Original Article

Delays in subsequent antibiotic dosing for septic patients undergoing early interhospital transfer

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Background: Prior studies have demonstrated worse outcomes among septic patients who undergo interhospital transfer. Our objective was to identify the incidence of delay in subsequent antibiotic administration for patients transferred from regional emergency departments (EDs) to a tertiary intensive care unit (ICU).

Methods: This was a retrospective cohort study. Critically ill adult patients with sepsis, severe sepsis, and septic shock transferred from regional EDs to a tertiary care center from July 2014 to June 2019. Exclusion criteria included: (I) no pre-transfer antibiotics administered; (II) hospitalization >24 hours at the sending facility; (III) receipt of >1 dose of antibiotics prior to transfer; (IV) diagnosis of cerebrovascular accident, ST-elevation myocardial infarction; (V) expired or admitted to hospice within 24 hours. We defined delay as an actual interval between first and second doses >25% longer than the appropriate dosing interval calculated based on initial antibiotic selection and patient's renal function.

Results: One hundred and eighty-one patients were included, 28 (15.5%) had a delay in subsequent antibiotic administration. Baseline Sequential Organ Failure Assessment (SOFA) scores were similar in both groups (delay: 4.1 *vs.* no delay: 4.7; P=0.308; 95% CI: −0.559, 1.759). Overall mortality was similar in both groups (14.3% *vs.* 14.3%; P=1.000). Mean ICU (delay: 5.9 *vs.* no delay: 4.6; P=0.282; 95% CI: −1.078, 3.678) and hospital (delay: 12.5 *vs.* no delay: 11.5; P=0.646; 95% CI: −15.855, 17.855) lengths of stay were longer in the Delay group, though these differences did not reach statistical significance.

Conclusions: In this study, 15.5% of patients with sepsis transferred to a tertiary care center ICU had a delay in post-transfer antibiotic administration. This represents a potential target for interventions aimed at improving care of septic patients undergoing interhospital transfer. Further studies with improved statistical power are needed to demonstrate an impact of these delays on patient-centered outcomes.

Keywords: Sepsis; antibiotics; patient transfer

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Introduction

Despite improvements in recognition and management, sepsis morbidity and mortality remain high (1). Bundled resuscitation involving early antibiotic administration, adequate volume repletion, and serial monitoring of end organ perfusion is associated with improved outcomes in septic patients (2). In addition, recent data suggest that delays between the first and second dose of broad spectrum antibiotics are associated with worse hospital mortality (3).

Early transfer to a tertiary center has been associated with improved outcomes among patients with several different acute disease processes (trauma, stroke, myocardial infarction) (4-6). However, similar mortality improvement has not been reported among septic patients undergoing transfer. In fact, mortality and cost of care seem to significantly increase for septic patients that are transferred to tertiary medical centers (7). With a rising number of transferred septic patients, additional data is needed to better understand this impact of interhospital transfer.

For septic patients presenting to a regional emergency department (ED) who ultimately require transfer, a first dose of antibiotics is typically administered prior to transfer while the subsequent doses are due after transfer. The interhospital transition of care that occurs between these early doses of antibiotics is a plausible mechanism for delay, however the frequency of these delays has not been well-described. Our objective was to define the incidence of delayed subsequent antibiotic dosing in septic patients undergoing early interhospital transfer.

Methods

This was a retrospective observational study, reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-21-100/rc). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was authorized by the Cleveland Clinic Institutional Review Board (IRB number: 19-623). Due to the retrospective nature of this study, a waiver of consent was obtained from our IRB. Our study included patients managed within a single hospital system, comprised of 13 regional hospitals and a 1,400-bed main campus hospital.

We included a convenience sample of all adult patients transferred from regional EDs within our health system to the intensive care unit (ICU) of an academic referral center from June 2014 to June 2019 who had sepsis, severe sepsis, or septic shock present on admission. We did not include patients transferred from outside our hospital system given limited availability of transferring hospital documentation. We excluded patients who: (I) did not receive antibiotics prior to transfer; (II) were hospitalized >24 hours at the sending facility; (III) received >1 dose of antibiotics prior to transfer; (IV) had a diagnosis of cerebrovascular accident, intracranial hemorrhage, ST-elevation myocardial infarction; or (V) expired or were admitted to hospice within 24 hours of transfer.

Demographics, comorbidities, age, and outcome data were abstracted from an internal ICU database. Resuscitative variables, antimicrobial selection and dosing, and organ failure markers were abstracted by the research team from the electronic medical record. For organ failure scores collected from pre-transfer, missing variables (primarily bilirubin) were replaced with the first value documented after hospital transfer. We attempted to address bias by including patients transferred from 13 different community EDs in a shared hospital system. Anticipated antibiotic frequency was calculated based on the initial agent administered and the patient's renal function. Subsequent antibiotic dose was defined as the first antibiotic dose administered after transfer to the tertiary care center ICU. Subsequent antibiotic doses were considered delayed if the administered dose interval was 25% greater than the calculated dosing interval. This definition of delay has been utilized in similar studies (3). Patients on multi-drug regimens were considered to have delayed antibiotics if any of the continued antibiotics met our threshold for delay.

Baseline Sequential Organ Failure Assessment (SOFA) scores were calculated from the most abnormal clinical variables present at pre-transfer hospitals. For patients with missing data points, SOFA scores were calculated according to the methodology originally described by Vincent (8). For the respiratory SOFA, when arterial blood gases were unavailable, arterial oxygen saturation to the inspired fraction of oxygen (SaO_2/FiO_2) was used as described by Pandharipande (9). For all SOFA scores, the modified SOFA score excluding the GCS as a measure of neurological dysfunction was calculated (10). Patients were stratified into delay and no delay groups based on presence of significant delay in post-transfer antibiotics.

Statistical analysis

Continuous variables were compared with the Student's *t*-test,

Table 1 Demographic, prognostic, and process of care variables

Variables	No delay	Delay	P value
N (%)	153 (84.5)	28 (15.5)	
Age (years), mean (SD)	62 (16.0)	58 (18.4)	0.236
Race, n (%)			
White	122 (79.7)	20 (71.4)	0.328
Black	23 (15.0)	6 (21.4)	0.397
Other	5 (3.3)	2 (7.1)	0.340
Male, n (%)	82 (53.6)	18 (64.3)	0.297
Infectious source, n (%)			
Intra-abdominal	32 (20.9)	7 (25.0)	0.629
Pulmonary	34 (22.2)	6 (21.4)	0.925
Urinary	33 (24.8)	7 (21.4)	0.700
Pre-transfer IV fluids (mL/kg), mean (SD)	30.2 (18.2)	31.5 (24.1)	0.742
Baseline SOFA score, mean (SD)	4.7 (2.9)	4.1 (2.6)	0.308
APACHE III score, mean (SD)	80.0 (31.8)	70.9 (31.7)	0.165
Hospital LOS (hours), mean (SD)	5.6 (6.2)	6.5 (2.7)	0.452
Broad spectrum antibiotic, n (%)			
Piperacillin/tazobactam	100 (65.3)	20 (71.4)	0.531
Ceftriaxone	18 (11.8)	4 (14.3)	0.711
Meropenem	15 (9.8)	1 (3.6)	0.289
Aztreonam	7 (4.6)	2 (7.1)	0.577

IV, intravenous; mL, milliliter; kg, kilogram; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiological Assessment and Chronic Health Evaluation; LOS, length of stay.

while categorical variables were compared using Z-test.

Results

We identified 227 patients presenting to regional hospital EDs prior to transfer to a tertiary academic medical ICU with a diagnosis of sepsis, severe sepsis or septic shock. 30 patients were excluded because they did not receive antibiotics prior to transfer, 6 were excluded because they did not receive antibiotics after hospital transfer, 4 patients received more than one dose of antibiotics prior to transfer, and 6 were duplicates. Of the remaining 181 patients, 28 (15.5%) had a significant delay in their subsequent antibiotic doses (*Table 1*).

No data were missing for any of the patients in the final cohort. Patients were similar with respect to demographic variables and comorbidities. There was no difference with respect to baseline SOFA scores [delay: 4.1 (2.6) *vs.* no delay: 4.7 (2.9); P=0.293]. The most common sources of infection were the same in Delay and No Delay groups: pulmonary, intra-abdominal, and urinary. The most common initial broad spectrum antibiotic was piperacillin/tazobactam in both groups. Hospital mortality was similar in delay and no delay groups (14.3% *vs.* 14.3%) (*Table 2*). Differences in ICU mortality (delay: 14.3% *vs.* no delay: 11.1%), ICU length of stay (LOS) (delay: 5.9 *vs.* no delay: 4.6), and hospital LOS (delay: 12.5 *vs.* no delay: 11.5) did not show statistical significance.

Discussion

Among 181 critically ill patients with sepsis transferred

Table 2 Outcomes

Outcomes	No delay	Delay	P value
ICU LOS (days), mean (SD)	4.6 (5.8)	5.9 (6.2)	0.282
Hospital LOS (days), mean (SD)	11.5 (10.6)	12.5 (10.4)	0.646
ICU mortality, n (%)	17 (11.1)	4 (14.3)	0.628
Hospital mortality, n (%)	22 (14.3)	4 (14.3)	1.000

ICU, intensive care unit; LOS, length of stay.

acutely from regional EDs to a tertiary hospital, 28 (15.5%) experienced significant delays in administrations of post-transfer antibiotics. Given the added complexity of transfers between hospitals without a shared electronic medical record, our cohort may underestimate the incidence of post-transfer delays among patients transferred from outside of our hospital system.

In contrast to other disease states that benefit from time sensitive interventions, patients with sepsis are at higher risk for mortality when they undergo interhospital transfer. Our data suggest that delays in subsequent antibiotic doses occur frequently in this population and may contribute to this phenomenon. Accounting for the 30 patients excluded from our study who did not receive appropriate antibiotics prior to transfer, 58 total patients (25.5%) in our cohort experienced a significant irregularity in their early antibiotic administration.

Our study adds to the body of literature describing septic patients who undergo interhospital transfer. Our primary objective was to report the incidence of these delays and we did not power our study to detect differences in outcomes. These data emphasize the importance of additional studies on this unique patient population and how variability in their care impacts outcomes.

Conclusions

Among patients with sepsis who undergo transfer from regional EDs to a tertiary ICU, delays in subsequent antibiotic dosing are common. Our study did not show a difference in mortality between patients who experienced a delay and those that did not. Additional studies are needed to determine whether delays in this patient population are associated with clinically significant outcomes.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-21-100/rc

Data Sharing Statement: Available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-21-100/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-21-100/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was authorized by the Cleveland Clinic Institutional Review Board (IRB number: 19-623). Due to the retrospective nature of this study, a waiver of consent was obtained from our IRB.

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