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Original Article

Association between appropriate empiric antimicrobial therapy and mortality from bloodstream infections in the intensive care unit

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ABSTRACT

Background: Empirical antimicrobial treatment for patients presenting with bloodstream infections is considered to affect patients' outcome.
Method: We conducted a single-center, retrospective study of critically-ill patients hospitalized in the intensive care unit, to examine whether the appropriateness of antimicrobial therapy is associated with mortality from bloodstream infections. The primary study endpoints were the mortality and survival time up to 60 days after the sampling of the blood cultures.
Results: We enrolled 62 patients with bloodstream infection, of whom 46 received appropriate and 16 received inappropriate, empirical, antimicrobial therapy. The 60-day mortality of appropriately treated (35%) was significantly lower than that of inappropriately treated (88%) patients ($p = .0003$), with an adjusted odds ratio of dying = 0.043 (95% confidence interval 0.0047–0.23; $p = .0011$). Survival time differed significantly between the two groups ($p = .0004$), with an adjusted hazard ratio = 0.34 (95% confidence interval 0.16–0.70; $p = .0043$).
Conclusion: Appropriate antimicrobial therapy administered to critically-ill patients presenting with bloodstream infections was associated with a lower 60-day mortality than inappropriate therapy.

1. Introduction

Bloodstream infections are life-threatening, and often prompt an admission to, or occur in an intensive care unit (ICU). Empirical antimicrobial treatment for patients presenting with bloodstream infections is considered to affect patients' outcome [1]. However, a systematic review suggested that the association between mortality and the appropriateness of antimicrobials for patients presenting with bloodstream infections remains unsettled [2]. In addition, studies limited to patients hospitalized in the ICU, where the severity of illness is greater, the causative pathogens may be resistant to antimicrobials [3], and appropriate empiric therapy is problematic, have been scarce. Given the differences in the epidemiologic features of antibiotic-resistant pathogens and the drugs available among countries/regions, it remains necessary to consider studies in Japanese intensive care settings.

We conducted a single-center, retrospective study of critically-ill patients hospitalized in the ICU, to examine whether the appropriateness of antimicrobial therapy is associated with mortality from bloodstream infections.

2. Patients and methods

2.1. Study design and population

We retrospectively reviewed the medical files of patients hospitalized in a single, 24-bed ICU between January and December 2014. Our sample includes all patients with ≥1 positive blood culture, admitted from the emergency department or from the general wards of our hospital. Single blood cultures positive for *Bacillus* species, *Corynebacterium* species or *Staphylococcus* species, except *Staphylococcus aureus* (e.g. Coagulase-negative staphylococcus or *Staphylococcus epidermidis*) were considered contaminated and were excluded from this analysis. Patients who, during a single hospitalization, developed a positive blood culture after successful completion of treatment of a first infection, were counted as two cases. Repetitive positive blood culture detected during treatment of a first infection were excluded from the analysis. We defined antimicrobial therapy as *appropriate* when the causative

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List of abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
CI	confidence interval
ICU	intensive care unit
IQR	interquartile range
SD	standard deviation
SOFA	Sequential Organ Failure Assessment

microorganism was sensitive to the antimicrobial agent administered within 24 h of the blood culture sampling. Antimicrobial therapy was defined as *inappropriate* when the causative microorganism was not sensitive to the antimicrobial agent, or if its administration had been delayed for >24 h of the blood culture sampling. The blood culture sampling was obtained in patients with suspected sepsis or septic shock, or whenever physicians judged it necessary. The clinical effectiveness of empiric antimicrobial therapy was assessed at 3 days after the administration. Switch to definitive therapy (de-escalation or escalation) was thereafter performed based on the susceptibility profile of identified pathogen. The bloodstream infections were classified as originating from the lower respiratory tract, intra-abdominal, urinary tract, skin/soft-tissue, catheter-related, osteitis/arthritis, infective endocarditis, or from other or unknown sources. This study has been approved by the research ethics committee of Hiroshima University.

2.2. Data collection

We collected the patient's baseline characteristics, including age, sex, concomitant disorders, use of a central vein catheter, vasopressor support, mechanical ventilation, Sequential Organ Failure Assessment (SOFA) score [4] at the time of blood culture sampling, the classification of sepsis and septic shock [5] and the empiric antimicrobial agents.

2.3. Outcome

The primary study endpoints were 1) all-cause mortality, and 2) survival time, each up to 60 days after the sampling of the blood cultures. The secondary endpoints were in-hospital, in-ICU and 28-day mortality, treatment with mechanical ventilation, vasopressor support, renal replacement therapy and low-dose hydrocortisone.

2.4. Statistical analysis

The number of patients with bloodstream infections during the study period determined the sample size. Continuous variables are expressed as means ± standard deviations (SD) or medians and interquartile ranges (IQR), and categorical variables are expressed as counts and percentages. Single variable analyses of continuous and categorical variables were compared, using the Mann-Whitney's *U* test and Fisher's exact test, respectively. Survivals, shown as Kaplan-Meier curves, were compared, using the log-rank test. Adjustments of 60-day, in-hospital, in-ICU and 28-day mortality and survival time for SOFA score, classified into two groups based on the median value, as the severity of organ dysfunction known to be associated with increased mortality from bloodstream infection and sepsis, were made by logistic regression and Cox proportional-hazards analysis, respectively [6,7]. All analyses were performed, using the JMP 12 software (SAS Institute Inc., Cary, NC). A two-sided p value < .05 was considered to indicate statistical significance.

3. Results

3.1. Study sample

We identified 86 positive blood cultures, of whom 24 were excluded from this analysis, as they were suspected of having been contaminated or repeatedly detected during the treatment course of a first blood culture. Our study sample ultimately included 62 patients, of whom 46 received appropriate and 16 received inappropriate, empirical, antimicrobial therapy. Within the 16 patients received inappropriate antimicrobial therapy, 13 were defined as *inappropriate* because of insusceptibility of antimicrobial agents for causative pathogens and 3 were because of delay of its administration. The baseline characteristics of the two groups of patients were similar (Table 1). The median SOFA score of the appropriately treated group was 9 (IQR = 5–14), and that of the inappropriately treated group was 10.5 (IQR = 6–17; ns).

3.2. Source of bloodstream infections and microbial data

The most frequent sources of bloodstream infections were the lower respiratory tract in 24%, the skin or soft tissues in 15%, an intra-abdominal process in 13%, a catheter in 11%, and the urinary tract in 11% of patients. The most often isolated microorganisms were *Escherichia coli* in 16%, followed by methicillin-sensitive *Staphylococcus aureus* in 9%, *Enterobacter species* in 7%, *Klebsiella pneumoniae* in 6%, and *Enterococcus faecium* in 6% (Table 1). Pathogens resistant to multiple drugs, including methicillin-resistant *Staphylococcus aureus* and extended-spectrum β-lactamase-producing *Escherichia coli* were isolated in 3 patients (4%).

3.3. Outcomes

Survival time differed significantly between the two groups (p = .0004; Fig. 1) by the log-rank test. At 60 days, the mortality associated with appropriate antimicrobial therapy for bloodstream infections was 35%, versus 88% with inappropriate antimicrobial therapy (p = .0003; Table 2). The relative risk of death within 60 days with appropriate compared with inappropriate antimicrobial therapy was 0.19 (95% confidence interval [CI] 0.052–0.71). At 60 days of appropriate versus inappropriate antimicrobial therapy (Table 3), the adjusted odds ratio by logistic regression analysis was 0.043 (95% CI 0.0047–0.23; p = .0011) and the adjusted hazard ratio by Cox proportional hazards analysis was 0.34 (95% CI 0.16–0.70; p = .0043).

There were also significant differences between appropriate and inappropriate antimicrobial therapy in 28-day mortality (30% vs. 63%, p = .036), in in-hospital mortality (30% vs. 81%, p = .0011) and in ICU mortality (24% vs. 69%, p = .0022). The adjusted odd ratio for ICU, in-hospital and 28-day mortality with appropriate versus inappropriate antimicrobial therapy were 0.24 (95% CI 0.058–0.89; p = .038), 0.068 (95% CI 0.0099–0.32; p = .0020) and 0.10 (95% CI 0.019–0.43; p = .0035), respectively. Mechanical ventilation, vasopressor support, renal replacement therapy and low-dose hydrocortisone were used similarly in both study groups (Table 2). There was no patient who had no chance to get appropriate antimicrobial therapy because of death before the 24 h.

4. Discussion

In this retrospective, observational study, we found a significant correlation between a lower 60-day mortality and appropriate antimicrobial therapy after adjustment for baseline organ dysfunction score. The ICU, in-hospital and 28-day mortalities were

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