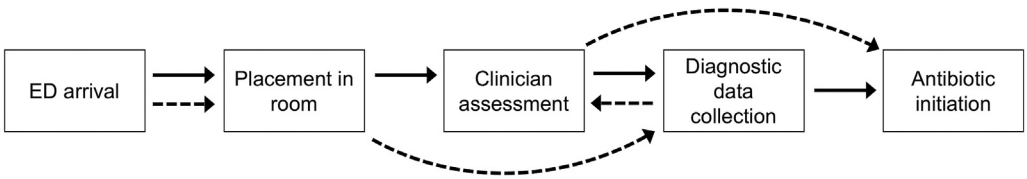

Figure 1. Multistate model for care processes leading from ED arrival to antibiotic initiation. Two care pathways were identified: the simple/default pathway (solid arrows) or a pathway involving initiation of diagnostic testing before clinician assessment (dashed arrows).

Triage and Acuity Scale scores 1 to 2) versus low ones (Canadian Triage and Acuity Scale scores 3 to 5) yielded a binary variable for acuity score. Using previously validated MEDS score categorizations,[34] we categorized illness severity as low (category 1; score 0 to 4), moderate (category 2; score 5 to 7), or high (category 3 to 5; score greater than or equal to 8).

Analyses were performed in Stata (version 14.2; StataCorp, College Station, TX) and R (version 3.5.1; R Foundation, Vienna, Austria).

RESULTS

Characteristics of Study Subjects

A total of 3,572 ED patients with clinical sepsis were included in the analysis (Figure E2, available online at http://www.annemergmed.com), 2,492 (70%) of whom arrived when the ED occupancy rate was greater than or equal to 0.5 and 497 (14%) of whom arrived to an overcrowded ED (occupancy rate greater than or equal to 1). ED crowding exhibited diurnal variation, with lowest occupancy from midnight to 10 AM (Figure E3, available online at http://www.annemergmed.com). Patients treated in an overcrowded ED were less likely to arrive by ambulance and tended to have lower ED triage acuity scores (Table 1).

Main Results

Median door-to-antibiotic time was 158 minutes (interquartile range 109 to 216 minutes). Antibiotic

Table 1. Demographic and clinical characteristics of ED sepsis patients by ED overcrowding at patient arrival.

	ED Occupancy Rate <1 (N=3,075)		ED Occupancy Rate ≥1 (N=497)	
Female sex, No. (%)	1,680	(54.6)	262	(52.7)
Age, median (SD)	64.6	(17.5)	63.7	(17.9)
Hispanic or nonwhite race, No. (%)	480	(15.6)	89	(17.9)
Married, No. (%)	1,565	(50.9)	237	(47.7)
Type of insurance, No. (%)				
Private	675	(22.0)	121	(24.4)
Medicare	1,863	(60.6)	275	(55.3)
Medicaid	280	(9.1)	63	(12.7)
Uninsured	257	(8.4)	38	(7.7)
Nighttime ED arrival, No. (%)	361	(11.8)	4	(0.8)
Weekend ED arrival, No. (%)	899	(29.4)	78	(15.7)
Received medical care out-of-hospital, No. (%)	1,149	(37.4)	163	(33.8)
Weighted Elixhauser score, median (SD)	8.3	(13.1)	8.3	(14.0)
ED acuity score, median (SD)	2.4	(0.5)	2.3	(0.5)
ED admission data				
Systolic blood pressure, median (SD), mm Hg	125	(28)	124	(28)
Pulse rate, median (SD), beats/min	102	(24)	102	(22)
Respiratory rate, median (SD), breaths/min	20.9	(5.7)	21.2	(6.0)
Temperature, median (IQR), °C [°F]	37.5 [99.5]	(36.6–38.5) [97.9-101.3]	37.7 [99.9]	(36.8–38.6) [98.2-101.5]
First Glasgow Coma Scale score, median (SD)	14.6	(1.8)	14.7	(1.5)
Lactate >2 mmol/L, No. (%)	1,351	(43.9)	203	(40.8)
WBC count, median (SD) (1,000/dL)*	13.6	(8.2)	13.1	(7.0)
ED management data				
Time to antibiotic initiation, median (IQR), min	154	(106–212)	183	(129–250)
Antibiotic initiation ≤3 h, No. (%)	1,929	(62.7)	240	(48.3)
MEDS score, median (SD)	5.4	(3.4)	5.1	(3.5)
Initial SOFA score, median (SD)	5.3	(2.9)	5.4	(3.0)
Hospital mortality, No. (%)	189	(6.2)	26	(5.3)
ED length of stay, median (IQR), min	259	(205–334)	289	(229–362)

IQR, Interquartile range.
*One patient had no recorded value.

initiation occurred within 3 hours of ED arrival for 2,169 patients (61%). In the unadjusted analysis, door-to-antibiotic time was associated with a 5.4-minute increase (95% confidence interval [CI] 4.4 to 6.4 minutes) for each 10% increase in ED occupancy rate. Similarly, the likelihood of antibiotic initiation within 3 hours of ED arrival decreased (odds ratio [OR] 0.88; 95% CI 0.86 to 0.91) for each 10% increase in ED occupancy rate (Table E3, available online at http://www.annemergmed.com).

After adjustment, door-to-antibiotic time exhibited a significant association with all measures of ED crowding except the number of ED boarders (Table 2). Each 10% increase in ED occupancy rate was associated with a 4.0-minute increase (95% CI 2.8 to 5.2 minutes) in the door-to-antibiotic time. This translated to door-to-antibiotics times that were 27 minutes (95% CI 18 to 37 minutes) longer when the most crowded quartile of ED occupancy rate was compared with the least crowded (Figure 2) and a decreased likelihood (adjusted OR 0.90; 95% CI 0.88 to 0.93) of receiving antibiotics within 3 hours for each 10% increase in ED occupancy rate (Figure 3). The adjusted odds of door-to-antibiotic time less than or equal to 3 hours were lower (OR 0.65; 95% CI 0.53 to 0.81) for patients presenting to an overcrowded ED. Sensitivity analyses yielded similar results (Table E4, available online at http://www.annemergmed.com). For the Cox-based model, we allowed a time-varying effect of ED crowding on antibiotic timing because of violation of the proportional hazards assumption (proportional hazards test P=.004 [Figure E4, available online at http://www.annemergmed.com]). This analysis suggested that the magnitude of the association between ED occupancy rate and door-to-antibiotic time decreased during the course of patients' ED stay (Table E4, available online at http://www.annemergmed.com).

The analysis of care process transitions preceding antibiotic initiation using Markov multistate models included 3,324 patients (Table E5, available online at http://www.annemergmed.com). For the 2,450 subjects who progressed sequentially through ED arrival, room placement, clinician assessment, diagnostic testing, and finally antibiotic initiation, increasing ED crowding was associated with slower transitions between all measured care

Table 2. Adjusted association of ED crowding with door-to-antibiotic time.

Measure of ED Crowding (Exposure Format)	Observed Range	Median (Interquartile Range)	Adjusted Change in Door-to-Antibiotic Time per Unit Increase in ED Crowding Measure (95% CI)s	Adjusted OR for Antibiotic Initiation Within 3 Hours of ED Arrival (95% CI)
Primary measure of ED crowding				
Model 1: ED occupancy rate (continuous, reported per 10% increase in ED occupancy rate)*	0 to 1.53	0.68 (0.44 to 0.89)	4.0 (2.8 to 5.2)	0.90 (0.88 to 0.93)
Secondary measures of ED crowding				
Model 2: ED occupancy rate, quartiles				
1	0 to 0.44	NA	1 [Reference]	1 [Reference]
2	0.45 to 0.68	NA	10.8 (2.9 to 18.6)	0.69 (0.56 to 0.86)
3	0.69 to 0.89	NA	16.9 (8.2 to 25.6)	0.64 (0.51 to 0.80)
4	0.90 to 1.53	NA	27.4 (18.2 to 36.7)	0.46 (0.36 to 0.59)
Model 3: ED overcrowding (binary, yes/no)	NA	NA	18.0 (9.1 to 26.8)	0.65 (0.53 to 0.81)
Model 4: patient-to-nurse ratio (continuous)*	0 to 5.8	2.25 (1.82 to 2.67)	15.1 (10.8 to 19.4)	0.70 (0.63 to 0.78)
Model 5: patient-to-physician ratio (continuous)*	0 to 16.7	6.67 (5.00 to 8.13)	4.5 (3.1 to 5.9)	0.90 (0.87 to 0.93)
Model 6: No. of patients arriving at ED within 30 min of subject patient (continuous)*	0 to 29	9 (4 to 14)	1.74 (0.96 to 2.52)	0.96 (0.94 to 0.98)
Model 7: No. of ED boarders (continuous)*	0 to 9	1 (0 to 2)	0.5 (−1.5 to 2.4)	0.95 (0.90 to 1.00)
Model 8: EDWIN score (continuous)*	0 to 2.5	0.46 (0.36 to 0.62)	34.3 (22.4 to 46.3)	0.39 (0.28 to 0.54)

EDWIN, Emergency Department Work Index score; *NA*, not applicable.

Each ED crowding metric was evaluated in a separate multivariable model adjusted for hospital, nighttime ED arrival, weekend ED arrival, arrival by ambulance, marital status, type of insurance, illness severity as measured by the MEDS score, triage acuity score, weighted Elixhauser comorbidity score, first systolic blood pressure after ED arrival, Hispanic ethnicity or nonwhite race, sex, and age.

*For crowding metrics analyzed as continuous variables, the change in door-to-antibiotic time is reported per the following unit change in the exposure measure: a 10% increase in ED occupancy rate (eg, 0.3 to 0.4), an increase in patient-to-nurse or patient-to-physician ratio by 1, an increase in ED arrivals or ED boarders by 1, and an increase in EDWIN score by 1.

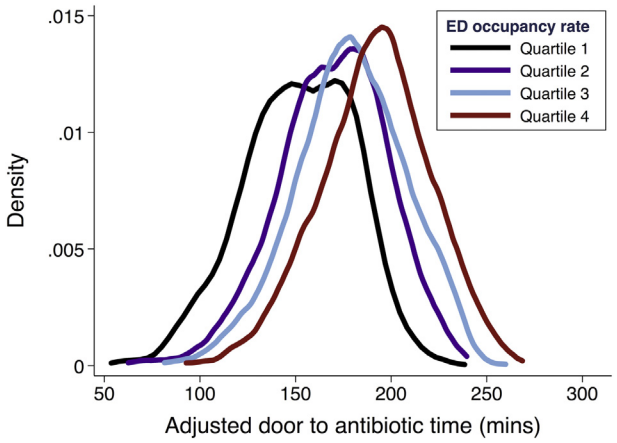

Figure 2. Adjusted door-to-antibiotic time by quartile of ED occupancy rate.

processes except for the final transition from diagnostic testing to antibiotic initiation (Figure 4*A* and Table E6 [available online at http://www.annemergmed.com]).

Among the 874 patients who underwent nurse-initiated diagnostic testing before clinician assessment, increasing ED crowding was associated only with delays in room placement and initial clinician assessment (Figure 4*B*). The adjusted likelihood that diagnostic testing preceded clinician assessment increased with ED crowding (OR 1.06 per 10% increase in ED occupancy rate; 95% CI 1.02 to 1.09). After adjustment for ED occupancy rate and other covariates, however, door-to-antibiotic time was not significantly different for patients who had nurse-initiated diagnostic testing before clinician assessment (–5 minutes; 95% CI –11 to 1).

No patient or clinical characteristic significantly modified the adjusted association between ED occupancy rate and door-to-antibiotic time (Figure 5). For all 3

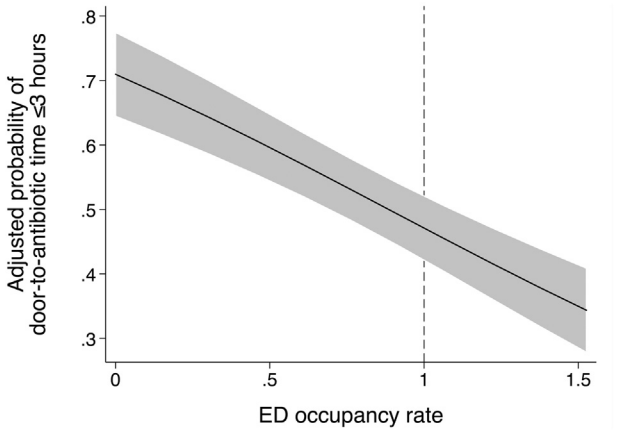

Figure 3. Adjusted association between ED occupancy rate and the probability (with 95% CI) of antibiotic initiation within 3 hours of ED arrival, with covariates fixed at their median values.

measures of illness severity—hypotension on ED arrival, MEDS score, and ED acuity score—there was a tendency toward larger increases in door-to-antibiotic time with higher ED occupancy rate when illness severity was lower, but these associations were not statistically significant.

LIMITATIONS

Although early antibiotic initiation appears to be an important predictor of risk-adjusted sepsis mortality in observational studies,[5-7,46] this finding has not been confirmed in studies free from indication bias.[47] It remains possible that the association of door-to-antibiotic time with mortality is nonlinear or even that prompt antibiotic initiation does not cause improved sepsis outcomes but is instead a marker of other beneficial sepsis care. Although some data link ED crowding and mortality for both general inpatient and critically ill populations,[48,49] our study was neither designed nor powered to investigate an association between ED crowding and sepsis mortality, so the effect of our findings on patient-centered outcomes is unclear.

Other limitations of this study include its observational design and the inability to exclude residual confounding despite adjustment for a wide range of plausible confounders and patient characteristics. As a result, our findings should be considered hypothesis generating. We were unable to examine all potentially useful crowding measures, including total patient care hours or the number of waiting room patients. We measured ED crowding on patient arrival and did not attempt to account for fluctuations in crowding during patients' subsequent ED course. Although it seems unlikely, it is possible that changes in crowding after ED arrival affect antibiotic timing.

We restricted our analysis to patients who exhibited clinical sepsis in the ED and who had inpatient discharge diagnoses consistent with sepsis. Even for these patients with confirmed sepsis who all ultimately received antibiotics before ED departure, increasing door-to-antibiotic time may not be harmful beginning at ED arrival. In addition, the association of ED crowding with antibiotic timing could differ for clinical sepsis patients, typically less severely ill,[27] who did not have a sepsis discharge diagnosis. We also did not evaluate whether ED crowding impeded ED sepsis recognition or influenced antibiotic timing for ED patients with incipient but not yet fully manifest sepsis. Additionally, although inclusion of EDs from both community and referral hospitals was a strength, our results from a single health care system may not generalize to other systems, ED types (eg, freestanding EDs), or EDs outside the United States.

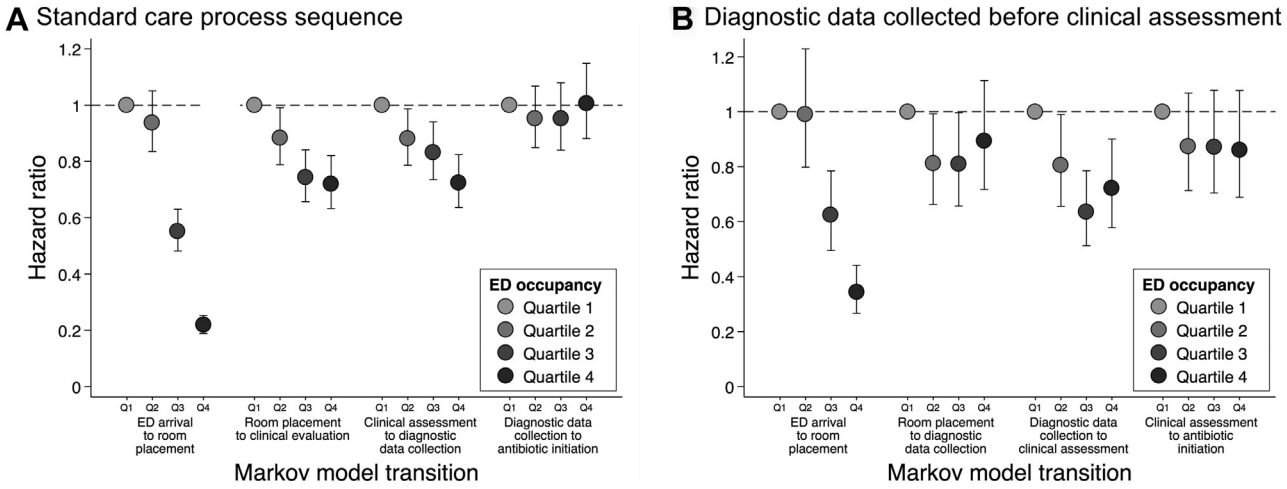

Figure 4. Adjusted association of ED occupancy rate with rate of transition through care processes preceding antibiotic initiation for (*A*) patients (N=2,450) progressing sequentially through ED arrival, room placement, clinical assessment (physician assignment), diagnostic data collection (laboratory sample collection), and antibiotic initiation, and (*B*) patients (N=874) who had nurse-initiated diagnostic testing before clinician assessment. For this Markov multistate model analysis, a hazard ratio less than 1 indicates a decreased likelihood of moving from the preceding care process ("state") to the subsequent care process at any given time. Alternatively, the hazard ratios are inversely proportional to the relative difference in average time required to complete the preceding care process ("sojourn time") across quartiles of ED occupancy rate.

Finally, creation of an interpretable multistate model using high-quality data required exclusion of some care processes plausibly associated with ED crowding, such as ED triage, delivery of diagnostic test results, and vascular access placement. Although missingness for the multistate model evaluation was only 6% and less than 1% of patients were excluded because of invalid data or rare care pathways, inclusion of only complete cases in this analysis could have biased the results. Our data set also did not include markers for some care processes of potential interest (eg, the time antibiotics were ordered).

Discussion

In this multicenter study including over 3,500 ED sepsis patients, we observed a consistent association between increased ED crowding and decreased antibiotic timeliness. When ED occupancy rate was in the highest quartile, the adjusted probability of starting antibiotics within 3 hours was more than 50% lower than when ED occupancy rate was at or below the 25th percentile. The association between ED crowding and antibiotic timing seemed to be strongest early in the ED visit. Analysis using multistate models suggested that crowding-associated antibiotic delays resulted from delays in initial patient assessment (patient triage, evaluation by a clinician, and diagnostic data collection) rather than delay occurring between initial assessment completion and antibiotic initiation.

Some studies suggest that ED crowding is associated with delays in time-critical care processes for myocardial infarction, stroke, and trauma.[15,16,50-52] Our study of patients with sepsis—another condition in which time to treatment likely influences outcomes—used multicenter data to build on 2 previously published single-center studies investigating ED crowding and sepsis care. Among 770 sepsis patients presenting to a Korean ED, each 10% increase in ED occupancy rate was associated with a 10% decrease (95% CI 4% to 16%) in the odds of full compliance with the institution's sepsis bundle, a difference driven by a 7% decrease (95% CI 2% to 12%) in the odds of antibiotic initiation within 3 hours.[53] More recently, Gaieski et al[18] studied 2,913 ED sepsis patients and found that increased ED occupancy was associated with a reduction in antibiotic initiation within 3 hours, although the observed difference was smaller than in our study (adjusted OR 0.77; 95% CI 0.61 to 0.96). ED crowding was also associated with antibiotic initiation delays in most but not all studies of antibiotic timing for community-acquired pneumonia.[17,54-57] Besides using more detailed antibiotic timing data and multiple metrics of ED crowding, novel aspects of our study include its exploration of potential modifiers of the association between crowding and treatment delays as well as use of Markov multistate models to investigate its potential mediators.

The ED is a unique clinical environment with multiple competing patient care demands. Acknowledging these realities, as well as the challenges of early sepsis recognition, targeted early resource reallocation for patients with

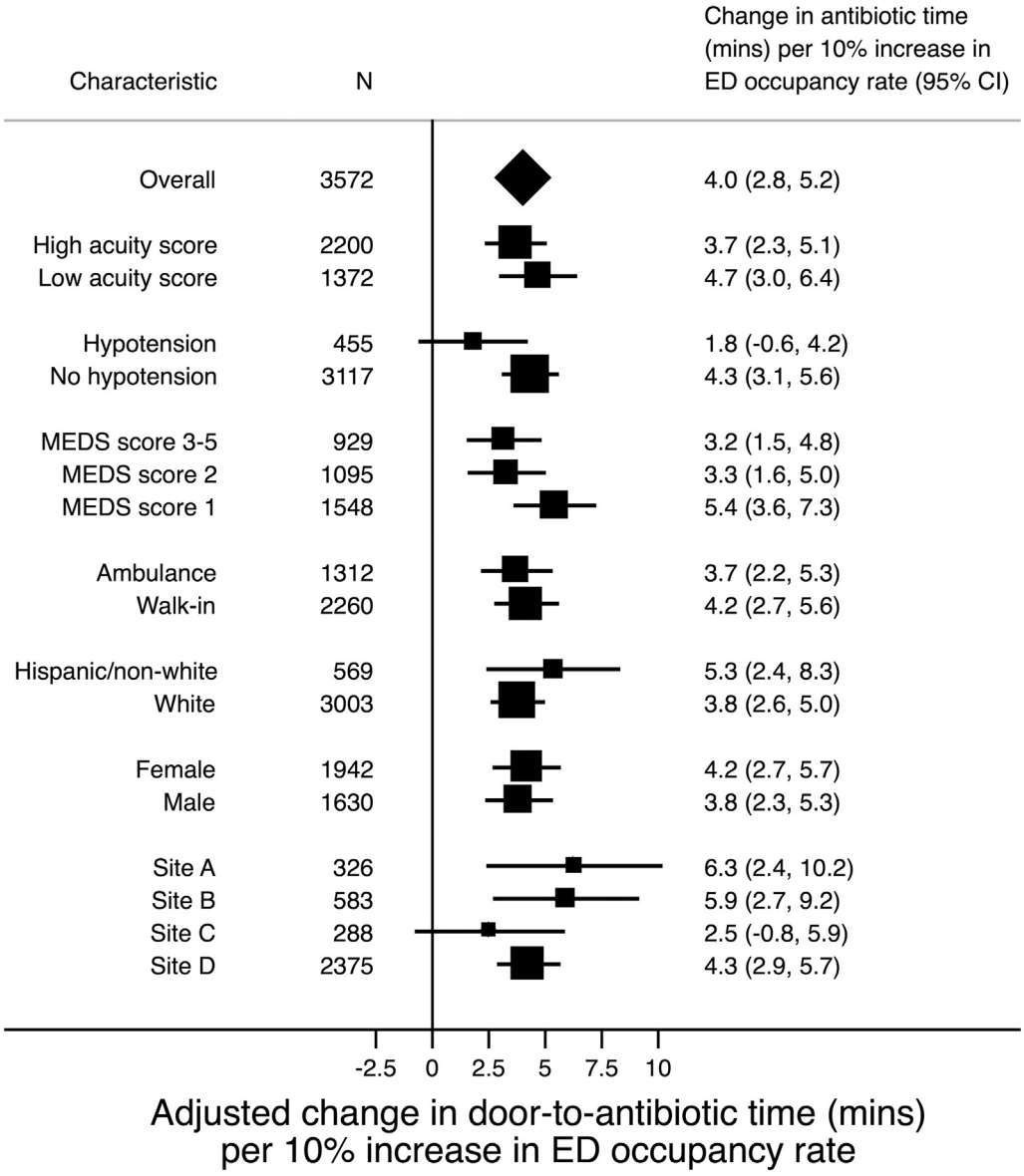

Figure 5. Association between a 10% increase in ED occupancy rate and door-to-antibiotic time, stratified by select patient characteristics.

suspected sepsis could mitigate the delays in initial patient assessment. The fact that nurse-driven diagnostic testing did not seem to shorten door-to-antibiotic time in our study suggests that more comprehensive care redesign may be necessary. Possible options include incorporating out-of-hospital providers in care and activating specialized multidisciplinary teams on or before patients' ED arrival, interventions that have proven effective in expediting evaluation and treatment initiation for other conditions such as stroke, myocardial infarction, and trauma.[58,59]

We did not find clear evidence that patients' demographic or clinical characteristics affected the association between ED crowding and door-to-antibiotic time. However, there was a trend toward a weaker association between antibiotic initiation and ED crowding in the presence of either hypotension on ED arrival or a higher illness severity score. Although this finding in particular should be considered hypothesis generating, this trend deserves investigation in future studies as it may suggest that patients without obviously severe illness are more vulnerable to delayed antibiotics when the ED is crowded.

In summary, ED crowding was associated with delays in door-to-antibiotic time for patients presenting with sepsis in this large, multicenter cohort. Our findings also help illuminate when and how crowding may influence antibiotic initiation: the observed association was strongest

early in septic patients' ED stay, consistent with the fact that crowding was associated with delays for initial ED assessment more than for pre-antibiotic care processes occurring after the initial assessment. Given the barriers to directly improving ED resource strain as a means to aid high-quality sepsis care, clinicians and ED leadership could consider methods to redirect resources to ensure timely evaluation for patients presenting with this emergent condition.

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