Diagnostic Microbiology and Infectious Disease 80 (2014) 136–140

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

The impact of previous hospitalization in the preceding 90 days on the outcome in critically ill patients with gram-negative bloodstream infection

Qiaojun Zeng [a,1], Fengqin Xu [b,1], Shanping Jiang [a,c,*]

[a] Department of Respiratory Medicine, Sun Yat-Sen Memorial hospital, Sun Yat-Sen University, Guangzhou, China
[b] Department of Nosocomial infections management, Sun Yat-Sen Memorial hospital, Sun Yat-Sen University, Guangzhou, China
[c] Institute of Antibiotics, Sun Yat-Sen Memorial hospital, Sun Yat-Sen University, Guangzhou, China

ARTICLE INFO

Article history:
Received 3 March 2014
Received in revised form 15 June 2014
Accepted 15 June 2014
Available online 28 June 2014

Keywords:
Previous hospitalization
Bloodstream infections
Gram-negative bacteria infections
Severe sepsis
Septic shock
Poor prognostic factors

ABSTRACT

We conducted a retrospective cohort study to evaluate the impact of previous hospitalization in the preceding 90 days on mortality in critically ill patients with gram-negative bloodstream infection (BSI) and to identify the risk factors for 30-day mortality in these patients. Of 89 critically ill patients with gram-negative BSI, 42 patients had previous hospitalization in the preceding 90 days. Multivariate Cox regression analysis revealed previous hospitalization in the preceding 90 days as a significant predictor for 30-day mortality (hazard ratio [HR], 2.10; 95% confidence interval [CI], 1.11–3.94; $P = 0.022$), along with Acute Physiology and Chronic Health Evaluation II score at BSI onset (HR, 1.08; 95% CI, 1.04–1.12; $P < 0.001$), liver cirrhosis (HR, 3.61; 95% CI, 1.46–8.94; $P = 0.006$), and inappropriate definitive antimicrobial therapy (HR, 4.28; 95% CI, 2.17–8.45; $P < 0.001$). The effect of previous hospitalization in the preceding 90 days should be considered in evaluating the risk for 30-day mortality when treating such patients, and further study is required.

1. Introduction

Despite the great advances in medical science in the past century, bloodstream infection (BSI) remains a growing public health concern in the modern world and ranks among the top 7 causes of death in North America and Europe (Goto and Al-Hasan, 2013). Although gram-negative bacteria have become less common than gram-positive bacteria as the cause of BSI over the past 2 decades, the incidence of gram-negative BSI shows an upward trend recently and accounts for more than 40% of all BSIs (Artero et al., 2010; Blot et al., 2009; Gudiol et al., 2013; Montassier et al., 2013; Munoz et al., 2008; Reunes et al., 2011; Tabah et al., 2012; Vlieghe et al., 2013). BSI-associated severe sepsis or septic shock accounts for 20–44% of gram-negative BSI (Kang et al., 2004, 2011a; Marra et al., 2006a; Ortega et al., 2011). The overall crude case mortality rate of patients with severe sepsis or septic shock caused by gram-negative BSI is more than 40% (Artero et al., 2010; Kang et al., 2011a; Marra et al., 2006a). Several investigators have shown that various factors are associated with poor prognosis in severe sepsis or septic shock patients with BSI, including old age (≥65 years), male gender, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, nosocomial acquisition, septic shock, comorbidities, and pathogens other than *Escherichia coli* (Artero et al., 2010; Jang et al., 1999; Kang et al., 2011a; Sancho et al., 2012). However, there are few data on patients with sepsis or septic shock caused by gram-negative BSI.

Previous hospitalization (especially in the preceding 90 days) is a well-recognized risk factor for colonization and infection with multidrug-resistant (MDR) pathogens, which is associated with an increase in mortality (American Thoracic Society and Infectious Diseases Society of America, 2005; Cavalcanti et al., 2005; Chen et al., 2008; Colodner et al., 2004; Cornejo-Juarez et al., 2012; Sostarich et al., 2008; Stryjewski and Boucher, 2009; Tumbarello et al., 2012a). In a 3-center prospective cohort study, McDonald et al. (2005) demonstrated that previous hospitalization in the preceding 90 days was an independent predictor of ineffective empirical therapy for BSI. Inappropriate initial antimicrobial therapy may have an adverse effect on patient. Thus, the conventional view is that patients with previous hospitalization in the preceding 90 days are at greater risk for mortality because of underlying conditions, increased infection with MDR pathogens and increased use of inappropriate initial antimicrobial drugs, and these factors increase the risk of mortality. However, Bader (2006)investigated 135 older patients with *Staphylococcus aureus* BSI (SABSI) to determine the predictors of 7-day mortality and to identify the risk factors associated with BSI due to methicillin-resistant *S. aureus* (MRSA). He found that previous hospitalization in the preceding 90 days was associated with both increased mortality due to SABSI and isolation of MRSA, while MRSA was not an independent risk factor for mortality (Bader, 2006). So we hypothesize that previous hospitalization

* Corresponding author. Tel.: +86-20-81332199; fax: +86-20-81332960.
E-mail address: shanpingj_sys@126.com (S. Jiang).
[1] Qiaojun Zeng and Fengqin Xu are the co-first authors.

http://dx.doi.org/10.1016/j.diagmicrobio.2014.06.015
0732-8893/

is an independent risk factor for mortality. Up to now, there are no data regarding the association between previous hospitalization in the preceding 90 days and mortality of patients with severe sepsis or septic shock caused by gram-negative BSI.

The aims of this study were to evaluate the impact of previous hospitalization in the preceding 90 days on mortality in patients with severe sepsis or septic shock caused by gram-negative BSI and to identify the risk factors for 30-day mortality in these patients.

2. Materials and methods

2.1. Study population

We performed a retrospective study at Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University between 1 January 2008 and 31 December 2012. Sun Yat-Sen Memorial hospital is a 1200-bed primary care and tertiary referral center in South China. Patients with gram-negative BSI were chosen from the computerized database of the hospital's clinical microbiology laboratory. We only included adult patients who were ≥18 years of age and those who were diagnosed as severe sepsis or septic shock at BSI onset. For the analyses presented herein, the first episode of gram-negative bloodstream was selected.

2.2. Study design

A retrospective observational cohort study was used. We reviewed the medical records of the patients and compared data from patients with previous hospitalization in the preceding 90 days with data from patients without previous hospitalization in the preceding 90 days. The data collected included demographic, clinical, microbiological, hospital course, and outcome data. The main outcome measure used was the 30-day mortality rate.

2.3. Definitions

Gram-negative BSI was defined as the isolation of gram-negative bacilli in a blood culture. Polymicrobial infections were associated with more than 1 significant gram-negative isolate within a 2-day period. BSI onset was defined as the date of collection of the index blood culture. Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension. Hypoperfusion abnormalities included lactic acidosis, oliguria, and acute alteration of mental status. Septic shock was defined as sepsis-induced hypotension, persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction (Bone et al., 1992). The source of BSI was established after clinical evaluation based on the review of medical records and laboratory results, according to the Centers for Disease Control and Prevention criteria (Horan et al., 2008). Catheter-related BSI was defined according to the Infectious Diseases Society of America definition (Mermel et al., 2009).

Nosocomial BSI was defined as the following i) BSI that occurred in hospital more than 48 h after admission; ii) BSI that occurred less than 48 h after admission in patients who had 1 of the following medical histories: hospitalized for more than 2 days in the preceding 90 days; transferred from another hospital, nursing home, or long-term care facility; renal failure requiring hemodialysis, received intravenous therapy at home, or in an outpatient clinic in the preceding 30 days. All other cases of BSI were classified as community acquired. Chronic renal failure was defined as a chronic serum creatinine level >177 μmol/L (>2.0 mg/dL) or levels similar to those of a patient receiving regular hemodialysis. Corticosteroid therapy was defined as use of prednisolone ≥20 mg per day or other equivalent steroid for at least 2 weeks before the development of BSI. Neutropenia was defined as an absolute neutrophil count $<0.5 \times 10^9$/L at the onset of BSI. The initial empirical antimicrobial therapy was considered appropriate if the initial antibiotics, which were administered within 48 h after acquisition of a blood culture samples, included at least 1 antibiotic that was active in vitro against the causative microorganisms and when the dosage and route of administration conformed with current medical standards. A therapy that was continued or commended on the day that antibiogram results were reported for more than 2 days was considered appropriate definitive antimicrobial therapy. We considered antimicrobial therapy to be inappropriate if the drugs used did not have in vitro activity against the isolated strain or if the patient did not receive antimicrobial therapy. MDR was defined according to the European Society of Clinical Microbiology and Infectious diseases (Magiorakos et al., 2012). According to this classification scheme, bacteria other than Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter* species were considered susceptible.

To calculate APACHE II score, we collected the necessary laboratory and clinical data from patient's medical records at admission and at BSI onset. If multiple values were obtained on that day, the most abnormal value was used. If a value was missing, the measurement from the nearest day was used in its place. If no values were available, it was considered a missing value in the analysis (Marra et al., 2006b). The 30-day survival status was confirmed by either hospital records or telephone interviews for all enrolled patients.

2.4. Microbiological methods

Blood cultures, each consisting of aerobic and anaerobic samples, were processed at the clinical laboratory of our hospital. The Vietk 2 system (bioMérieux, Marcy l'Etoile, France) was used for isolate identification and antimicrobial susceptibility testing. Minimum inhibitory concentrations were classified according to the 2011 Clinical Laboratory and Standards Institute criteria.

2.5. Statistical analysis

Continuous variables were described as means ± SD or median (inter-quartile range [IQR]). Means were compared using Student's t test. Medians and comparative analysis were executed with Mann–Whitney U test, Kruskal–Wallis test, or chi-square test when appropriate. The Kaplan–Meier survival curve was used for the survival analysis to assess the association between previous hospitalization in the preceding 90 days and mortality, and log rank test was done to compare the 2 survival curves. A Cox proportional hazards regression model was performed, in which hazard ratio (HR) and 95% confidence interval (CI) were reported, to assess predictors of 30-day mortality. Variables entered in the multivariate Cox regression model were required to have a relationship with mortality in univariate analysis ($P < 0.05$). All P-values were 2-tailed and statistical significance was set at $P < 0.05$. All statistic analyses were performed using the SPSS version 13.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Study population

During the study period, a total of 437 patients with gram-negative BSI were identified. Among these patients, 89 (20.4%) patients were diagnosed as severe sepsis or septic shock. The mean age (±SD) of these patients was 58.9 ± 16.7 years, and 59.6% were male (n = 53). A total of 97.8% of the episodes were nosocomial infections. The most common underlying disease was solid tumor (n = 26, 29.2%), followed by hypertension (n = 17, 19.1%). The most common primary site of infection was respiratory tract (n = 30, 33.7%).

Comparison between 42 patients with previous hospitalization in the preceding 90 days and 47 patients without previous hospitalization in the preceding 90 days was summarized in Table 1. APACHE II score at admission was higher in patients with previous