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Original Article

Inadequate empiric antimicrobial therapy and mortality in geriatric patients with bloodstream infection: A target for antimicrobial stewardship

Hitoshi Honda [a, *], Naofumi Higuchi [a], Kensuke Shintani [a], Masanori Higuchi [a], David K. Warren [b]

[a] Division of Infectious Diseases, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan
[b] Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA

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ABSTRACT

Background: Bloodstream infections are responsible for a large proportion of deaths among geriatric patients. Japan is a rapidly aging society; however, little is known about the epidemiology of bloodstream infections in geriatric patients in Japanese institutions.
Methods: We conducted a retrospective cohort study of patients aged ≥65 years old with a bloodstream infection in a Japanese tertiary care hospital in 2013. We defined inadequate empiric antimicrobial therapy as either antimicrobial treatment that was ineffective against subsequently isolated organisms or treatment initiated after notification of a positive culture. Predictors of inadequate antimicrobial therapy and 30-day mortality among geriatric patients with bloodstream infections were evaluated.
Results: We identified 275 patients with a bloodstream infection, of which 42.2% of cases (116/275) were healthcare-associated, hospital-onset. The most common source of bloodstream infection was hepatobiliary (28.0%). Inadequate empiric antimicrobial therapy occurred in 29.8% of the patients. Factors associated with inadequate empiric therapy included a history of surgery prior to bloodstream infection during index hospitalization (adjusted odds ratio [aOR] 3.27; 95% confidence interval [CI] 1.18–9.12). In 275 patients, 38 (13.8%) died within 30 days after the first positive blood culture. Predictors of 30-day mortality was Pitt bacteremia score >6 (aOR 9.80; 95% CI 4.72–20.36).
Conclusion: Inadequate empiric antimicrobial therapy occurred in approximately one-third of episodes of bloodstream infection in geriatric patients. Severity at the time of bloodstream infection was likely to have contributed to mortality. The initiation of adequate empiric antimicrobial therapy may have important implications for antimicrobial stewardship even in the elderly population.

1. Introduction

Bloodstream infections result in substantial morbidity and mortality. The reported mortality rates in geriatric patients with bloodstream infections range from 11% to 42% [1,2]. Because of the unique clinical characteristics of geriatric patients, the diagnosis and management of bloodstream infections in this population can be challenging. Bloodstream infections among the elderly may present with atypical, nonspecific or unpredictable clinical features [3,4], which may lead to a delay in initiating antimicrobial therapy. A higher frequency of recent healthcare exposure in elderly patients may increase contact with a wide diversity of causative pathogens and thus also increase the risk of inappropriate empiric antimicrobial therapy.

Various patient and treatment-related factors including older age, the presence of comorbidities, severity of illness at presentation, bedridden status, the presence of healthcare-associated bloodstream infection, and inappropriate empiric antimicrobial therapy are associated with mortality in this population [5–9]. Optimizing treatment-related factors is considered essential to improving the patient outcomes in this vulnerable population [7].

* Corresponding author.
E-mail address: hhhhonda@gmail.com (H. Honda).

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The appropriate choice of empiric antimicrobial therapy for patients with bloodstream infection is an important determinant of favorable outcomes and has implications for antimicrobial stewardship [10].

Currently, Japan has an aging population [11]. Increasing numbers of elderly patients have been admitted to hospital for serious illnesses including infectious diseases. The proportion of hospitalized patients age ≥65 years has increased by 20% over the last 20 years and currently accounts for over 70% of all hospitalized patients [12]. Despite this, little is known of the epidemiology of bloodstream infection among geriatric patients in Japanese institutions. A better understanding of the situation in Japan would also be helpful to other countries facing the same demographic trend. The purposes of our study were to assess the current epidemiology of bloodstream infection in the geriatric population and to investigate the predictors of inadequate empiric antimicrobial therapy and poor treatment outcomes at a Japanese tertiary care center.

2. Patients and methods

2.1. Participants and setting

A retrospective cohort study of patients with bloodstream infections in the geriatric population (age ≥ 65) was performed between January 2013 and December 2013 at Tokyo Metropolitan Tama Medical Center, a 790-bed tertiary care center.

Patients with the diagnosis of bloodstream infection were included. We identified eligible patients based upon microbiological data and a positive blood culture. We then reviewed the electronic medical records to determine if patients had a true bloodstream infection. The diagnosis of bloodstream infection was defined as one or more blood cultures positive for known pathogenic organisms (e.g., *Staphylococcus aureus*, Gram-negative bacilli, and fungi). For organisms considered to be normal skin flora or potential contaminants (i.e., coagulase-negative staphylococci, *Bacillus* species [spp.], and *Corynebacterium* spp.), at least two sets of positive blood cultures were required for the diagnosis of bloodstream infection [13]. For patients with multiple episodes of bloodstream infection during the study period, we included only the first episode of bloodstream infection for analysis. Patients aged <65 years at the time of the diagnosis of bloodstream infection and those who died within 24 h of diagnosis were excluded.

Once a positive blood culture was detected by the microbiology laboratory at the study institution, preliminary results based on blood culture Gram stain were entered into the electronic medical records. No rapid molecular diagnostic systems were used during the study period. The institutional review board at Tokyo Metropolitan Tama Medical Center approved this study.

2.2. Data collection

The demographic characteristics, clinical data, and microbiological data of patients who were eligible for the study were obtained from the electronic medical records. The Charlson comorbidity index and the Pitt bacteremia score for each patient were computed after obtaining the clinical data [14,15]. Data on comorbidities, other clinical characteristics, and the severity score were obtained at the time of bloodstream infection.

We also tracked 30-day all-cause mortality from the day on which a positive blood culture was obtained to assess the impact of empiric antimicrobial therapy on mortality in the target population. Mortality data were obtained from the electronic medical charts, but if the data were unavailable, we contacted the patients or their family by telephone to determine whether the patient was alive at day 30.

2.3. Definition

Empiric therapy was defined as newly administered, initial antimicrobial therapy between the time of blood culture sampling and the identification of the pathogens in the blood culture. Inadequate empiric antimicrobial therapy was defined as the following: empiric antimicrobial therapy that was ineffective against the causative organisms subsequently identified in the blood culture based on antimicrobial susceptibilities or no administration of antimicrobial agents between obtaining the blood culture and notification of a positive blood culture [16]. Onset of bloodstream infection was classified as either community-onset, healthcare-associated, or nosocomial as previously described [17].

2.4. Statistical analysis

Categorical variables were compared using Fisher's exact test while continuous variables were compared using the Mann-Whitney test. All tests for significance were two-tailed. We performed multivariable logistic regression analysis to identify factors associated with inadequate empiric antimicrobial therapy and the Cox proportional hazard analysis to predict 30-day mortality in geriatric patients with bloodstream infections. Factors previously reported in the literature (i.e., age, onset of bacteremia, and pathogen distribution) [18–20] as associated with inadequate empiric antimicrobial therapy were considered to be *a priori* candidate variables for multivariate analysis. Other variables with $P < 0.25$ in univariate analysis were also considered for inclusion in the multivariate model. Similarly, for factors associated with mortality, several previously confirmed variables (i.e., age, Charlson comorbidity index, higher Pitt bacteremia score, and status of empiric antimicrobial therapy) and variables with $P < 0.10$ in univariate analysis were considered for inclusion in the final model [5,7–9]. We examined the multicollinearity of each candidate variable before entering into a final model. Although the rule-of-thumb of one covariate per ten events would have been ideal, the ratio of event to independent variable in the final model for assessing the factors associated with mortality was not achieved due to the lower number of outcome events.

The Hosmer-Lemeshow test was used for goodness of fit for the logistic regression model. The proportional hazard assumption was evaluated via Shoenfeld residuals [21]. All statistical analyses were performed using SPSS version 22 (IBM, Armonk, NY, USA).

3. Results

We identified 275 elderly patients with a bloodstream infection during the study period. Common sources of bloodstream infection and the proportion of empiric antimicrobial therapy are shown in Table 1. Inadequate empiric antimicrobial therapy occurred in 82 patients (29.8%) (62 [75.6%] were due to inappropriate empiric antimicrobial therapy, and in 20 episodes [24.4%] no empiric antimicrobials were administered). Inadequate empiric antimicrobial therapy was commonly observed in treating bloodstream infection due to extended-spectrum beta lactamase producing enterobacteriaceae, methicillin-resistant Gram-positive cocci, and *Candida spp.* (Appendix 1). Factors significantly associated with inadequate empiric therapy included a history of surgery prior to bloodstream infection during index hospitalization (adjusted odds ratio [aOR] 3.27; 95% CI [confidence interval] 1.18–9.12), and higher Pitt bacteremia score (Pitt bacteremia score 4–6, aOR 2.65; 95% CI

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