

Dosing errors of empirical antibiotics in critically ill patients with severe sepsis or septic shock: A prospective observational study

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ABSTRACT

Background: Effective antibiotic therapy is crucial in sepsis management. Studies have emphasized on antibiotic administration timing more than dosing. We evaluated the frequency and risk factors of antibiotic dosing errors in sepsis.

Materials and Methods: This prospective observational study compared the doses of intravenous empirical antibiotics in the 1st day of sepsis diagnosis with those recommended by Micromedex, considering sepsis source and glomerular filtration rate estimated by the modification of diet in renal disease equation. The doses were classified as under-dosed, over-dosed, or appropriate. We excluded antibiotics which did not need a dose adjustment. The under-dosing rate was retrospectively evaluated according to the creatinine clearance estimated by the Cockcroft-Gault equation.

Results: Between October 1, 2013, and April 30, 2014, 189 patients were evaluated (age 61.6 ± 18.6 years, acute physiology and chronic health evaluation II score 22.8 ± 7.0 , 58.7% septic shock) with 415 antibiotic prescriptions (2.2 ± 0.9 prescriptions per patient). Antibiotic dosing was appropriate in 50.8% of patients; under-dosing in 30.7% and overdosing in 25.9%. Under-dosing prevalence was 39.4% when kidney function was assessed by the Cockcroft-Gault equation. Vancomycin was associated with the highest under-dosing rate (39.4%), followed by piperacillin/tazobactam (12.1%). The cohort mortality was 35.4%. Age, shock, chronic kidney disease, and cirrhosis independently predicted mortality on multivariable logistic regression analysis. Antibiotic dosing error was not associated with mortality: Over-versus appropriate dosing (odds ratio [OR], 1.41; 95% confidence interval [CI], 0.57–3.47), under-versus appropriate dosing (OR, 0.57; 95% CI, 0.24–1.35).

Conclusions: Antibiotic dosing errors were common in patients with sepsis. Vancomycin had the highest under-dosing rate. Antibiotic dosing errors were not associated with increased mortality.

Keywords: Antimicrobial, critical care, dose, medication error, sepsis

Introduction

Severe sepsis and septic shock are major causes of morbidity and mortality in the intensive care unit (ICU).^[1] Severe sepsis occurs in three out of every 1000 individuals in the United States, leading to 750,000 cases per year with a mortality of 28.6%.^[2] It is considered as the leading cause of death in non-cardiac ICUs and is responsible for 40% of all ICU expenses.^[1,3] A cornerstone of severe sepsis management is early and appropriate antimicrobial therapy, which has been shown to be among the most important factors to reduce mortality and costs of treating sepsis.^[4] An appropriate antimicrobial agent is commonly defined in clinical studies as the one to which the offending microorganism is susceptible.^[4,5]

There is less emphasis on the antimicrobial dose,^[5,6] which is important to achieve appropriate pharmacokinetics and pharmacodynamics,^[7] and to reach a therapeutic concentration in the blood and the site of the infection.^[8] During critical illness, the absorption and metabolism of antibiotics can be altered, and the volume of distribution and clearance can be highly variable making appropriate antibiotic dosing important and challenging in this population.

In 2006, the Institute of Medicine (Washington, DC) reported that medication errors are the most common medical mistakes which harmed at least 1.5 million people every year in the United States. It also found that 400,000 preventable drug-related injuries occurred each year in hospitals, 800,000

in long-term care settings, and roughly 530,000 among Medicare recipients in outpatient clinics.^[9] Medication errors may include errors in dosing of antibiotics,^[10] which can lead to worse outcomes in patients with sepsis.^[10] While there is ample evidence on the impact of timing and appropriateness of antibiotics on ICU mortality,^[4-6] there is less information on the epidemiology and impact of appropriate dosing on clinical outcomes of patients with severe sepsis or septic shock.^[11] Gentamicin and vancomycin dosing errors have been described in the critical care setting with potential harm.^[12] In a retrospective chart review of 1044 patients >80 years admitted to the University of California Davis Medical Center between January 1997 and December 1997 with a diagnosis of infection, all prescribed antibiotics were evaluated and dosing errors were found in 34% of prescribed antibiotics.^[13]

The aim of the study was to assess the frequency and the risk factors of antimicrobial dosing errors in adult critically ill patients with severe sepsis or septic shock and the association with outcomes.

Materials and Methods

Patients and setting

This was a prospective observational study of all consecutive patients who had sepsis and were admitted under the ICU service of King Abdulaziz Medical City, a 900-bed tertiary care center in Riyadh, Saudi Arabia. The inclusion criteria were: Age ≥ 18 years, the requirement for ICU care and the use of intravenous antibiotics. Exclusion criteria included the use of antibiotics with standard dosing that was usually not modified by kidney or liver dysfunction. Examples of such antibiotics included azithromycin, moxifloxacin, and linezolid. The study was performed in the following units: Emergency critical care unit (15 beds), the general ICU (21 beds), trauma ICU (8 beds), neurosciences critical care unit (8 beds), surgical ICU (9 beds), and the intermediate care unit (14 beds). The critical care units were covered by board-certified intensivists with onsite coverage 24 h/day, 7 days/week.^[14] Registrars and rotating residents from different specialties rotated in the units. Physicians ordered antibiotics through a computerized physician order entry system (Quadramed®). The system calculated an estimated glomerular filtration rate (eGFR) based on modification of diet in renal disease (MDRD) equation ($eGFR = 186 \times SCR^{-1.154} \times age^{-0.203} \times 1.210$ if black, $\times 0.742$ if female)^[15] for every basic metabolic panel. It also had an optional antibiotic order set with predetermined doses according to kidney function. Clinical pharmacists were also available to all the units and routinely participated in the clinical rounds in the general ICU and trauma ICU during the weekdays. During the study, a sepsis improvement project was active in the emergency critical care unit and consisted of an electronic sepsis alert for early identification of patients with severe sepsis or septic shock and early referral to the sepsis response team, which consisted of an ICU physician

and a nurse.^[16] The sepsis response team then implemented the Surviving Sepsis Campaign bundles for patients who had severe sepsis or septic shock.^[16,17] During the study period, prolonged antibiotic infusions were not used. The Institutional Review Board of King Abdullah International Medical Research Center approved the study.

Classification of dosing errors

One attending intensivist and a senior medical student compared the doses of antibiotics administered in the first 24 h of sepsis diagnosis against the recommended doses by Micromedex, a commonly used reference about drugs.^[18] Micromedex was available to physicians as a browser-based application in the electronic hospital health information system and could be accessed from any computer. It took into consideration kidney and liver functions as well as the site and severity of infection to determine the recommended dose. It was also used as a reference by the ICU clinical pharmacists. In this study, the eGFR present in the electronic health record of each enrolled patient was used to determine the recommended dose in the case of kidney dysfunction. We also assessed liver function using the Child-Pugh score. Dosing was classified as appropriate or inappropriate (under- or over-dosing), and both were considered as dosing errors. Retrospectively, we classified dosing errors according to the creatinine clearance (Cr Cl) estimated by the Cockcroft-Gault equation ($([140 - age] \times \text{weight in kg} \times 0.85 \text{ if female}) \div (72 \times \text{serum creatinine in mg/dL})$).^[19]

Collected data

The following data were collected on the study day: Demographic information, acute physiology and chronic health evaluation (APACHE) II score,^[20] presence of chronic health illnesses as defined by APACHE II system and diabetes mellitus, presence of severe sepsis versus septic shock, requirement for renal replacement therapy on the study day, serum creatinine, eGFR, and Child-Pugh score.

Statistical analysis

Analysis was done using SPSS statistical software. Quantitative variables were presented as means with standard deviation or medians with the 25th and 75th percentiles as appropriate. Qualitative variables were presented as frequencies and percentages. Chi-square test was used for comparing the qualitative variables, and student *t*-test was used to compare the quantitative variables. Linear regression analysis was performed to evaluate the relationship between eGFR and Cr Cl. The classification of dosing appropriateness was compared between eGFR and Cr Cl. Multivariate logistic regression analysis was done to assess the predictors of antimicrobial under-dosing. Independent variables entered in the model were baseline characteristics with $P < 0.1$ between patients with and without under-dosing. Multivariable logistic regression analysis was also done to assess the predictors of hospital mortality. The variables entered in the model were baseline characteristics with

$P < 0.1$ between survivors and nonsurvivors (age, APACHE II score, presence of septic shock, chronic kidney disease, and chronic liver disease) and the different types of antibiotic dosing errors. The results of these analyses were presented as odds ratio (OR) with 95% confidence interval (CI).

Results

Characteristics of patients

We evaluated 200 patients and 11 were excluded as they received antibiotics that did not require dose adjustment. The enrolled 189 patients were admitted in the six adult critical care

areas of the hospital with the vast majority being in the critical care area of the emergency department ($N = 120$, 63.5%) and the general ICU ($N = 48$, 25.3%). The characteristics of the patients are described in Table 1. The mean eGFR was 61 ± 51 ml/min with 14 patients having eGFR >130 ml/min/1.73 m² body surface area. Twenty patients were on renal replacement therapy on the study day. Five patients had clinically significant liver cirrhosis with median Child-Pugh score of 10 (25th and 75th percentiles, 7 and 12.5, respectively).

The 189 patients received 415 empirical antibiotic prescriptions in the 1st day of sepsis diagnosis (2.2 ± 0.9 prescriptions per patient). Most patients (60.4%) received

Table 1: Patient characteristics for all patients and according to the presence of antibiotic under-dosing

Characteristic	All patients $N=189$	Under-dosing $N=58$	No under-dosing $N=131$	<i>P</i> value
Age (years), mean \pm SD	61.6 \pm 18.6	64.2 \pm 17.3	60.1 \pm 19.6	0.51
Male gender, <i>N</i> (%)	104 (55.0)	34 (58.6)	70 (53.4)	0.51
Height (cm), mean \pm SD	159.2 \pm 12.5	159.6 \pm 10.5	159.8 \pm 10.8	0.90
Weight (kg), mean \pm SD	74.1 \pm 24.5	77.3 \pm 23.4	71.3 \pm 20.8	0.08
Body mass index (kg/m ²), mean \pm SD	28.8 \pm 8.8	30.2 \pm 9.1	28.2 \pm 8.6	0.14
APACHE II score, mean \pm SD	22.8 \pm 7.0	23.6 \pm 5.2	22.0 \pm 5.1	0.05
Location, <i>N</i> (%)				
Emergency department	120 (63.5)	37 (63.8)	83 (63.4)	0.95
Intensive care unit	69 (36.5)	21 (36.2)	48 (36.6)	
Type of admission, <i>N</i> (%)				
Medical	180 (95.2)	55 (94.8)	125 (95.4)	0.5
Surgical	7 (3.7)	3 (5.2)	4 (3.1)	
Trauma	2 (1.1)	0 (0)	2 (1.5)	
Comorbid conditions, <i>N</i> (%)				
Diabetes	87/178 (49.4)	24 (44.4)	63 (50.8)	0.44
Chronic cardiovascular disease	46/178 (25.8)	14 (25.0)	32 (26.2)	0.86
Chronic respiratory disease	36/178 (20.2)	9 (16.1)	27 (22.1)	0.35
Chronic renal disease	26/179 (14.5)	8 (14.3)	18 (14.6)	0.95
Chronic liver disease	27/179 (15.1)	5 (8.9)	22 (17.9)	0.12
Immunocompromised state	23/178 (12.9)	6 (10.7)	17 (13.9)	0.55
Obesity (body mass index >30 kg/m ²), <i>N</i> (%)	66 (35.7)	42 (33.1)	24 (41.4)	0.27
Septic shock, <i>N</i> (%)	111 (58.7)	40 (69.0)	71 (54.2)	0.06
Severe sepsis, <i>N</i> (%)	78 (41.3)	18 (31.0)	60 (45.8)	
White blood cells	14.3 \pm 11.9	17.1 \pm 17.1	13.2 \pm 8.1	0.18
Serum lactate (mmol/L), mean \pm SD	3.8 \pm 3.3	4.5 \pm 4.9	3.7 \pm 2.9	0.35
Serum creatinine (micromole/L)	175 \pm 131	184 \pm 133	174 \pm 144	0.66
Estimated GFR* (ml/min), mean \pm SD	61 \pm 51	54 \pm 53	64 \pm 50	0.24
GFR <20 , <i>N</i> (%)	50 (26.5)	16 (27.6)	34 (26.0)	
GFR 20–50, <i>N</i> (%)	46 (26.5)	20 (34.5)	26 (19.8)	0.06
GFR >50 , <i>N</i> (%)	93 (49.2)	22 (37.9)	71 (54.2)	
Estimated Cr Cl** (ml/min), mean \pm SD	59 \pm 44	53 \pm 53	62 \pm 46	0.24
Cr Cl <20 , <i>N</i> (%)	32 (16.5)	8 (13.8)	23 (17.7)	
Cr Cl 20–50, <i>N</i> (%)	69 (36.7)	27 (46.6)	42 (32.3)	0.17
Cr Cl >50 , <i>N</i> (%)	88 (46.8)	23 (39.7)	65 (50.0)	

*GFR was estimated using the modification of diet in renal disease equation. **Creatinine clearance estimated by the Cockcroft-Gault equation. APACHE: Acute physiology and chronic health evaluation, Cr Cl: Creatinine clearance, GFR: Glomerular filtration rate, SD: Standard deviation

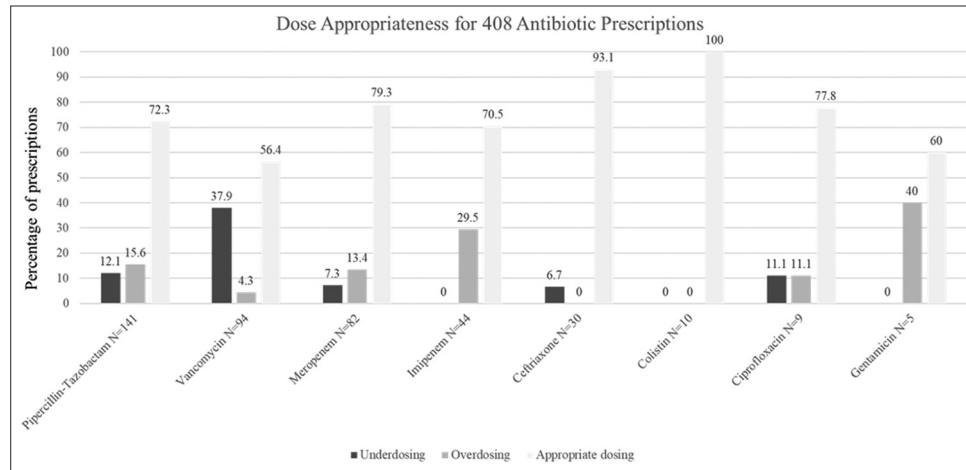


Figure 1: Appropriateness of the dose of different antibiotics administered in the first 24 h of diagnosing severe sepsis or septic shock

two or more antibiotics. The prescribed antibiotics were piperacillin/tazobactam ($N = 141$), vancomycin ($N = 94$), meropenem ($N = 82$), imipenem ($N = 44$), ceftriaxone ($N = 30$), colistin ($N = 10$), ciprofloxacin ($N = 10$), and gentamicin ($N = 5$). Antibiotic treatment was switched from piperacillin/tazobactam to a carbapenem or vice versa in 72 patients (38.1%).

Dosing errors

Antibiotic dosing was appropriate in 96 patients (50.8%). Under-dosing alone occurred in 44 patients (23.3%) and overdosing alone in 35 patients (18.5%). The combination of over-dosing and under-dosing occurred in 14 patients (7.4%). As most patients received more than one antibiotic, only five patients (2.6%) had all prescribed antibiotics under-dosed.

Figure 1 describes the rates of under-dosing and over-dosing for the 415 prescribed antibiotics. Under-dosing was found in 63 prescriptions (15.2%). Vancomycin was associated with the highest rate of under-dosing (39.4%), followed by piperacillin/tazobactam (12.1%). Under-dosed vancomycin prescription occurred in 63.8% of the under-dosed patients. There were also 35 antibiotic prescriptions (8.4%) with error in frequency. Piperacillin/tazobactam had the highest rate of frequency error (12.1%) followed by imipenem (11.3%) and meropenem (7.3%).

Table 1 describes the characteristics of patients who received at least one under-dosed antibiotic ($N = 58$) compared with the rest of the patients. Under-dosed patients tended to have higher weight and had higher APACHE II score and a higher prevalence of septic shock. There was no significant difference in the eGFR between under-dosed and appropriately dosed patients. However, more under-dosed patients were with eGFR < 50 ml/min compared with appropriately dosed patients (62.1% vs. 45.8%, $P = 0.04$).

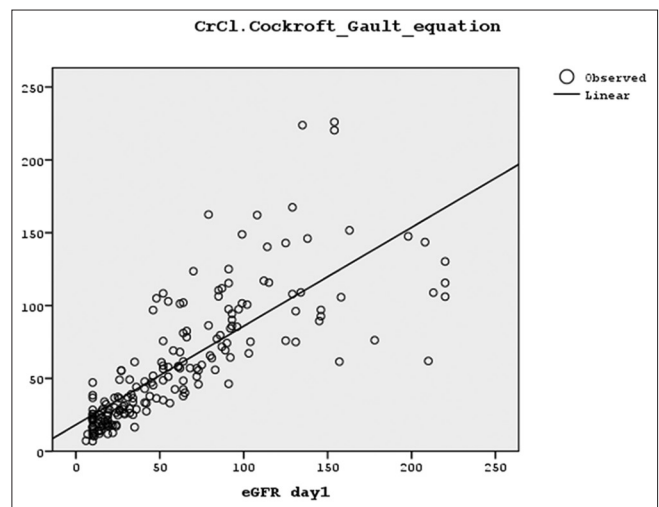


Figure 2: The correlation between the estimated glomerular filtration rate based on the modification of diet in renal disease equation and the creatinine clearance based on the Cockcroft-Gault equation in patients with severe sepsis or septic shock

Antibiotic dosing classification according to Cr Cl estimated by the Cockcroft-Gault equation

In this study, GFR estimated by the MDRD equation correlated well with Cr Cl estimated with the Cockcroft-Gault equation with $R^2 = 0.62$ [Figure 2].

Table 2 compares under-dosing classification according to GFR estimated by the MDRD equation and Cr Cl estimated by Cockcroft-Gault equation. When the Cr Cl estimated with Cockcroft-Gault equation was used to classify dosing appropriateness, under-dosing prevalence was 39.4% with a presumed false positive rate of 14.6% and false negative rate of 5.2%.

Predictors of under-dosing

On multivariable logistic regression analysis, vancomycin was independently associated with under-dosing (OR, 5.01; 95%

Table 2: Comparing antibiotic under-dosing rates according to Cr Cl by Cockcroft-Gault equation and eGFR by the MDRD equation

Under-dosing according to the Cr Cl estimated by the Cockcroft-Gault equation*, N	Under-dosing according to the GFR estimated by the MDRD equation, N		
	Yes	No	Total
Yes	55	19	74
No	3	111	114
Total	58	130	188

*Cr Cl could not be calculated for one patient because of missing weight. eGFR: Estimated glomerular filtration rate, Cr Cl: Creatinine clearance, GFR: Glomerular filtration rate, MDRD: Modification of diet in renal disease

CI, 2.45–10.21). The other variables in the model (weight: OR per kg increment, 1.01; 95% CI, 0.99–1.02; APACHE II score: OR, 1.03; 95% CI, 0.96–1.10; septic shock vs. severe sepsis: OR, 1.33; 95% CI, 0.64–2.80; eGFR <50 vs. ≥50 ml/min: OR, 1.56; 95% CI, 0.74–3.33) were not associated with under-dosing.

Among the patients who received vancomycin, the under-dosed patients had higher weight (80.2 ± 21.4 vs. 69.2 ± 24.8 kg, $P = 0.03$) and APACHE II score (24.1 ± 5.4 vs. 21.9 ± 4.0 , $P = 0.02$). There was no significant difference in the age, body mass index, and eGFR between the under and appropriately dosed patients. However, obesity was more prevalent in the under-dosed patients (47.7% vs. 26.5%, $P = 0.03$).

Outcomes

The hospital mortality of the cohort was 35.4%. The mortality rate was 38.5% in patients who had no dosing error, 27.3% in the patients who had under-dosing, 40% for those with overdosing and 28.6% for those with both over- and under-dosing ($P = 0.51$). Similarly, there was no significant difference in ICU mortality between the groups (24.0%, 18.2%, 34.3%, and 21.4%, respectively; $P = 0.41$). The five patients in whom all given antibiotics were under-dosed had a hospital mortality rate of 40%.

On multivariable logistic regression analysis, age (OR per year increment, 1.03; 95% CI, 1.00–1.05), chronic kidney disease (OR, 2.60; 95% CI, 1.01–6.71), chronic liver disease (OR, 2.59; 95% CI, 1.02–6.55), and septic shock versus severe sepsis (OR, 2.20, 95% CI, 1.04–4.63) were independent predictors of hospital mortality. Antibiotic dosing error was not associated with mortality: Over-versus appropriate dosing (OR, 1.41; 95% CI, 0.57–3.47), under-versus appropriate dosing (OR, 0.57; 95% CI, 0.24–1.35), over- and under-versus appropriate dosing (OR, 0.52; 95% CI, 0.14–1.97).

Discussion

The main findings of this study are the following: Antibiotic dosing errors were common in patients with severe sepsis or septic shock; vancomycin was associated with the highest rate of antibiotic under-dosing and dosing errors were not independently associated with hospital mortality.

The optimal antibiotic dosing in the ICU remains a controversial issue that most clinicians face daily. Although the first antibiotic doses are probably the most important ones in the management of critically ill patients due to sepsis,^[21] it is believed that these dosages are frequently inappropriate. A prospective pharmacokinetic study that evaluated 343 critically ill patients receiving eight different β -lactam antibiotics found that antibiotic concentrations remained below the minimal inhibitory concentration during 50% and 100% of the dosing interval in 19.2% and 41.4% of patients, respectively.^[22] Furthermore, a retrospective study at an emergency department evaluated the first antibiotic doses for patients with weight >100 kg and body mass index >40 kg/m² and found that the adherence of the first dose of cefepime, cefazolin, and ciprofloxacin to the hospital guidelines was 8.0%, 3.0%, and 1.2%, respectively.^[23] In our study, inappropriate dosing of antibiotics for patients with severe sepsis or septic shocks was common (50.8%) and under-dosing was more frequent than over-dosing (30.7% vs. 25.9%).

In our study, vancomycin was frequently under-dosed. The recommended vancomycin dosing regimen is a loading dose of 25–30 mg/kg for seriously ill patients and a maintenance dose of 15–20 mg/kg every 8–12 h with a target trough level of 15–20 mg/L.^[24] Multiple studies showed that vancomycin dosing is frequently inadequate. A retrospective study of vancomycin administered in the emergency department of an academic, tertiary-care center found that the dose was correct in only 22.1%, under-dosed in 70.7%, and overdosed in 7.2%.^[25] Increased weight was associated with vancomycin under-dosing.^[25] Potential explanations include that physicians lack knowledge of dosing guidelines or do not adhere to them for various reasons that may include the fear of adverse events.^[26,27] We observed that the vancomycin dose was fixed at 1 g in most cases, suggesting that such dosing was a habitual phenomenon and might be related to the prescribing culture among physicians.^[28,29]

Most guidelines adjust antibiotic dosing based on renal function. However, the optimal measurement of kidney function in critically ill patients is still uncertain.^[30] Renal clearance is frequently augmented in these patients.^[30] Analysis of a pooled dataset ($N = 5504$ participants) found that the MDRD equation had 78% concordance with measured GFR by ¹²⁵I-iothalamate urinary clearance compared with 73% concordance for the Cockcroft-Gault equation.^[19] Another

study in critically ill patients with normal serum creatinine found that the MDRD equation correlated with the measured Cr Cl better than the Cockcroft-Gault equation although both equations were not specific enough for assessment of kidney function.^[31] We found that the prevalence of dosing errors was higher when using the Cockcroft-Gault equation rather than the MDRD equation for dosing classification. Moreover, only 14 patients in the cohort had augmented renal clearance (eGFR >130 ml/min/1.73 m² body surface area), making it difficult to perform meaningful analysis in this group.

Antibiotic under-dosing may result in inadequate tissue penetration leading to sub-therapeutic drug concentrations, potentially contributing to decreased bacterial killing, therapeutic failure, and emergence of resistance.^[8] Multiple studies showed that adequate antibiotic therapy was associated with lower mortality in sepsis.^[4-6,32] However, it is not clear if the antibiotic dose was assessed as part of the adequacy definition and assessment.^[5,6] In the current study, dosing errors were not associated with increased mortality. Actually, the mortality of the group of patients who had over-dosing was the highest. There are many possible explanations for these findings. One of the explanations is that while one antibiotic was under-dosed, another appropriately dosed antibiotic with similar antibacterial coverage was provided on the same day. Of note, physicians frequently bypassed established order sets and protocols and entered orders manually. Besides, the clinical significance of empiric vancomycin, the most commonly under-dosed antibiotic in the current study, is questionable in sepsis management. One multicenter retrospective cohort study found that adding empiric vancomycin to other antibiotics in noncritically ill septic patients was not associated with lower mortality.^[33] In a *post hoc* analysis of the study to optimize peritoneal infection therapy trial, empirical addition of vancomycin to piperacillin/tazobactam or a carbapenem in patients with complicated intra-abdominal infections was associated with no difference in undesired outcomes.^[34] Another explanation is the indication bias, where higher doses were prescribed to patients more likely to die, thus explaining the higher mortality in the over-dosed patients. Whether the toxic effects of over-dosed antibiotics contributed to mortality is unclear. Other factors, such as timing of antibiotics, adequacy of resuscitation, and presence of organ dysfunction, which are important determinants of sepsis outcomes, were not evaluated in this study.

Multiple interventions have been suggested to optimize antibiotic dosing. Having a clinical pharmacist as a member of the ICU team can reduce prescribing errors and adverse drug events,^[35-37] but may not be associated with decreased mortality or length of stay.^[36] Standardizing medication orders in the ICU may decrease dosing errors.^[38] Computerized physician order entry has been associated with less medication errors and improvement in nephrotoxic drug dose and frequency.^[39] However, dosing errors were common in our study despite computerized physician order entry. However, in our current

system, physicians frequently bypassed established order sets and protocols and entered orders manually. Dosing software to individualize antibiotic dosing of the critically ill patient may improve antibiotic prescription.^[11] Nevertheless, the pharmacokinetic variability associated with critical illness means that some patients may still receive suboptimal doses. Thus, the only way to safely ensure that all patients achieve a therapeutic antibiotic concentration is through therapeutic drug monitoring.^[40]

This study has limitations. We did not have data about the details of sepsis management. However, sepsis management was standardized during the study period in the emergency department.^[16] A possible criticism of this study is that the decision on the inappropriateness of the doses was based on Micromedex. Clinical factors that were unavailable to us may have led to an antibiotic dose different from what is recommended by Micromedex. However, antibiotic dosing in Micromedex takes into consideration the infection focus and illness severity.^[18] In addition, we only looked at data of the first ICU day and did not have pharmacodynamics data. We also did not have the allergy history of patients. Furthermore, many patients received different beta-lactams in the same day, making the ability to analyze the association between specific antibiotics and outcomes difficult. In addition, the sample size was probably not powered to detect differences in mortality.

Conclusions

Errors in dosing empiric antibiotics in the early management of sepsis were common in the current study. Vancomycin was the most commonly under-dosed antibiotic. The reasons for dosing errors may include physicians overestimating the degree of kidney dysfunction, not routinely checking the patient's eGFR or body weight, being unfamiliar with the dosing guidelines or the antibiotic pharmacokinetic/pharmacodynamic properties and fearing toxicity. We did not find an association between antibiotic under-dosing and mortality, but the study was limited in its design and sample size. Appropriate antibiotic dosing should be considered an integral part of antibiotic adequacy in sepsis management, and physicians should pay attention to the antibiotic selection, timing of administration as well as dosing. Education, order sets, and proper computer decision support may help in choosing the optimal antibiotic dose. Further research is warranted to understand the antibiotic prescribing behaviors and practices of physicians, which may help to optimize sepsis management.

Authors' Contributions

HD made substantial contributions to conception and design, acquisition, analysis, and interpretation of data; drafted the manuscript and revised it critically for important intellectual content. AE made substantial contributions to acquisition and interpretation of data and revised the manuscript for important intellectual content. RK made substantial contributions to the

interpretation of data and contributed to manuscript drafting and revised it critically for important intellectual content. SH made substantial contributions to the study design and interpretation of data and contributed to manuscript drafting and revised it critically for important intellectual content. TD made substantial contributions to the interpretation of data and contributed to manuscript drafting and revised it critically for important intellectual content. YA made substantial contributions to the interpretation of data and contributed to manuscript drafting and revised it critically for important intellectual content. All authors read and approved the final manuscript.

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Conflicts of Interest

All authors report no conflicts of interest.

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