Presepsin Guidance Reduces the Duration of Antibiotic Treatment in Patients with Sepsis: A Multicenter, Prospective Cohort Trial

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Research

Keywords: Presepsin, Sepsis, Antibiotics

Posted Date: April 28th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-432564/v1>

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Abstract

Background: Long-term use of antibiotics for septic patients leads to antibiotic resistance. This study aimed at assessing the benefit and safety of an emerging biomarker presepsin on guiding antibiotic courses for patients with sepsis.

Methods: In this multicenter prospective cohort trial, patients were assigned to the presepsin or control groups. In the presepsin group, antibiotics were ceased based on predefined cut-off ranges of presepsin concentrations. The control group stopped antibiotics according to international guidelines. The primary endpoints were the number of days without antibiotics within 28 days (superiority analysis) and mortality at 28 and 90 days (non-inferiority analysis). The margin of non-inferiority was 10%.

Results: Overall, 656 out of an initial 708 patients were eligible and assigned to the presepsin group (n=327) or the control group (n=329). Patients in the presepsin group had significantly more days without antibiotics than those in the control group (14.54 days [SD 9.01] vs 11.01 days [SD 7.73]; absolute difference 3.64 days, $p=0.000$). Mortality in the presepsin group was non-inferior to that in the control group at days 28 (17.7% vs 18.2%; absolute difference -0.5%, 90% CI -5.4 to 4.4) and 90 (19.9% vs 19.5%; 0.4%, -4.7 to 5.5). Patients in the presepsin group had a significantly shorter mean length of stay in the hospital and lower hospitalization costs than control subjects.

Conclusions: Presepsin guidance reduces the duration of antibiotic treatment in patients with sepsis without increasing mortality.

Trial registration: ChiCTR, ChiCTR1900024391. Registered 9 July 2019. Retrospectively registered.

Introduction

Sepsis is a life-threatening organ dysfunction caused by host's maladjustment to infection. Antibiotic therapy is recommended to be administered within 1 hour after the diagnosis of sepsis [1]. However, the optimal duration of antibiotic treatment is at the doctor's discretion based on treatment guidelines. Thus, long-term use of antibiotics is frequently seen in real clinical setting [2]. Antibiotic resistance related with long-term application of antibiotics may affect patients' outcomes and healthcare resources [3].

Biomarkers reflecting the infection resolution is promising for an individualized guidance for antibiotic duration. Regularly suggested biomarkers for infection resolution include C-reactive protein (CRP) and procalcitonin (PCT) [4–6]. However, large studies evaluating the values of PCT or CRP for guiding the duration of antibiotic treatment provided controversial results [7–11]. Recently, presepsin has been proven to be a valuable biomarker for diagnosing the presence [12], severity [13, 14] or prognosis [14] of sepsis. It seems be superior to PCT and CRP for the diagnosis and prognosis of sepsis [15, 16]. Presepsin is a subtype of soluble CD14 formed by a 13-kDa fragment [17]. CD14 is a glycoprotein receptor for lipopolysaccharide (LPS)/LPS binding protein complexes mainly expressed on the surface of monocyte macrophages and plays an important role in the systemic inflammatory response syndrome (SIRS)

mediated by LPS [18]. Masson et al. [19] explored the potential of presepsin as a biomarker in sepsis and found that presepsin levels tended to increase in patients with positive microbiology and inappropriate antibiotic therapy. Increasing evidence suggests the potentially promising strategies of presepsin-directed antibiotic escalation and de-escalation [19]. However, whether presepsin guidance could reduce the duration of antibiotic treatment and its safety have never been determined. Therefore, we performed a multicenter, prospective cohort study to assess the benefit and safety of presepsin-guided antibiotic treatment in patients with sepsis.

Materials And Methods

Study design

A prospective, multicenter, cohort trial was conducted in the emergency intensive care unit (EICU), general intensive care unit (ICU) and infectious disease department of ten university-affiliated teaching hospitals in China between November 2017 and December 2019. This study was approved by the ethics committee of Beijing Friendship Hospital affiliated to Capital Medical University (2017-P2-103-02) and has been registered in Chinese Clinical Trial Registry (ChiCTR1900024391).

Patients

The inclusion criteria were as follows: 1) at least 18 years of age, 2) met diagnostic criteria for sepsis or septic shock (Sepsis-3) [20], 3) admitted to the hospital or ICU within 24 hrs, 4) received antibiotics with the presepsin levels at least 350 pg/ml. Patients who developed sepsis during their stay in hospital were also assessed for enrollment. The exclusion criteria included prolonged therapy (eg, liver abscess, infective endocarditis), expected stay in hospital or ICU of less than 2 days, pregnancy, cancer.

Written informed consent was obtained from all participants. Patients were assigned to the control group in odd-numbered days, and to the presepsin group in even-numbered days. Patients and investigators were aware of treatment assignment. A unified case report form was used to record patient information. All investigators were trained and registered by the coordinating center. A specially assigned coordinator was responsible for supervising the quality of data collection. All investigators were unaware of aggregate outcomes. The patients were followed up for 28 days and 90 days.

Data collection and definitions

Data were recorded at baseline after inclusion and thereafter every other day during the follow-up. Collected data included age, sex, vital signs, admission category, comorbidities, indicators of severity [sequential organ-failure assessment (SOFA) score, acute physiology and chronic health evaluation (APACHE) score (at inclusion only), disseminated intravascular coagulation (DIC) score (at inclusion only), organ or system failure [21], septic shock [20], serum lactate], reason for admission to ICU, type of infection (community-acquired or hospital-acquired infection), infection site, pathogen culture, interventions [vasoactive drugs, noninvasive or mechanical ventilation, continuous renal replacement

therapy (CRRT), extracorporeal membrane oxygenation], antibiotics and biomarkers (PCT and CRP). Multidrug-resistant bacteria were defined as resistance to three or more antibiotics at the same time [7].

Presepsin measurements

For presepsin measurements, venous blood samples were obtained and collected in tubes containing heparin after inclusion and thereafter every other day between 5:00 AM and 6:00 AM, stored at -80°C , and then tested between 7:00 AM and 8:00 AM using a compact automated immunoanalyzer (PATHFAST; Mitsubishi Chemical Medience Corporation, Tokyo, Japan) based on a chemiluminescent enzyme immunoassay [22] by a project coordinator who was blinded to the patient groups, but not the clinicians. This test has a normal reference range of 20-200 000 pg/ml. Attending physicians in the presepsin group but not the control group were informed of the results before 8 AM. PCT and CRP were concurrently measured after inclusion and every other day as part of the standard of care in all patients.

Procedures

The attending physician was advised to stop the antibiotics if the blood presepsin concentration was lower than 350 pg/ml or decrease by 80% or more compared with the value at the first day for two consecutive times (initial stopping threshold). Two days later, the physician continued to stop the antibiotics if the blood presepsin concentration was lower than 350 pg/ml or decrease by 80% or more from peak concentration and no obvious sign of infection exhibited (final stopping threshold). Otherwise, reassumption of antibiotics was required. Antibiotic adjustment (sensitive to bacteria, if the blood culture is positive) was encouraged when the blood presepsin concentration had no decline compared with the first day and more than 350 pg/ml for 3 consecutive times (Fig. 1). The physician was free to decide whether to stop antibiotics in patients who had reached these thresholds. Antibiotics in the control group were guided according to the current clinical guidelines [23] and discretion of physicians for patient's condition.

Outcomes

The primary outcomes were the number of days without antibiotics during 28 days after inclusion and 28-day and 90-day mortality during the follow-up. Secondary outcomes were the percentage of patients with a recurrent infection within 90 days, length of stay in ICU and hospital, hospitalization costs, days of first episode of antibiotic treatment within the 28 days, percentage of antibiotic administration and multidrug-resistant bacteria, and SOFA score.

Statistical analysis

The aim of this trial was to determine whether the presepsin-guided strategy was superior in the duration of antibiotic treatment, as estimated by the number of days without antibiotics during 28 days, and its non-inferiority in terms of 28-day and 90-day mortality. For the superiority test, we assumed a mean of 11.6 days and an SD of 8.2 days without antibiotics for the control group [7]. With a two-sided $\alpha=0.05$ and a β of 0.1 and a 2.7-day increase in the number of days without antibiotics [7], we would need 130

patients per study group. For the non-inferiority test, we assumed 30% mortality for the control group [7]. With a 10% α -risk and a β of 0.2 and a 10% margin for presepsin-guided treatment regarding mortality, we would need 280 patients per study group. The study required 700 patients to account for 20% patients lost to follow up.

Statistical analyses were performed using SPSS, version 20 (IBM software). Comparability of the presepsin group and the control group was analyzed by the chi-square test (categorical variables), student's t tests or Mann-Whitney U test (continuous variables) as appropriate. For the primary outcome of mortality, the absolute difference of mortality between the two study groups was calculated with two-sided 90% CI (non-inferiority analysis). In addition, the absolute mean difference of number of days without antibiotics between the two study groups was estimated with a univariate general linear model and calculation of 95% CI for this mean difference (superiority analysis). The comparison of accuracy of the presepsin, PCT and CRP in prediction of stopping antibiotics within 28 days was assessed by the areas under the receiver operating characteristic curves (AUCs). The independent risk factors of death were determined by Binary Logistic regression. Time-to-event analyses were estimated by Kaplan-Meier survival curves and Cox proportional hazards models.

Results

Baseline characteristics

A total of 708 patients with sepsis and a presepsin level ≥ 350 pg/ml were screened in the 10 participating ICUs and infectious disease departments from November 29, 2017 to December 12, 2019. Of these, 14 patients were excluded and 694 were enrolled and assigned to the presepsin group ($n = 345$ patients) or the control group ($n = 349$ patients). A total of 38 patients were lost to follow-up. Finally, 656 patients were eligible and divided in the presepsin ($n = 327$) and control ($n = 329$) groups (Fig. 2). The baseline clinical characteristics were comparable between the two groups (see Additional Table 1).

Table 1
Main Outcome Variables

Variables	Presepsin group (n = 327)	Control group (n = 329)	Between-group absolute difference in means (95% CI)	<i>p</i>
Primary endpoints				
Number of days without antibiotics	14.64 (9.01)	11.00 (7.73)	3.64 (2.35–4.93)	0.000
28-day mortality*	58 (17.7%)	60 (18.2%)	-0.5% (-5.4-4.4)	0.868
90-day mortality*	65 (19.9%)	64 (19.5%)	0.4% (-4.7-5.5)	0.891
Secondary endpoints(days1-90)				
Recurrent infection	9 (2.75%)	10 (3.04%)	-0.3% (-2.9-2.3)	0.827
Length of stay in ICU from inclusion (days)	11.17 (9.70)	14.16 (11.23)	-2.99 (-5.06- -0.93)	0.005
Length of stay in hospital from inclusion (days)	12 (10.77)	14.74 (10.50)	-2.73 (-4.36- -1.10)	0.001
Hospitalization costs	36032.13 (21304.67- 74125.03)	43430.02 (25623.12- 94632.76)	NA	0.021
Duration of first episode of antibiotic treatment (days)				
Overall population	9.86 (6.53)	13.42 (6.72)	-3.56 (-4.57- -2.54)	0.000
Respiratory tract infection	10.74 (7.68)	14.68 (8.19)	-3.94 (-5.61- -2.27)	0.000
Gastrointestinal tract	10.7 (6.62)	12.42 (7.47)	-1.71 (-5.57- 2.13)	0.375
Urinary tract	13.33 (9.11)	15.57 (8.13)	-2.23 (-5.95-1.49)	0.236
Biliary tract	8.36 (3.64)	12.57 (4.10)	-4.21 (-5.16- -3.25)	0.000
CNS	7.5 (3.53)	22.71 (7.78)	-15.2 (-29.11- -1.32)	0.036
Skin infection	11.43 (9.72)	11.66 (14.15)	-0.23 (-17.74- 17.27)	0.976
Positive blood culture				
Yes	14.4 (1.15)	13.89 (1.06)	0.51 (-3.18- 4.20)	0.783
Data are mean (SD), difference (95% CI), number (%), or median (IQR). Between-group absolute differences were calculated using the mean values, percentage differences, and 95% CIs. NA = not applicable. *Difference (90% CI).				
ICU: intensive care unit, CNS: central nervous system, SOFA: sequential organ failure assessment				

Variables	Presepsin group (n = 327)	Control group (n = 329)	Between-group absolute difference in means (95% CI)	<i>p</i>
No	9.37 (0.38)	13.36 (0.38)	-3.99 (-5.03- -2.95)	0.000
Antibiotic exposure rate at 28 days follow-up				
β-lactam antibiotics	301 (92.0%)	317 (96.4%)	-4.3% (-7.9- -0.7)	0.018
Glycopeptide	77 (23.5%)	111 (33.7%)	-10.2% (-17.1- -3.3)	0.004
Quinolones	64 (19.6%)	55 (16.7%)	2.9% (-3.1-8.8)	0.343
Aminoglycoside	26 (8.0%)	22 (6.7%)	1.3% (-2.7-5.3)	0.534
Tetracycline	13 (4.0%)	17 (5.2%)	-1.2% (-4.4-2.0)	0.465
Macrolide	4 (1.2%)	4 (1.2%)	0.01% (-1.7-1.7)	0.993
Sulfonamides	3 (0.9%)	3 (0.9%)	0.01% (-1.5-1.5)	0.994
Antifungal drugs	32 (9.8%)	46 (14.0%)	-4.2% (-9.2-0.8)	0.097
Antiviral drugs	11 (3.4%)	14 (4.3%)	-0.9% (-3.8-2.0)	0.551
Multidrug-resistant bacteria	40 (12.2%)	46 (14.0%)	-1.7% (-6.9- 3.4)	0.507
SOFA score				
Day 1	4.46 (3.11)/307	4.91 (3.84)/298	-0.45 (-1- 0.1)	0.115
Day 7	3.13 (3.38)/181	2.77 (3.67)/221	0.36 (-0.34- 1.05)	0.313
Day 13	3.75 (3.53)/44	3.27 (4.29)/77	0.47 (-1.03- 1.98)	0.533
Day 19	7.08 (4.62)/12	6.38 (5.08)/18	0.69 (-3.05- 4.44)	0.707
Day 25	8 (NA)/1	8 (7.87)/4	0 (28.01–28.01)	1.000
Data are mean (SD), difference (95% CI), number (%), or median (IQR). Between-group absolute differences were calculated using the mean values, percentage differences, and 95% CIs. NA = not applicable. *Difference (90% CI).				
ICU: intensive care unit, CNS: central nervous system, SOFA: sequential organ failure assessment				

Adherence To Antibiotic Strategies

Antibiotic strategy adherence was recorded for 276 (84.4%) patients in the presepsin group. In the remaining 51 patients in the presepsin group, physicians stopped antibiotics in 38 patients before reaching the stopping rules because they regarded the infection as clinically cured. For 13 out of 51 patients, physicians continued antibiotics based upon achievement of the stopping standard because of

clinical instability (3 patients, 2 with infection by multidrug-resistant bacteria) and ward transfer. As expected, the recurrence rate among patients who stopped antibiotics before reaching the suspension standard was significantly higher than that among those who did not (10.5% vs. 1.7%, $p = 0.013$). One death during 28 days and 3 deaths during 90 days were recorded as related to recurrent infection.

Primary Outcome

The duration of antibiotic treatment within the 28 days in the presepsin group was lowered by 33.1% compared to the control group (Table 1). The absolute mean difference of days free of antibiotics in 28 days between groups was 3.64 days ($p = 0.000$). The 28-day and 90-day mortality rates in the presepsin group were non-inferior to those in the control group, and the Kaplan-Meier analyses of 28-day and 90-day survival probability showed no differences between the two groups (Fig. 3, A and B). Patients in the presepsin group had similar mean survival time in 28 days and 90 days with control subjects (24.57 d vs. 24.45 d for 28 days; 74.92 d vs. 74.87 d for 90 days, respectively).

After adjustment for age and gender, the odds ratio for death in the presepsin group compared with the control group was 0.96 (90% CI 0.71–1.31) for day 28 and 1.01 (0.76–1.36) for day 90. After adjustment for multiple independent factors of death (septic shock, immunosuppressant, APACHE score and infection site of pulmonary), the odds ratio was 0.97 (90% CI 0.70–1.34) for day 28, and 1.02 (0.74–1.39) for day 90.

Secondary Outcome

The presepsin group had a significantly shorter mean length of ICU stay and hospital stay than control subjects as well as a tendency to have lower hospitalization costs. The mean antibiotic duration for the first infectious episode was significantly shorter in the presepsin group than in the control group for the overall population. Same tendency was observed for patients with respiratory tract infections, biliary tract infections, central nervous system (CNS) infections and negative blood cultures (Table 1).

Patients in the presepsin group had a significantly shorter median duration of first episode of antibiotic treatment than those in the control group (9 d vs. 13 d; $p = 0.000$, Fig. 3C). The probability of antibiotic suspension within 28 days in presepsin group was 1.72 times higher than that in the control group (95%CI 1.44–2.06; $p = 0.000$) and 1.74 times after adjusting for age and gender (95%CI 1.45–2.08; $p = 0.000$). Interestingly, more men in the presepsin group seemed to cease antibiotics compared with the control group (76.3% vs. 67.9%, $p = 0.06$), but not the women (78.5% vs. 79.1%, $p = 0.893$). The same tendency was observed in that men were 30.9% less likely to stop antibiotics than women in the control group ($p = 0.005$, 95%CI 0.536–0.893), but not in the presepsin group ($p = 0.598$, 95%CI 0.721–1.207).

During 28-day follow-up, the rate of antibiotic use in the presepsin group was significantly lower than the control group, especially broad-spectrum antibiotics and advanced antibiotics such as β -lactam

antibiotics and glycopeptide antibiotics (Table 1). There were no differences in the rate of recurrent infection and multidrug-resistant bacteria and the SOFA score between the two groups.

Subgroup Analysis Between Groups

In subgroups of CNS infection, skin infection, positive blood culture, septic shock, immunocompromise, diabetes, chronic renal failure (CRF), cirrhosis, connective tissue disease and SOFA score at inclusion ≥ 7 , the duration of antibiotic treatment was not significantly shorter in the presepsin group than in the control group. However, the duration of antibiotic treatment was slightly shorter in the following subgroups: hospital-acquired, urinary tract infection, vasoactive drugs and chronic obstructive pulmonary disease (see Additional Table 2). In addition, the 90-day mortality in the presepsin group was non-inferior to that in the control group, but not for some subgroups (see Additional Table 3).

Comparing Presepsin With Pct And Crp In Guiding Antibiotics

In order to compare the efficacy of presepsin, PCT and CRP in guiding antibiotic suspension during 28 days, the AUC from ROC curve analysis was used, and the results showed that the AUC of presepsin on day 9 (presepsin 9th) was 0.926 (95%CI 0.863–0.988, $p = 0.000$), which was higher than that for PCT 11th (0.883, 95%CI 0.789–0.977, $p = 0.000$) and CRP 9th (0.867, 95%CI 0.767–0.967, $p = 0.000$) (see Additional Fig. 1). The optimal predictive thresholds were 622.50 pg/ml for presepsin 9th (sensitivity 100.0% and specificity 84.3%), 0.96 $\mu\text{g/L}$ for PCT 11th (sensitivity 78.6% and specificity 84.3%) and 32.94 mg/L for CRP 9th (sensitivity 92.9% and specificity 74.5%). The probability of antibiotic suspension during 28 days for those with presepsin 9th levels lower than 622.50 pg/ml was 3.22 times that for those with levels higher than 622.50 pg/ml (95 % CI 2.25–4.61, $p = 0.000$). The Kaplan-Meier survival curves for presepsin 9th, PCT 11th and CRP 9th are shown in Additional Fig. 2.

Discussion

Presepsin is a novel biomarker for the diagnosis of bacterial infections [24, 25], especially Gram-negative organisms. Elevated presepsin level has been confirmed to be associated with the severity [26], number of organs dysfunction [27], ICU death and death before 90 days of sepsis [19, 28]. However, whether presepsin could guide antibiotic strategies for septic patients has not yet been studied. The ALBIOS substudy proposed that presepsin may be valuable to guide therapy in sepsis [19]. Our findings to the best of our knowledge demonstrated for the first time that presepsin guidance could safely reduce the duration of antibiotic treatment.

Our findings revealed that presepsin guidance could reduce the duration of antibiotic treatment by 3.64 days in septic patients. Although controversial results existed [29, 30], previous large randomized controlled trials, the PRORATA and SAPS trials, aimed to assess whether PCT reduced antibiotic exposure

showed that a PCT-guided strategy could similarly reduce antibiotic duration by 2.7 or 1.22 days without obvious adverse outcomes in critically ill patients, respectively [7, 8].

The prognostic effect of presepsin on sepsis was also evaluated in the current study. The results showed that antibiotic guidance with presepsin did not have a detrimental effect on 28-day and 90-day survival, which seemed to be superior to other conventional infection-related biomarkers such as PCT. PCT has been widely studied for the diagnosis [31] and outcome prediction [32]. In the PASS trial, PCT-guided antimicrobial escalation did not improve survival, and lead to organ-related harm and prolonged admission to the ICU [9]. On the contrary, in the SAPS study, PCT guidance reduced the 28-day and 1-year mortality which might be attributed to a prompt diagnosis and initiation of antibiotics [8]. However, presepsin in this study was not used to guide the initiation of antibiotic treatment.

The secondary outcome analyses in the current study revealed that presepsin guidance decreased length of ICU and hospital stay and hospitalization costs. Moreover, antibiotic adjustment based on presepsin did not affect recurrence rate of infection. These findings are in accordance with the PRORATA trial [7]. Evelien et al. [8] showed that 16 (26%) of 61 patients with a recurrent infection had a short initial duration of antibiotics. Thus, we found that early discontinuation of antibiotics before reaching suspension requirements may increase the recurrence rate of infection (from 1.7–10.5%). As expected, shorter antibiotic duration for the first infectious episode [8, 33] and decreased antimicrobial exposure [34] especially β -lactam antibiotics and glycopeptide antibiotics were observed. The presepsin group was almost twice as likely to stop antibiotics as the control group during 28 days. Despite lower antibiotic exposure in the presepsin group than in the control group, the rates of multidrug-resistant bacteria showed no difference as a result of unavoidable nosocomial cross infection. An interesting finding was that presepsin guidance seemed to be more beneficial to male patients. which needs further evaluation.

There are several limitations in this study. First, the design was not randomized although this was a multicenter and prospective study. Second, the ideal threshold for stopping antibiotics has not been determined. In previous clinical trials, the presepsin cut-off for diagnosing sepsis ranged from 317 to 700 pg/ml [35]. The reference range for normal populations and the diagnostic cut-off value of sepsis were considered in the determination of optimal cut-off values to trigger discontinuation of antibiotics. According to the English instructions, the presepsin values range from 60 to 365 pg/ml with a 95th percentile of 320 pg/ml in healthy individuals. Based on the Japanese instructions, the normal reference value is 314 pg/ml and the cut-off value for diagnosis of sepsis is 500 pg/ml. In our previous study, the presepsin cut-off value was 317 pg/ml for diagnosing sepsis and 449 pg/ml for predicting severe sepsis based on the diagnostic criteria of sepsis 2.0 based on the diagnostic criteria of sepsis 2.0 [26, 36]. Carpio et al. reported cut-off values for diagnosing sepsis (300 pg/mL to 500 pg/mL) [37]. It would be too early to stop antibiotics based on the diagnostic value of presepsin for sepsis (500 or 449 pg/ml) as mentioned above, since these patients are still at high risk of infection. However, a presepsin value of 320 pg/ml (95th percentile of the normal level) is too low to guide antibiotic discontinuation. Therefore, we chose 350 pg/ml as the optimal and low-risk cutoff value to trigger discontinuation of antibiotics. Third, from the subgroup analysis, we found that presepsin could not guide the use of antibiotics in special

populations such as those with positive blood culture, septic shock, SOFA score more than 7 and immune compromise. For these patients, physician preferred to extend the duration of antibiotic treatment due to severe infection or unstable condition. For patients with a relatively severe condition (hospital-acquired infection, mechanical ventilation, vasoactive drugs, CRRT, septic shock, chronic heart failure and positive blood culture), immunocompromised and diabetic patients, insufficient evidence for non-inferiority of presepsin guidance on 28-day and 90-day mortality was observed. In this study, we identified the septic patients suitable to use of presepsin for guiding antibiotic therapy. Fourth, the differences on the predictive efficiency for sepsis among presepsin and other potential biomarkers need to be further evaluated in large-scale randomized control trials [38, 39].

Conclusions

This multicenter study validated that presepsin guidance could reduce the duration of antibiotic treatment in patients with sepsis without increasing recurrent infection rate and 28-day or 90-day mortality. Moreover, the guidance strategy based on presepsin shortened the length of stay in ICU or hospital and reduced hospitalization costs.

Abbreviations

CRP: C-reactive protein; PCT: Procalcitonin; LPS: Lipopolysaccharide; SIRS: Systemic inflammatory response syndrome; EICU: Emergency intensive care unit; SOFA: Sequential organ-failure assessment; APACHE: Acute physiology and chronic health evaluation; DIC: Disseminated intravascular coagulation; CRRT: Continuous renal replacement therapy; CNS: Central nervous system; CRF: Chronic renal failure; AUC: Area under the receiver operating characteristic curve.

Declarations

Acknowledgements

We thank Drs. Jiandong Zhang, Jie Yang, Shuai Xia, Meiyang Zhang, Sijia Wang and Zheng Wang for collecting cases. We also thank Dr Shanshan Wu for statistical analyses and Medjaden Bioscience Limited for polishing the manuscript. And we gratefully acknowledge all health care workers on the front line and all patients involved in the study.

Authors' contributions

CSL, MRX, HLX and GXW contributed to the conception and design of the study, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. HLX, GXW, YW, ZMT, XLS, JZ, MLD, DYZ, ZRT, CCH, GQZ, YL, CJW, FJL, HYZ, JW, YZ, X CZ, WG and WJQ contributed to the acquisition of data. CSL, MRX, HLX and GXW contributed to the analysis and interpretation of the data. HLX and CSL contributed to the statistical analyses. HLX and CSL drafted the

manuscript and revised it critically for important intellectual content. All authors read and approved the final manuscript. Drs. HLX and GXW contributed equally and share first authorship.

Funding

This work was supported by the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support “Yangfan” Project (ZYLX201802), the Beijing Municipal Administration of Hospitals' Youth Program (QML20170105), as well as the National Natural Science Foundation of China (81374004 and 81773931). The funding source had no role in the design and conduct of the study, the analysis and interpretation of the data, or in the writing of the manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

Ethical approval

This study was approved by the Ethics Commission of Beijing Friendship Hospital affiliated to Capital Medical University (2017-P2-103-02).

Consent for publication

Not applicable.

Competing interests

All authors declare no competing interests.

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Figures

Figure 1

Guidelines of antibiotic management based on presepsin concentration *Excludes situations requiring immediate antibiotic treatment (e.g., septic shock, purulent meningitis). The presepsin concentration was obtained every other day

Figure 2

Study flowchart

Figure 3

Survival curves. Kaplan-Meier estimates of the probability of 28-day survival (A) and 90-day survival (B) and receiving antibiotics for days 1-28 (C). HR=hazard ratio

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