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Original Contribution

Pharmacist impact on time to antibiotic administration in patients with sepsis in an ED☆,☆☆

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ABSTRACT

Purpose: The purpose was to determine if the physical presence of a clinical pharmacist in the emergency department (ED) would decrease antibiotic order to administration time in adult patients with sepsis, severe sepsis, or septic shock.
Methods: We conducted a retrospective review of adult patients presenting to the ED between January and December 2014 with a diagnosis of sepsis, severe sepsis, or septic shock who required intravenous antibiotics.
Results: A total of 186 patients (92 patients when an ED pharmacist was present and 94 when no ED pharmacist was present) were included in the analysis. Baseline characteristics were similar between groups. When a pharmacist was present, patients received antibiotics sooner (median 0.61 vs 0.88 hour, $P = .001$), Surviving Sepsis Campaign goals for antibiotic administration time were more likely to be met (88% vs 72%, $P = .0097$), and initial antibiotics were appropriate more often (97% vs 81%, $P = .0008$). No significant differences were noted in intensive care unit length of stay, hospital length of stay, ventilator days, or in-hospital mortality.
Conclusions: Physical presence of a clinical pharmacist in the ED decreased time to administration and increased appropriateness of intravenous antibiotics for adult patients with sepsis, severe sepsis, or septic shock.

1. Introduction

Sepsis, severe sepsis, and septic shock are major health care problems affecting 750 000 patients annually in the United States and have high morbidity, mortality, and health care resource utilization [1-4]. Early goal-directed therapy has been identified as an important method for managing patients with sepsis in the emergency department (ED) and is promoted by the Surviving Sepsis Campaign (SSC) [5,6]. Early and appropriate antimicrobial administration has been shown to decrease mortality and hospital length of stay (LOS) in patients with sepsis, and the SSC 2012 guidelines recommend that patients be administered broad-spectrum antibiotics within 1 hour of recognition of severe sepsis or septic shock and within 3 hours of sepsis recognition [6-12].

Clinical pharmacists in the ED can help manage patients with sepsis by promoting early and appropriate antimicrobial therapy [13-16]. Although several studies have identified services that clinical pharmacists in the ED can provide, there is a lack of research demonstrating if ED pharmacists can help meet antibiotic timing goals recommended by the SSC. We hypothesized that the presence of a clinical pharmacist in the ED would decrease antibiotic order to administration times in adult patients with sepsis, severe sepsis, or septic shock.

2. Methods

2.1. Study design

A retrospective analysis of consecutive patients diagnosed with sepsis, severe sepsis, or septic shock and treated at an academic medical center from January 1, 2014, through December 31, 2014, was conducted. Only patients ≥18 years of age who were admitted to an intensive care unit (ICU) from the ED and received intravenous (IV) antibiotic therapy in the ED were included. Sepsis diagnosis was based on the final progress note entered by the ED physician before the patient was transferred to the ICU. Definitions available to physicians were listed in SSC 2012 guidelines and included the following: *sepsis* is defined as the presence (probable or documented) of infection together with systemic manifestations of infection, *severe sepsis* is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion, and *septic shock* is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation [6]. Rates of patients who converted from sepsis to severe sepsis or severe sepsis to septic shock in the ICU were not recorded. Only patients admitted from the ED to ICU were selected

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because we hypothesized that this patient population was most likely to be affected by antibiotic timing. The primary outcome of this study was to determine if the physical presence of a clinical pharmacist in the ED was associated with decreased order to administration time for IV antibiotics in patients with sepsis compared with when a clinical pharmacist was not present. Secondary outcomes were to determine if achievement of SSC 2012 antibiotic timing goals, appropriateness of initial administered antibiotic, nursing medication requests, ICU LOS, hospital LOS, ventilator days, or in-hospital mortality were affected by having a clinical pharmacist in the ED.

Data collected from patients' medical records included age, sex, sepsis category, suspected source or sources of infection, admitting ICU, and clinical variables required for Acute Physiology and Chronic Health Evaluation (APACHE II) score (on a scale from 0 to 71, with higher scores indicating more severe organ dysfunction and increased risk of mortality) [17]. The difference between time of antibiotic order entry by an ED provider and time of administration by an ED registered nurse was used to measure the order to administration time. For patients who received more than one antibiotic during treatment in the ED, only the order to administration time for the first administered antibiotic was recorded. Antibiotic administration goals were based on SSC 2012 guideline recommendations (within 1 hour of recognition of severe sepsis or septic shock and within 3 hours for all other patients) [6]. Time of antibiotic order entry was considered the time of recognition of sepsis, severe sepsis, or septic shock. Appropriateness of antibiotics administered in the ED was based on recommendations enumerated in Table 1 of the "Clinical Approach to Initial Antimicrobial Therapy" in the *Sanford Guide to Antimicrobial Therapy 2014* (*44th Edition*) [18]. This table encompasses numerous guideline recommendations for antimicrobial selection based on anatomic site, diagnosis, modifying circumstances, and usual etiologies. For the purposes of this study, appropriateness only referred to selection of antibiotics consistent with recommendations listed in the *Sanford Guide*. If the initial antibiotic was inappropriate, the order to administration time of the first appropriate antibiotic was recorded and used to determine the time to appropriate antibiotics. If the ED physician could not identify a source of infection, appropriateness was based on the admitting ICU physician's suspected source or sources of infection and antibiotics administered in the ED. Final institutional review board approval, number 5140092, was obtained on January 6, 2015.

Table 1
Baseline demographics

	ED pharmacist (n = 92)	No ED pharmacist (n = 94)	*P* value
Years of age (median [IQR])	63.5 (48-74.8)	63 (48-84.7)	.925
Male (%)	52	59	.1858
Comorbidities, n (%)			
Cirrhosis	7 (8%)	8 (9%)	1
Heart failure	11 (12%)	13 (14%)	.8276
Chronic lung disease	12 (13%)	16 (17%)	.5398
Chronic dialysis	14 (15%)	12 (13%)	.6764
Immunocompromised	19 (21%)	31 (33%)	.0694
Sepsis type, n (%)			
Sepsis	25 (27%)	29 (31%)	.6297
Severe sepsis	29 (32%)	29 (31%)	1
Septic shock	38 (41%)	36 (38%)	.7647
Suspected source of infection, n (%)			
Lung	48 (52%)	52 (55%)	.7688
Abdominal	17 (18%)	19 (20%)	.8534
Urinary tract	35 (38%)	35 (37%)	1
Central nervous system	2 (2%)	2 (2%)	1
Skin/soft tissue	5 (5%)	9 (10%)	.4058
Blood/catheter related	8 (9%)	3 (3%)	.1309
Unknown	7 (8%)	6 (6%)	.7811
Admitting ICU, n (%)			
Medical	85 (93%)	91 (97%)	.2101
Surgical	1 (1%)	2 (2%)	1
Cardiac	2 (2%)	1 (1%)	.6189
Neurologic	4 (4%)	0 (0%)	.0579
APACHE II score[a] (median [IQR])	26 (19.25-34)	24 (19-30)	.141

[a] Scores on APACHE II range from 0 to 71, with higher scores indicating greater severity of illness.

2.2. Study setting and population

Loma Linda University Medical Center is a 797-bed university teaching hospital that is designated as a level I adult/pediatric trauma center and houses a 65-bed adult/pediatric ED with 76 000 patient visits per year. Physician and nursing coverage in the ED is consistent throughout the time of day and day of the week. Patient to nurse ratios are typically 2:1 or 3:1 depending on acuity, with nurses typically having fewer patients if their acuity is higher (ie, expected to be admitted to an ICU). ED clinical pharmacists are physically present in the ED from 9:00 AM to 7:30 PM, 7 days per week. A designated ED pharmacy technician is also physically present in the ED during the same days and times as the ED pharmacist. ED clinical pharmacist responsibilities include the following: medication order evaluation (including evaluation of dose, route, frequency, and appropriateness of therapy); providing consultative pharmacotherapy services; implementing and modifying evidence-based medication regimens; assisting during medical emergencies; developing institutional guidelines and protocols; providing drug monitoring services; facilitating medication preparation and delivery; performing medication reconciliation; and educating nurses, physicians, and other ED staff. All medication orders are entered by providers via computerized physician order entry (EpicCare Inpatient Clinical System, Verona, WI) and must be reviewed by the ED pharmacist when the ED pharmacist is present. Outside of the ED pharmacist's designated hours, medication orders are reviewed by pharmacists located in the central inpatient pharmacy. Nursing staff must wait for pharmacist evaluation and verification of medication orders prior to administration; however, during medical emergencies, this process may be overridden. Orders verified by the pharmacist are electronically time stamped and list the name of the pharmacist who verified the order. This allows recognition of orders that have been verified by the ED or central inpatient pharmacist. Many commonly used antibiotics are located in automated dispensing cabinets in the ED. Commonly and uncommonly used antibiotics can be prepared and delivered from the central inpatient pharmacy during any time of the day depending on pharmacist preference. Nurses have the option of using antibiotics in automated dispensing cabinets or can request antibiotics from the pharmacy. Antibiotics are usually administered by nurses but can be given by physicians or clinical pharmacists during emergencies.

2.3. Data analysis

A sample size of 196 patients was estimated to detect a 20% difference in order to administration time between groups (power 0.8, alpha .05). Continuous variables were reported as medians with interquartile ranges (IQRs). The Student *t* test was used when comparing normally distributed data, and the Mann-Whitney *U* test was used to analyze nonnormally distributed data. Categorical data were expressed as frequency distributions, and the χ^2 test or Fisher exact test for small samples was used to determine if differences existed between groups. All tests were 2-tailed, and a *P* value of less than .05 was determined to represent statistical significance. Statistical analysis was completed using SPSS 23.0 (IBM, Inc, Armonk, NY).

3. Results

From January 1, 2014, to December 31, 2014, 186 patients were identified as having sepsis, severe sepsis, or septic shock while in the ED and admitted to an ICU. Ninety-two patients received antibiotics while an ED pharmacist was present, and 94 patients received antibiotics when an ED pharmacist was not present. No significant differences

Table 2
Differences in timing and appropriateness of initial antibiotic administration when an ED pharmacist was physically present and not physically present in the ED

	ED pharmacist (n = 92)	No ED pharmacist (n = 94)	*P* value
Order to administration, h (median [IQR])	0.61 (0.37-0.95)	0.88 (0.525-1.23)	.001
Order to administration time within SSC goal,[a] n (%)			
Sepsis	25 (100%)	28 (97%)	1
Severe sepsis	26 (90%)	18 (62%)	.0295
Septic shock	30 (79%)	22 (61%)	.1279
Overall	81 (88%)	68 (72%)	.0097
Order to administration within 3 h, n (%)	92 (100%)	89 (95%)	.025
Initial antibiotic appropriate,[b] n (%)	89 (97%)	76 (81%)	.0008
Order to administration of first appropriate antibiotic, h (median [IQR])	0.64 (0.35-0.98)	1 (0.6-1.7)	<.0001

[a] Goals based on SSC 2012 (within 1 hour of recognition of severe sepsis or septic shock and within 3 hours for all other patients).
[b] Appropriateness based on recommendations enumerated in Table 1 of the "Clinical Approach to Initial Antimicrobial Therapy" in the *Sanford Guide to Antimicrobial Therapy 2014* (*44th Edition*).

in baseline characteristics were observed (Table 1). Lung and urinary tract were the most commonly suspected sources of infection. The most frequently used first antibiotic in both groups was piperacillin/tazobactam (54% when an ED pharmacist was present and 38% when not present). There was no significant difference in proportion of first doses that were available in ED automated dispensing cabinets when an ED pharmacist was present and not present (97% vs 97%; $P = 1$). Overall in-hospital mortality was 23%.

Presence of an ED pharmacist was found to significantly decrease median order to administration time of antibiotics (0.61 [IQR, 0.37-0.95] vs 0.88 [IQR, 0.525-1.23] hours; $P = .001$). Presence of an ED pharmacist also significantly increased the number of patients who received antibiotics within SSC 2012 goals (88% vs 72%; $P = .0097$), antibiotics within 3 hours (100% vs 95%; $P = .025$), and appropriate initial antibiotics (97% vs 81%; $P = .0008$) and decreased the time to appropriate antibiotics (0.64 [IQR, 0.35-0.98] vs 1 [IQR, 0.6-1.7] hours; $P < .0001$) (Table 2). Fewer requests for antibiotics from nursing staff were observed when an ED pharmacist was present (1 vs 17 requests; $P = .0001$). No significant differences were observed regarding days of mechanical ventilation, ICU LOS, hospital LOS, or in-hospital mortality (Table 3).

Patient medical records were further examined for the 5 patients who did not receive antibiotics within 3 hours of being ordered. Reasons for delayed administration were identified in 2 of those patients and included difficult IV access and nursing staff waiting for delivery of antibiotics from pharmacy staff. Reasons for delay could not be identified in physician, nursing, or pharmacy notes for the other 3 patients. All 5 of these patients received antibiotics when an ED pharmacist was not present in the ED.

4. Discussion

To our knowledge, this is the first study to assess if ED pharmacists can be used to prevent delays in initial antibiotic administration for adult patients diagnosed with sepsis, severe sepsis, or septic shock. We found that the physical presence of an ED pharmacist significantly reduced time to administration of antibiotics and significantly increased the amount of patients receiving appropriate antibiotics within timing goals recommended by the SSC 2012 guidelines. These findings are similar to those reported by Bailey et al [19] who found that pediatric patients admitted through the ED were more likely to receive appropriate doses of antimicrobials in a more timely fashion when an ED pharmacist was present in the ED. Previous studies have also found that ED pharmacists help patients with health care–associated pneumonia receive empiric antimicrobial therapy consistent with guideline recommendations and assist prescribers in the selection of and dosing of fluids, antimicrobials, and vasopressors for patients with sepsis [15,16]. Our study highlights that ED pharmacists can also be used to help providers select and administer antibiotics to septic patients as soon as possible, an intervention that has been shown to be critically important to survival and length of hospital stay [7-12]. Kumar et al [7] found that for patients with septic shock, each hour of delay in antimicrobial administration was associated with an average decrease in survival of 7.6%. Puskarich et al found that for patients with septic shock treated in the ED, those that received antibiotics after shock recognition had a significant increase in the mortality (odds ratio, 2.4; 95% confidence interval, 1.1-4.5) [9]. Zhang et al [12] found that for patients with severe sepsis or septic shock, each hour of delay in time to deliver appropriate antibiotic therapy increased hospital LOS by 0.134 days. Equally important is appropriateness of antibiotic selection. Kumar et al [11] found that inappropriate initial antimicrobial therapy administered to patients with septic shock was associated with a 5-fold reduction in survival. These studies illustrate why SSC guidelines emphasize the importance of minimizing delays when initiating appropriate antimicrobial treatment for patients with sepsis [6].

There are several explanations for why the ED pharmacists decreased time to appropriate antibiotic administration. Our ED pharmacists are aware of the importance of rapid administration of antimicrobials to patients with sepsis, which could have prompted them to quickly process, prepare, and deliver antimicrobials to this patient population. This could explain why nursing medication requests were significantly fewer in number when an ED pharmacist was present (1 vs 17 requests). In addition, our ED has designated ED pharmacy technicians who can assist with medication preparation and delivery. Furthermore, our ED pharmacists frequently educate our ED physicians and nurses on sepsis-related topics, including the importance of prompt identification and treatment, and are available to remind providers of these topics if needed. This education is provided electronically to all ED physician and nursing staff, but in-person education can only occur when the ED pharmacist is present in the ED. Because our ED pharmacists are physically present in the ED, they are able to instantly assist nurses with issues which may delay administration, such as IV compatibility. This could explain why antibiotics were administered faster when the ED pharmacist was present, despite there being no difference

Table 3
Differences in clinical outcomes when an ED pharmacist was physically present and not physically present in the ED during initial antibiotic administration

	ED pharmacist (n = 92)	No ED pharmacist (n = 94)	*P* value
Days of mechanical ventilation (median [IQR])	1.5 (0-6.8)	0 (0-5.3)	.267
ICU LOS, d (median [IQR])	4 (2-11)	3.5 (2-8)	.37
Hospital LOS, d (median [IQR])	10.5 (5-16.8)	8.5 (5-15)	.437
In-hospital mortality, n (%)	19 (21%)	23 (24%)	.534

in proportion of first doses located in ED automated dispensing cabinets (97% in both groups). After hours, pharmacists are available for physician or nursing consults via telephone but are not physically present in the ED. This could discourage physicians or nurses from seeking pharmacist recommendations on antibiotic selection. Alternatively, pharmacists not physically present in the ED could have difficulty contacting providers to discuss antibiotic changes necessary to prevent administration of inappropriate therapy. Both of these reasons could explain why administered antibiotics were more likely to be inappropriate when the ED pharmacist was not present. The services an ED pharmacist can provide have been outlined in the literature and illustrate the potential benefits of having this type of provider at an institution [13,14].

5. Limitations

This study has several limitations. First, we assumed that the time antibiotics were ordered would correlate closely with time of sepsis identification. Times of patient triage, collection of vital signs and laboratory tests, and time of ED provider diagnosis were not collected, and it is possible that sepsis identification was earlier than antibiotics were ordered. In a recent trial assessing early goal-directed therapy in septic shock, Peake et al [3] found that the median time between presentation to the ED and administration of the first dose of IV antimicrobial therapy was 70 minutes in the early goal-directed therapy group and 67 minutes in the usual care group. In our study, median order to administration times were 37 minutes (0.61 hour) when an ED pharmacist was present and 53 minutes (0.88 hour) when an ED pharmacist was not present, which are similar to the findings of Peake et al and suggest that time of antibiotic order entry correlates with sepsis identification and diagnosis. Second, we used ED physician diagnosis noted in the patient's medical record to identify if patients had sepsis, severe sepsis, or septic shock. We assumed that physicians were appropriately diagnosing based on definitions available to them at the time (SSC 2012 guidelines). The APACHE II scores observed in each group (26 when ED pharmacist present vs 24 when not present) suggest that patients may have been diagnosed with sepsis when they had severe sepsis or septic shock. Confusion over sepsis terminology and potential for misdiagnosis have been highlighted as important concerns for providers and were cited by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine as reasons for why they felt the need to update sepsis definitions in 2016 [20]. In our study, there were no significant differences between groups in regard to APACHE II scores or other demographic variables, and we do not believe that misdiagnoses would explain differences in timing or appropriateness. Third, we used recommendations listed in the *Sanford Guide to Antimicrobial Therapy 2014* (*44th Edition*) to assess for appropriateness of initial administered antibiotics. We did not collect results from blood or local site cultures to assess for appropriateness. However, several studies have questioned the usefulness of blood cultures collected in the ED, noting that they rarely yield growth not due to contaminants or provide results that influence patient management [21-24]. It is for these reasons that we felt it was reasonable to only use the *Sanford Guide*, which encompasses guidelines available for that edition, to assess appropriateness. Fourth, our study was likely underpowered to detect differences in clinical outcomes such as days of mechanical ventilation, LOS, and in-hospital mortality. This could explain why there were no significant differences in these outcomes despite patients receiving appropriate antibiotics faster when an ED pharmacist was present. It is also possible that a 0.3-hour, or 16-minute, decrease in median order to administration time was not clinically significant enough to impact clinical outcomes. Fifth, we did not assess if there were any cost differences between groups. Finally, our study was observational and susceptible to selection bias. To decrease this risk, we collected data on consecutive patients during the 1-year study period rather than collecting a convenience sample. Despite this method of data collection, the risk of selection or other types of bias can never be eliminated in observational studies.

6. Conclusions

We found that the physical presence of a clinical pharmacist in the ED significantly decreased antibiotic order to administration times for patients with sepsis, severe sepsis, or septic shock treated in the ED and helped patients receive appropriate antibiotics within SSC 2012 goals. Further study is needed to assess if the presence of an ED pharmacist can impact clinical outcomes such as mortality or hospital LOS.

Acknowledgments

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