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The Relationship Between First-Dose Antibiotic Delay Intervals and In-Hospital Mortality in Patients with Sepsis

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ABSTRACT

Background: Early antimicrobial therapy is the cornerstone for the treatment of sepsis, although the time targets of antibiotic delivery are unknown.

Objectives: In this study, we quantified the time interval of first antibiotic administration in sepsis patients to investigate the association between the first-dose antibiotic delay intervals and in-hospital mortality in sepsis patients.

Methods: Patients with sepsis were collected retrospectively from January 2020 to December 2022, and we divided the first-dose antibiotic use time into two intervals: emergency department (ED) triage to antibiotic order (diagnosis delay) and antibiotic order to antibiotic infusion (administration delay). We used logistic analysis to evaluate the associations between prognosis and these intervals in the patients.

Results: The median time for diagnosis delay was 3.38 h, and for administration delay, it was 0.23 h. Both delay intervals were associated with in-hospital mortality after adjusting for confounding factors, but there was no significant difference in diagnostic delay for less than 6 hours or administration delay for less than 3 hours when compared with the no-delay reference group.

Conclusion: Both delay times for first-dose antibiotics are associated with increased in-hospital mortality, but only for longer delays. Our results do not support the use of antibiotics in sepsis patients within 1 hour when they are diagnosed.

INTRODUCTION

Sepsis, a severe, potentially fatal, organic dysfunction, is caused by an inadequate or dysregulated host response to infection, which is an important public health concern, accounting for more than $20 billion (5.2%) of the total US hospital costs in 2011. Singer et al. (2016) The manifestations are various, such as fever, chills, palpitations, shortness of breath, mental symptoms and even septic shock Singer et al. (2016) Angus et al. (2001) Linde-Zwirble et al. (2004). According to some surveys, more than 5.3 million people die from sepsis each year, and the overall mortality rate is approximately 30% Song et al. (2019). Early application of antibiotics plays a crucial role in the treatment of sepsis.

Thus, to manage sepsis, the Surviving Sepsis Campaign (SSC) International Guidelines provided guidance on the care of hospitalized adult septic patients in 2008, 2012, and 2017. These guidelines were based largely upon retrospective studies and expert consensus, recommending initiating broad-spectrum antibiotic coverage within the first hour and as soon as possible Hicks et al. (2008) Dellinger et al. (2013) Briegel et al. (2019). Until now, the latest 2021 guidelines again have recommended delivering antimicrobials as soon as possible, ideally within 1 hour of sepsis recognition Evans et al. (2021) Rehn et al. (2022). And it now stratify antimicrobial timing recommendations based on the likelihood of sepsis and presence of shock. However, this idea has been controversial. For example, according to a 2006 study of 2,731 adults with sepsis, each 1 h delay in antibiotic use resulted in a 7.6% increase in mortality. But Taylor et al. (2021). found that their study did not support antibacterial use targets less than 1 h. Puskarich et al. (2011). pointed out that delayed antibiotic use did not lead to an increase in mortality in septic patients within 6 h after ED. In addition, it is not clear whether the time interval from ED to antibiotic infusion is the best time interval to measure. Delays in the time from antibiotic order to antibiotic infusion are common and associated with increased mortality, but that the time from ED to antibiotic order accounts for a larger portion of total antibiotic infusion time. Therefore, our study quantified the time interval of first antibiotic use

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to investigate its effect on in-hospital mortality in septic patients.

METHODS

Study design

This study was a retrospective study of sepsis patients who visited the ED of our hospital from 2020.01 to 2022.12. We collected the total time from ED to the first-dose antibiotic infusion and divided it into two intervals. We defined this first-time interval as the diagnostic delay time (T1), which was from the time the patient visited the ED to the time the antibiotic order was issued. The time between antibiotic order and antibiotic infusion was defined as the second time interval, named delay in administration (T2). At the same time, the associated clinical infections, age, gender, white blood cells, platelets, creatinine, lactic acid, CRP, and PCT were collected. The primary outcome was the in-hospital fatality rate. Finally, statistical analysis was used to analyze the relationship between these time intervals and the in-hospital fatality rate. The above information was obtained from the hospital's electronic information system.

Patient selection

According to the criteria SEPSIS-3, we chose two diagnostic criteria for sepsis: diagnosis of infection; diagnosis of organ dysfunction, which was assessed by a Sequential Organ Failure Assessment (SOFA score) with an increase of ≥2. Song et al. (2019). defined as one or more SOFA criteria present within 12 hours. We aimed to clarify eligibility and ensure consistency in eligibility, and duration of follow-up of enrolled patients. We defined infected patients as those who were prescribed antibiotics within 12 hours of emergency triage and ordered them to be used for blood or urine cultures and increased CRP, PCT, and blood cells Wagenlehner et al. (2022) Lykins et al. (2021). The exclusion criteria were as follows: Patients who did not meet the diagnosis of sepsis; Patients diagnosed with septic shock; patients who had incomplete clinical and diagnostic data within 12 hours; patients younger than 18 years of age; and patients or their legal representatives who did not consent to participate or presented with endotracheal intubation, cardiac arrest at arrival. A total of 1039 patients were retrospectively selected, and 452 patients were finally selected. All data included in this study were obtained with the informed consent of patients.

Statistical analysis

Statistical analysis was performed using SPSS 26.0. Descriptive statistics were used to describe the basic data and prognosis at each time point. Continuous variables that met the normal distribution are represented by the mean, those that did not meet the normal distribution are represented by the median (interquartile distance, IQR), and categorical variables are represented by (e.g., %). Model1 : In-hospital mortality was taken as the dependent variable, the time interval from ED to antibiotic order (< 1h, 1-3h, 3-6h, > 6h) was taken as the independent variable, and < 1h was taken as the reference. Clinical infections, age, gender, white blood cells, platelets, creatinine, lactic acid, CRP, PCT were taken as confounding factors.

The effect of independent variables on in-hospital mortality was analyzed by Logistic regression. Model2: In-hospital mortality was taken as the dependent variable, the time interval from antibiotic order to antibiotic infusion (< 0.5h, 0.5-1h, 1-2h, 2-3h, > 3h) was the independent variable, and < 0.5h was taken as the reference.

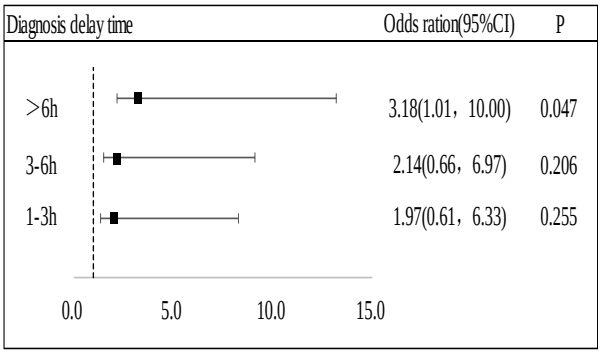
Clinical infections, age, gender, white blood cells, platelets, creatinine, lactic acid were used as confounding factors. The effect of independent variables on in-hospital mortality was analyzed by Logistic regression. Statistical significance was defined as $p < 0.05$.

RESULTS

As demonstrated in Table 1, the study included 452 patients with sepsis. The median total time was 3.85 h. The median time for T1 is 3.38 h and 0.23 h for T2

Figure 1 shows a significant correlation between inpatient mortality and diagnosis delay time (P<0.05). After controlling for confounding factors (clinical infections, age, sex, white blood cells, platelets, creatinine, lactic acid, CRP, PCT), pairwise comparisons showed that there were no significant effects at 1-3 hours and 3-6 hours (P=0.255 h and P=0.206 h). However, compared with < 1 hour, the in-hospital mortality was significantly increased at > 6 hours (P=0.047 h).

Figure 1: Effect of diagnosis delay time (T1) on in-hospital mortality.



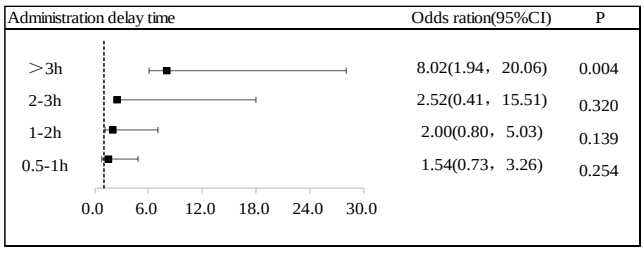
The results in Figure 2 displays that the delay time of administration was significantly correlated with in-hospital mortality (P < 0.05). After controlling for confounding factors (clinical infections, age, sex, white blood cells, platelets, creatinine, lactic acid, CRP, PCT),

Table 1: The basic patient information is shown.

Variables	Values
Sex (n, %)	
Male	257(56.86%)
Female	195(43.14%)
Age (year), median (IOR)	69.00(56.00, 77.00)
Diagnostic delay time (T1), hour, median (IOR)	3.38(1.57, 7.32)
<1 hour, n (%)	53(11.73%)
1-3 hour, n(%)	149(32.96%)
3-6 hour, n(%)	111(24.56%)
>6 hour, n(%)	139(30.75%)
Administration delay time (T2), hour, median (IOR)	0.23(0.10, 0.52)
0-0.5 hour, n(%)	338(74.78%)
0.5-1 hour, n(%)	64(14.16%)
1-2 hour, n(%)	33(7.30%)
2-3 hour, n(%)	6(1.33%)
>3 hour, n(%)	11(2.43%)
Total treatment time (T3), hour, median (IOR)	3.85(2.00, 7.94)
<1 hour, n(%)	30(6.64%)
1-3 hour, n(%)	153(33.85%)
3-6 hour, n(%)	124(27.43%)
>6 hour, n(%)	145(32.08%)
Chest infection	205(45.35%)
Abdominal infection	107(23.67%)
Genitourinary infection	109(24.12%)
Joint, skin and soft tissue infection	18(3.98%)
Blood and other infection	13(2.88%)
Platelet, median (IOR)	110.00(66.00, 186.00)
Lactic acid, median (IOR)	3.05(1.89, 5.42)
Creatinine, median (IOR)	134.00(81.00, 229.00)
Blood cells, median (IOR)	10.41(6.09, 16.91)
CRP, median (IOR)	118.54(41.06, 216.64)
PCT, median (IOR)	12.29(1.99, 50.97)

paired comparison showed that the administration delay time had no significant effect on in-hospital mortality, including 0.5-1 hour, 1-2 hours and 2-3 hours (P=0.254 h, P=0.139 h and P=0.320h). However, the in-hospital mortality was significantly higher with an administration time of > 3 hours compared with < 0.5 hours (P =0.004 h).

Figure 2: The influence of administration delay time (T2) on in-hospital mortality is shown in figure 2.



DISCUSSION

Sepsis is a life-threatening organ dysfunction caused by maladjustment of the host response to infection, with high morbidity and mortality. For the treatment of sepsis, early recognition and intervention, particularly early administration of antibiotics, is crucial. Although the time of the first antibiotic dose has been widely studied, most key guidelines recommend that empiric antibiotic therapy should be given within 1 hour of diagnosis for sepsis Evans et al. (2021) Gaieski et al. (2010). However, there are difficulties in achieving antibiotic administration within 1 hour in routine clinical practice. First, due to regional differences and the uneven distribution of medical resources, not all patients can be diagnosed quickly and given antibiotics within an hour after being diagnosed. Second, bacterial cultures will take

between 24 and 48 hours to give meaningful results and do not help to make decisions as to whether to start antibiotics. They may also be false negatives due to prior antibiotic therapy or inadequate sampling. Meanwhile, some scholars believed that the time of antibiotic treatment for sepsis patients should be decided according to the patient's condition. Otherwise, it will lead to overuse of antibiotics and increase antibiotic resistance rates Klompas et al. (2016) Rhee et al. (2014). Therefore, a consensus has not been reached regarding which time intervals during antibiotic use should be measured and shortened. Prescott et al. (2019) Some scholars have suggested shortening the time interval between the antibiotic order and antibiotic infusion time, especially for the first antibiotics Amoah et al. (2022). It has also been suggested to shorten the interval of the second antibiotic infusion time Lykins et al. (2021) Erickson et al. (2023). Most likely, the reason was that antibiotic infusion time was related to patient prognosis and is easier to control. Thus, in our study, we divided the first-dose antibiotic use intervals into two parts—the time interval between emergency department attendance and antibiotic order (diagnosis delay, T1) and the time interval between antibiotic delivery and infusion (administration delay, T2)—to understand the relationship between antibiotic use and outcome and the complexity of antibiotic administration management. We found that the administration delay time does have an impact on the prognosis of sepsis patients, but it is not significant for short intervals, such as 0.5-1 hour, 1-2 hours and 2-3 hours. Longer intervals, such as 3 hours, have a significant effect. This result may differ from the conclusion of the guidelines that recommend delivering antimicrobials as soon as possible, ideally within 1 hour of sepsis recognition Rehn et al. (2022). Our results also suggest that a diagnosis delay is associated with the prognosis of patients. It is only concentrated in longer times, such as > 6 hours. This result supports the guideline's recommendation to deliver antibiotics within 1 hour of sepsis recognition, rather than perform ED triage.

Thus, based on our study, we can perform additional tests to accurately diagnose sepsis within 6 hours. Therefore, above all, the point that all sepsis patients should be given antibiotics within 1 hour after being diagnosed may be too radical and even increase the rate of antibiotic resistance both in the patient and in the ICU, which even has a risk to the patient's prognosis.As recommended by the latest 2021 guidelines(the Surviving Sepsis Campaign ,SSC), in clinical practice, patients with sepsis without septic shock should be stratified in the duration of antibiotic use

Limitations

Our research results also have some limitations. First, the number of patients was only 452; the clinical conditions of the patients were complex, although we tried our best to exclude the responsible factors, and some confounding factors were not fully accounted for.

The observed association may be due to potential confounding factors that were not taken into account. Second, our study lacked a more detailed study based on age segments, which may have influenced the findings. Third, we did not perform this analysis on patients with septic shock and endotracheal intubation, so caution should be exercised when applying these data to that patient, where the consequences of delayed antibiotic use may be much more severe. Therefore, there are many uncertain factors between antibiotic use and patient prognosis in patients with sepsis. Further data collection is needed for research.

CONCLUSION

In summary, delayed diagnosis and delayed medication are closely related to the in-hospital mortality of sepsis. Therefore, attention should be given to the diagnosis time of sepsis as well as the time of antibiotic infusion.

Abbreviations

IQR = interquartile range.

ED=emergency department

CRP=C-reactive protein.

PCT=Procalcitonin

DECLARATIONS

Ethics approval and consent to participate

This retrospective study protocol was approved by the Medical ethical committee of Anqing Municipal Hospital (Ethics approval number: (2023) NO.32). All methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki). Informed consent was obtained from all participants in the study.

Consent for publication

Not applicable

Competing interests

There are no known conflicts of interest and no financial interests to disclose. The authors declare they have no competing interests.

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Authors' contributions

CHZ# is the first author, completed the clinical data collection, analyzed part of the morphology studies,

participated in the study design and drafted the manuscript. HH#as the Coauthor, interpreted the clinical data as the coauthors. # These authors contributed equally to this work. ZQB, as the corresponding author, conceived of the study, participated in its design and coordination and helped draft the manuscript. All the authors have read and approved the final manuscript.

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