Original Article

http://dx.doi.org/10.3947/ic.2012.44.3.168
Infect Chemother 2012;44(3):168-174
pISSN 2093-2340 eISSN 2092-6448

Infection & Chemotherapy

균혈증을 동반한 지역사회획득 중증패혈증환자의 예후인자: 전향적, 관찰연구

윤영경[1] · 김민자[1] · 박대원[1] · 권순선[1] · 천병철[1] · 정희진[1] · 최준용[2] · 최희정[3] · 최영화[4] · 김효열[5] · 엄중식[6] · 김상일[7] 송영구[2] · 백경란[8] · 김양수[9] · 김준명[2] · 손장욱[1]; 한국패혈증연구회

고려대학교 의과대학 내과학교실[1], 연세대학교 의과대학 내과학교실[2], 이화여자대학교 의과대학 내과학교실[3], 아주대학교 의과대학 내과학교실[4], 연세대학교 원주의과대학 내과학교실[5], 한림대학교 의과대학 내과학교실[6], 가톨릭대학교 의과대학 내과학교실[7], 성균관대학교 의과대학 내과학교실[8], 울산대학교 의과대학 내과학교실[9]

Prognostic Factors of Community-acquired Bacteremic Patients with Severe sepsis: A Prospective, Observational Study

Background: Characterization of clinical features of bacteremic severe sepsis acquired from the community has been inadequate; therefore, our goal in this study was to identify prognostic factors associated with outcome in patients with community-acquired bacteremic severe sepsis.

Materials and Methods: Adult patients (≥18 years) with community-acquired severe sepsis in whom pathogens were identified from blood cultures were included in the study. Data were collected prospectively from 12 teaching hospitals between May, 2005, and February, 2009. Data included demographic characteristics, co-morbid medical conditions, primary infection sites, sepsis severity, mortality, causative microorganisms, and the appropriateness of initial empirical antibiotic therapy.

Results: During the study period, 1,152 patients were diagnosed with community-acquired severe sepsis and 422 patients were found to harbor pathogens in their blood. Among the 422 patients analyzed, 253 (60.0%) patients went into shock and 121 patients (28.7%) died during hospitalization. Risk factors, including respiratory tract infection (odds ratio [OR], 2.60; 95% confidence interval [CI], 1.11-6.09), number of organ dysfunctions (OR, 1.39; 95% CI, 1.13-1.71), and higher APACHE II scores (OR, 1.08; 95% CI, 1.03-1.13) showed an association with poor survival, whereas *Escherichia coli* as a pathogen (OR, 0.31; 95% CI, 0.16-0.64) showed an association with lower mortality.

Conclusions: In addition to severity of illness, the primary site of infection and causative microorganisms were also identified as important prognostic factors in patients with community-acquired bacteremic severe sepsis.

Key Words: Prognostic factors, Severe sepsis, Septic shock, Community-acquired infections, Bacteremia

Young Kyung Yoon[1], Min Ja Kim[1], Dae Won Park[1], Soon Sun Kwon[1], Byung Chul Chun[1], Hee Jin Cheong[1], Jun Yong Choi[2], Hee Jung Choi[3], Young Hwa Choi[4], Hyo Youl Kim[5], Joong Sik Eom[6], Sang Il Kim[7], Young Goo Song[2], Kyong Ran Peck[8], Yang Soo Kim[9], June Myung Kim[2], and Jang Wook Sohn[1]; Korean Sepsis Working Group

[1]Department of Internal Medicine, Korea University College of Medicine; [2]Department of Internal Medicine, Yonsei University College of Medicine; [3]Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul; [4]Department of Internal Medicine, Ajou University School of Medicine, Suwon; [5]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju; [6]Department of Internal Medicine, Hallym University College of Medicine, Chuncheon; [7]Department of Internal Medicine, Catholic University College of Medicine; [8]Department of Internal Medicine, Sungkyunkwan University School of Medicine; [9]Department of Internal Medicine, University of Ulsan College of Medicine, Seoul, Korea

Submitted: November 22, 2011
Revised: April 17, 2012
Accepted: April 18, 2012
Corresponding author 1: Jang Wook Sohn, MD, PhD
Division of Infectious Diseases, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Inchon-ro 73, Seongbuk-gu, Seoul 136-705, Korea
Tel: +82-2-920-5018, Fax: +82-2-920-5616
E-mail: jwsohn@korea.ac.kr; jangwook.sohn@gmail.com
Corresponding author 2: June Myung Kim, MD, PhD
Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro Seodaemun-gu Seoul 120-752, Korea
Tel: +82-2-2228-1946, Fax: +82-2-393-6884
E-mail: jmkim@yuhs.ac
*Jang Wook Sohn and June Myung Kim contributed equally to this work.

Introduction

Occurrence of severe sepsis, which accounts for 10-30% of intensive care unit (ICU) admissions worldwide, is relatively common [1-4]. While severe sepsis is a deadly medical condition, previous studies involving large observational cohorts have reported an overall rate of mortality ranging between 28.6-56.0% [5, 6]. Many factors can be determinants of poor outcome in patients with severe sepsis; we argue that there are too many to apply in real clinical situations. Typically, the list includes age, severity of a patient's underlying disease, number of dysfunctional organ systems, severity of the illness, hypothermia, thrombocytopenia, lactic acidosis, multiple sources of infection, positive blood cultures, and type of organism [6, 7].

In most studies of severe sepsis, patients were not stratified according to whether the infection was community-acquired vs. hospital acquired or bacteremic vs. non-bacteremic. Previous studies of bacteremic diseases have focused on individual organisms or combined community- and hospital-acquired bacteremia [8, 9]. One study suggested an association of patient outcomes in cases of severe community-acquired bacteremic sepsis with scores for albumin and Acute Physiology and Chronic Health Evaluation II (APACHE II) [10]; however, more data are needed in order to validate these earlier findings.

Epidemiological and prognostic factors associated with severe community-acquired bacteremic sepsis could differ from those of hospital-acquired and/or non-bacteremic cases, and could inform treatment recommendations and aid in establishment of national health policies. Our aim in this study was to describe the clinical and microbiological characteristics of patients with severe community-acquired bacteremic sepsis, and to determine which of these variables are associated with mortality.

Materials and Methods

1. Study design and patients

A prospective, multicenter, observational study was conducted in the medical (n=12) and surgical (n=10) intensive care units (ICUs) of 12 university-affiliated teaching hospitals in the Republic of Korea from April, 2005 to February, 2009. A prospective analysis was conducted using data from adult patients (18 years and older) with severe community-acquired bacteremic sepsis who had been recently admitted to the ICUs of the participating centers. Patient follow-up continued until death or discharge from the hospital. Cases involving recurrence or relapse were excluded. There was no standardized intervention associated with management of sepsis, and physicians followed routine medical practices in treatment of their patients.

Prior to initiation of the study, the protocol was reviewed and approved by the institutional review board from each participating center.

2. Definitions

In this study, for diagnosis of severe sepsis, we used criteria developed by Bernard et al. [11, 12], as well as hepatic dysfunction (serum bilirubin >21 μmol/L), gastrointestinal dysfunction (stress upper gastrointestinal bleeding), and mental change (Glasgow coma scale ≤ 13). Diagnosis of severe sepsis required evidence of infection and at least two systemic inflammatory response syndrome conditions and at least one organ system dysfunction. Septic shock was diagnosed as sepsis with sustained hypotension lasting at least one hour despite adequate fluid resuscitation or as sepsis requiring vasopressors for maintenance of adequate systolic blood pressure [11]. Severe community-acquired sepsis was defined as the presence of severe sepsis upon admission or sepsis that developed within 24 hours of admission. According to the previously mentioned criteria, cases involving nosocomial infection were excluded [13]. Infections that became evident <48 hours after discharge from the hospital were deemed nosocomial [13]. Determination of the primary site of infection was based on the organs affected and was classified as one of the following: lower respiratory tract, intra-abdominal, genitourinary tract, skin and soft tissue, central nervous system, or primary bloodstream infection, which was defined as a positive blood culture without focus.

Isolation of one or more viable microorganisms from blood cultures resulted in diagnosis of bacteremia. Isolation of common skin-dwelling organisms, such as coagulase-negative *Staphylococcus* species and *Bacillus* species, from two or more blood cultures from a suspected patient was considered significant. The final diagnosis was made by infectious disease specialists.

Initial empirical antibiotic therapy was defined as appropriate when antibiotics were started intravenously with optimal dosing and intervals within 24 hours after recognition of severe sepsis or septic shock, and the infecting microorganism was subsequently found to be susceptible in vitro to the antibiotics administered.

3. Data collection

For the first 24 hours following admission, data for each patient were collected using the standardized web-based case report form via the website of the Korean Society of Infectious Diseases. Data included demographic characteristics, co-morbid medical

conditions, as determined by Charlson's comorbidity index [14], factors predisposing to infection, primary site of infection, APACHE II scores [15], and diagnosis of severe sepsis, septic shock, and organ dysfunction. Sepsis-related Organ Failure Assessment (SOFA) scores [16], microorganism isolates, and hospital mortality data were also collected at admission.

4. Statistical analyses

The Chi-square test or Fisher's exact test was used for comparison of categorical variables. Continuous variables were expressed as means±standard deviations, and t-tests were performed for comparison of means. For determination of independent factors sociated with mortality, variables that showed a significant association with in-hospital mortality in univariate analysis were further analyzed using multivariate logistic regression analysis. Statistical significance was defined as a two-tailed P value<0.05.

SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) was used in performance of statistical analyses.

Results

1. Patient characteristics

During the study period, data from 1,357 cases were collected and 1,152 patients were diagnosed with severe community-acquired sepsis. Among them, 422 patients documented as having severe community-acquired bacteremic sepsis were subsequently included in this study (Fig. 1). While occurrence of all-cause in-hospital mortality was observed in 121 patients (28.7%), 7-day and 28-day mortality rates were 14.9% (63 of 422) and 24.6% (104 of 422), respectively. The mean hospital stay was 3.96 ±93.08 days (range 0-939, median 16 days).

Sex distribution was nearly equal, and the mean age (years) of patients was 64.6±14.3 (range 18-97, median 66). Underlying disease was observed in 300 patients (71.1%), with a mean Charlson score index of 1.6±1.3 (range 0-9). Detailed co-morbidity and severity parameters for the enrolled patients are shown in Table 1. Initially detected major clinical manifestations were as follows: hypotension (58.3 %), hematologic dysfunction (58.3%), renal dysfunction (41.2%), liver dysfunction (37.4 %), mental change (36.0%), respiratory failure (32.5%), metabolic acidosis (29.6%), cardiac dysfunction (13.5%), and gastrointestinal bleeding (3.3%). The mean number of organ dysfunctions was 2.7±1.6 (range, 0-7).

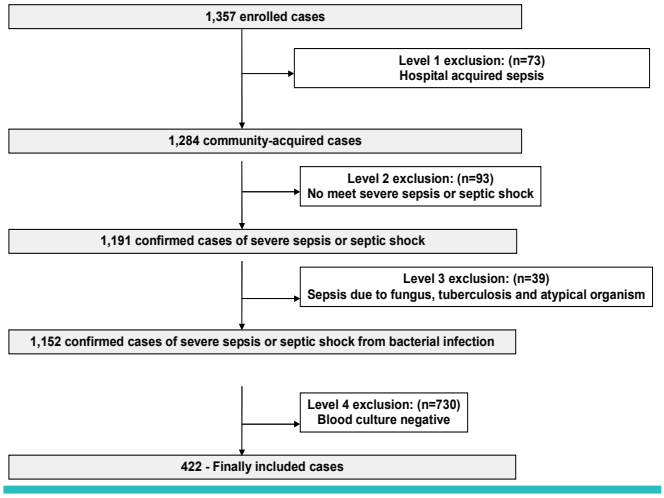

Figure 1. Process used for selection of eligible patients with bacteremia from among those with severe community-acquired sepsis.

Table 1. Demographic and Clinical Characteristics and Mortality in Community-acquired Bacteremic Patients with Severe Sepsis

Characteristics	Total	Survivors (%) (n=301)	Non-survivors (%) (n=121)	P-value[a]
Male gender, n (%)	223 (52.8)	163 (54.2)	60 (49.6)	0.395
Age, mean±SD, year	64.6±14.3	64.7±14.2	64.4±14.5	0.832
Co-morbidities, n (%)				
Cardiovascular disorders	160 (37.9)	114 (37.9)	46 (38.0)	0.978
Central nervous system disorders	64 (15.2)	50 (16.6)	14 (11.6)	0.192
Cancer	57 (13.5)	39 (13.0)	18 (14.9)	0.602
Trauma	6 (1.4)	5 (1.7)	1 (0.8)	0.678[b]
Renal diseases	20 (4.7)	16 (5.3)	4 (3.3)	0.380
Liver diseases	34 (8.1)	28 (9.3)	6 (5.0)	0.138
Lung diseases	31 (7.3)	23 (7.6)	8 (6.6)	0.714
Organ transplant	5 (1.2)	3 (1.0)	2 (1.7)	0.628[b]
Connective tissue diseases	8 (1.9)	7 (2.3)	1 (0.8)	0.449[b]
Metabolic diseases	120 (28.4)	89(29.6)	31 (25.6)	0.416
Hematological disorders	13 (3.1)	10 (3.3)	3 (2.5)	0.765[b]
Others	9 (2.0)	6 (2.0)	3 (1.7)	1.000[b]
Any underlying comorbidities, n (%)	300 (71.1)	219 (72.8)	81 (66.9)	0.233
Charlson's index score, mean±SD	1.6±1.3	1.3±0.1	1.2±0.2	0.761
Severity parameters				
APACHE II score, mean±SD	19.4±7.0	17.1±5.7	23.1±8.2	<0.001
SOFA score (day 1), mean±SD	7.2±3.8	7.3±3.8	6.8±3.8	0.208
SOFA score (day 2), mean±SD	6.5±4.3	6.6±4.4	6.3±4.1	0.580
SOFA score (day 3), mean±SD	6.1±4.5	6.2±4.7	5.7±4.9	0.318
SOFA score (day 4), mean±SD	5.7±4.8	5.8±4.8	5.5±4.8	0.629
SOFA score (day 5), mean±SD	5.2±4.8	5.2±4.8	5.0±4.8	0.759
Number of organ failures, n (%)	2.7±1.6	2.3±1.5	3.5±1.6	<0.001
Septic shock, n (%)	253 (60.0)	185 (61.5)	68 (56.2)	0.318
Inadequate empirical antimicrobial treatment, n (%)	32 (7.6)	9 (7.4)	23 (7.6)	0.878
Red blood cell transfusion, n (%)	144 (34.1)	81 (26.9)	63 (52.1)	<0.001

APACHE II, Acute Physiology and Chronic Health Evaluation II score; SOFA, Sepsis-related Organ Failure Assessment; SD, standard deviation
[a]P-values were obtained by using the Chi-square test, unless otherwise indicated.
[b]Fisher's exact test was used.

2. Primary site of infection

The most common primary site of infection was intra-abdominal (34.4%), followed by the urinary tract (28.4%), primary bloodstream (11.1%), and respiratory tract (10.9%). In-hospital mortality due to respiratory tract, primary bloodstream, skin and soft tissue, intra-abdominal, cardiovascular, and urinary tract infections was 54.3 %, 46.8%, 39.4%, 29.0%, 13.3%, and 9.2%, respectively (Table 2).

3. Microbiology

Compared with Gram-positive bacteria (25.1%), a greater percentage of pathogens were Gram-negative bacteria (72.0%). Polymicrobial infections and anaerobic infections accounted for 2.8% and 0.2% of infections, respectively. Among Gram-negative microorganisms, the most common pathogen was *Escherichia coli* (37.7%), followed by *Klebsiella pneumoniae* (22.0%). The most common Gram-positive pathogen was *Staphylococcus aureus* (11.8%), followed by *Streptococcus pneumoniae* (10.2%). The top three common causative microorganisms according to primary site of infection are shown in Table 3.

Table 2. Primary Site of Infection and Mortality in Community-acquired Bacteremic Patients with Severe Sepsis

	Total	Survivors (%) (n=301)	Non-survivors (%) (n = 121)	*P*-value[a]
Abdomen[b]	145 (34.4)	103 (34.2)	42 (34.7)	0.923
Urinary tract	120 (28.4)	109 (36.2)	11 (9.1)	<0.001
Primary bloodstream	47 (11.1)	25 (8.3)	22 (18.2)	0.004
Respiratory system	46 (10.9)	21 (7.0)	25 (20.7)	<0.001
Skin and soft tissue	33 (7.8)	20 (6.6)	13 (10.7)	0.156
Cardiovascular system	15 (3.6)	13 (4.3)	2 (1.7)	0.250[c]
Bone and joint	7 (1.7)	5(1.7)	2 (1.7)	1.000[c]
Central nervous system	5 (1.2)	3 (1.0)	2 (1.7)	0.628[c]
Head and neck	3 (0.7)	1 (0.3)	2 (1.7)	0.199[c]
Reproductive tract	1 (0.2)	1 (0.3)	0	1.000

[a]*P*-values were obtained using the Chi-square test, unless otherwise indicated.
[b]Abdominal infections include gastrointestinal tract infection (n=42), liver abscess (n=37), and other intra-abdominal infection (n=66).
[c]Fisher's exact test was used.

Table 3. The three most Common Microorganisms According to Primary Sites of Infection and Mortality in Community-acquired Bacteremic Patients with Severe Sepsis

	Total	Survivors (%)	Non-survivors (%)	*P*-value[a]
Abdomen	145	103	42	
Klebsiella pneumoniae	56 (38.6)	41 (39.8)	15 (35.7)	0.646
Escherichia coli	53 (36.6)	41 (39.8)	12 (28.6)	0.203
Streptococcus pneumoniae	6 (4.1)	5 (4.9)	1 (2.4)	0.673[b]
Urinary tract	120	109	11	
Escherichia coli	90 (75.0)	83 (76.1)	7 (63.6)	0.464[b]
Klebsiella pneumoniae	11 (9.2)	10 (9.2)	1 (9.1)	1.000[b]
Proteus mirabilis	7 (5.8)	7 (6.4)	0	1.000[b]
Primary bloodstream	47	25	22	
Staphylococcus aureus	11 (23.4)	3 (12.0)	8 (36.4)	0.049
Klebsiella pneumoniae	9 (19.1)	6 (24.0)	3 (13.6)	0.470[b]
Escherichia coli	6 (12.8)	4 (16.9)	2 (9.1)	0.670[b]
Respiratory system	46	21	25	
Klebsiella pneumoniae	14 (30.4)	5 (23.8)	9 (36.0)	0.371
Streptococcus pneumoniae	13 (28.3)	7 (33.3)	6 (24.0)	0.484
Staphylococcus aureus	8 (17.4)	4 (19.0)	4 (16.0)	0.786[b]

[a]*P*-values were obtained using the Chi-square test, unless otherwise indicated.
[b]Fisher's exact test was used.

4. Independent risk factors for in-hospital mortality

In univariate analysis of the demographic and clinical characteristics of patients and their severity of illness, the APACHE II score and the number of organ dysfunctions differed significantly between survivors and non-survivors (Table 1). Only a small proportion of patients (32/422, 7.6%) received inappropriate antibiotic treatment; therefore, inadequate initial antimicrobial treatment might not contribute to in-hospital mortality. Mortality rate is higher for patients with sepsis associated with respiratory tract infection, primary bloodstream infection, or caused by *Pseudomonas aeruginosa* or *S. aureus*, while a lower mortality rate was observed for patients with urinary tract infections and *E. coli* as a pathogen (Tables 2 and 4).

Multivariate logistic regression analysis was performed for further analysis of significant parameters found by univariate analyses. Respiratory tract infection (odds ratio [OR], 2.60; 95% confidence interval [CI], 1.11-6.09), number of organ system dysfunctions (OR, 1.39; 95% CI, 1.13-1.71), and APACHE II score (OR, 1.08; 95% CI, 1.03-1.13) showed an association with a greater

Table 4. Causative Microorganisms and Mortality in Community-acquired Bacteremic Patients with Severe Sepsis

	Total	Survivors (%) (n=301)	Non-survivors (%) (n=121)	*P*-value[a]
Microorganisms, n (%)				
Escherichia coli	159 (37.7)	137 (45.5)	22 (18.2)	<0.001
Klebsiella pneumoniae	93 (22.0)	63 (20.9)	30 (24.8)	0.387
Streptococcus pneumoniae	43 (10.2)	31 (10.3)	12 (9.9)	0.907
Staphylococcus aureus	50 (11.8)	25 (8.3)	25 (20.7)	0.001
Pseudomonas aeruginosa	13 (3.1)	5 (1.7)	8 (6.6)	0.012[b]
Enterococcus spp.	8 (1.9)	7 (2.3)	1 (0.8)	0.449[b]
Enterobacter cloacae	9 (2.1)	5 (1.7)	4 (3.3)	0.285[b]
Proteus mirabilis	10 (2.4)	7 (2.3)	3 (2.5)	1.000[b]
Haemophilus influenzae	3 (0.7)	2 (0.7)	1 (0.8)	1.000[b]
Citrobacter freundii	4 (0.9)	1 (0.3)	3 (2.5)	0.073[b]
Coagulase negative *staphylococcus*	5 (1.2)	4 (1.3)	1 (0.8)	1.000[b]
Bacteroides fragilis	4 (0.9)	2 (0.7)	2 (1.7)	0.325[b]
Others	21 (5.0)	12 (4.0)	9 (7.4)	0.140

[a]*P*-values were obtained using the Chi-square test, unless otherwise indicated.
[b]Fisher's exact test was used.

Table 5. Risk Factors Associated with Mortality Based on Multivariate Logistic Regression Analysis of the Characteristics of Community-acquired Bacteremic Patients with Severe Sepsis

Variable	In-hospital mortality[a]		7-day mortality[b]		28-day mortality[c]	
	OR	95% CI	OR	95% CI	OR	95% CI
E. coli bacteremia	0.314	0.16-0.64	0.34	0.14-0.81	0.36	0.18-0.74
Respiratory tract infection	2.60	1.11-6.09	3.51	1.458-8.46	2.89	1.24-6.76
No. of organ system dysfunctions (per 1-organ system increment)	1.39	1.13-1.71	1.44	1.14-1.80	1.47	1.19-1.82
APACHE II score (per 1-point increment)	1.08	1.03-1.13	1.08	1.03-1.13	1.06	1.02-1.111

OR, odds ratio; CI, confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II score
[a]In multivariate logistic regression analysis, age, sex, number of organ system dysfunctions, APACHE II score, primary bloodstream infection, respiratory tract infection, *Pseudomonas aeruginosa* bacteremia, *Escherichia coli bacteremia, Staphylococcus aureus* bacteremia, and red blood cell transfusion were included.
[b]In multivariate logistic regression analysis, age, sex, number of organ system dysfunctions, APACHE II score, primary bloodstream infection, respiratory tract infection, and *E. coli* bacteremia were included.
[c]In multivariate logistic regression analysis, age, sex, number of organ system dysfunctions, APACHE II score, primary bloodstream infection, respiratory tract infection, *E. coli* bacteremia, and red blood cell transfusion were included.

risk of death, whereas *E. coli* bacteremia (OR, 0.31; 95% CI, 0.16-0.64) was associated with a lower risk. Independent risk factors associated with 7-day and 28-day mortality in multivariate logistic regression analysis are shown in Table 5.

Discussion

In the present study, all-cause in-hospital mortality was 28.7% (121 of 422 patients). Patients who presented with shock showed a slightly lower rate of mortality (26.9%) than patients without shock. As reported in previous studies, mortality resulting from severe sepsis ranged from 28.6-56.0%, and mortality rate for patients with septic shock were higher (40-70%) than those of patients with sepsis alone (25-30%) [3, 5, 6, 17, 18]. In a study of patients with severe community-acquired bacteremic sepsis, Artero et al. reported an all-cause in-hospital mortality rate of 34.4% [10], higher than the mortality rate recorded in this study. The modest result for general mortality and the unexpected result for lower mortality in patients with shock may be due to inclusion of cases with different disease severities, as reflected by APACHE II scores, compared to the previous study (19.4 in our study vs. 22.0 in the other study), as well as a disparity in the most common site of primary infection (urinary tract infection in our study vs. respiratory tract infection in the previous study) [10].

Our finding that *E. coli* was the most common isolate from patients with severe community-acquired bacteremic sepsis (159 of 422, 37.7%) is in agreement with results reported by Diekema et al. [19]. However, other studies have reported a general, worldwide increase in occurrence of Gram-positive infections, such as *S. aureus* infections [10, 20, 21]. Differences in proportions of causative organisms may be the result of differences in the primary focus of infection. Mylotte et al. [20] reported pneumonia as the most common site of infection. However, in our study, the most common primary site of infection was intra-abdominal (34.4%), followed by the urinary tract (28.4%), primary bloodstream (11.1%), and respiratory tract (10.9%). Consistent with the findings of other studies, we found that lower respiratory tract infection, severity of illness upon admission, and the presence of multiple organ dysfunctions were the major factors associated with a poor prognosis in Korean patients with severe community-acquired bacteremic sepsis [8, 10, 20, 22, 23]. Infection with *E. coli* showed an association with lower mortality, which is also consistent with results reported by another study [24]. No significant association was observed between inadequate empirical antimicrobial treatment and higher mortality. However, administration of inadequate empirical antimicrobial treatment to critically ill patients with bloodstream infections has been reported as a key prognostic factor leading to a poor outcome [25, 26]. Discordance between results of our study and those of previous studies might be attributed to the fact that, in our study, only a few patients (7.6%) received inappropriate initial antibiotic treatment. The low rate of inadequate antimicrobial treatment may be due to the nature of the involved hospitals; all patients were recruited from university-affiliated teaching hospitals with specialists in infectious disease on staff.

This study had several limitations. First, it was performed within the ICUs of 12 university-affiliated teaching hospitals having a low prevalence of inadequate antimicrobial treatment. Therefore, it may be that the results of this study cannot be generalized to other hospitals. Second, it was an observational study, and, even though there was no standardized intervention for management of sepsis at different hospitals, the study center was not included as a separate variable. Nevertheless, specialists in infectious disease, especially those trained to care for critically ill patients, participated in management of these patients. Third, our patient

cohort did not include a consecutive series of ICU patients with community-acquired infections, which may have led to selection bias for more severe infections, with a higher likelihood of mortality. However, there is no reason to believe that this would have changed the predisposing factors associated with mortality.

In conclusion, we found that disease severity, based on both the number of organ system dysfunctions and APACHE II score, in addition to microbiological factors and primary site of bacteremia, are in-hospital prognostic determinants of outcome in patients with severe community-acquired bacteremic sepsis in Korea.

Acknowledgements

This study was supported by a research grant from the Korean Society of Infectious Diseases and by a grant from the National Research Foundation of Korea (NRF) funded by the Korean government (MEST) (No. K20902001448-10E0100-03010).

Conflict of Interest

We have no competing financial interests to declare.

References

1. van Gestel A, Bakker J, Veraart CP, van Hout BA. Prevalence and incidence of severe sepsis in Dutch intensive care units. Crit Care 2004;8:R153-62.
2. Burchardi H, Schneider H. Economic aspects of severe sepsis: a review of intensive care unit costs, cost of illness and cost effectiveness of therapy. Pharmacoeconomics 2004;22:793-813.
3. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D; Sepsis Occurrence in Acutely Ill Patients Investigators. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 2006;34:344-53.
4. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B; CUB-Réa Network. Current epidemiology of septic shock: the CUB-Réa Network. Am J Respir Crit Care Med 2003;168:165-72.
5. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303-10.
6. Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, Mercier JC, Offenstadt G, Régnier B. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. JAMA 1995;274:968-74.
7. Annane D, Sébille V, Troché G, Raphaël JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 2000;283:1038-45.
8. Laupland KB, Davies HD, Church DL, Louie TJ, Dool JS, Zygun DA, Doig CJ. Bloodstream infection-associated sepsis and septic shock in critically ill adults: a population-based study. Infection 2004;32:59-64.
9. Raymond NJ, Blackmore TK, Humble MW, Jones MR. Bloodstream infections in a secondary and tertiary care hospital setting. Intern Med J 2006;36:765-72.
10. Artero A, Zaragoza R, Camarena JJ, Sancho S, González R, Nogueira JM. Prognostic factors of mortality in patients with community-acquired bloodstream infection with severe sepsis and septic shock. J Crit Care 2010;25:276-81.
11. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Joseph L. Harrison's principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2011.
12. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699-709.
13. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16:128-40.
14. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245-51.
15. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
16. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001;286:1754-8.
17. Martin CM, Priestap F, Fisher H, Fowler RA, Heyland DK, Keenan SP, Longo CJ, Morrison T, Bentley D, Antman N; STAR Registry Investigators. A prospective, observational registry of patients with severe sepsis: the Canadian Sepsis Treatment and Response Registry. Crit Care Med 2009;37:81-8.
18. Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. Crit Care 2006;10:R42.

19. Diekema DJ, Beekmann SE, Chapin KC, Morel KA, Munson E, Doern GV. Epidemiology and outcome of nosocomial and community-onset bloodstream infection. J Clin Microbiol 2003;41:3655-60.
20. Mylotte JM, Kahler L, McCann C. Community-acquired bacteremia at a teaching versus a nonteaching hospital: impact of acute severity of illness on 30-day mortality. Am J Infect Control 2001;29:13-9.
21. Laupland KB, Gregson DB, Zygun DA, Doig CJ, Mortis G, Church DL. Severe bloodstream infections: a population-based assessment. Crit Care Med 2004;32:992-7.
22. Blanco J, Muriel-Bombín A, Sagredo V, Taboada F, Gandía F, Tamayo L, Collado J, García-Labattut A, Carriedo D, Valledor M, De Frutos M, López MJ, Caballero A, Guerra J, Alvarez B, Mayo A, Villar J; Grupo de Estudios y Análisis en Cuidados Intensivos. Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicentre study. Crit Care 2008;12: R158.
23. Guidet B, Aegerter P, Gauzit R, Meshaka P, Dreyfuss D; CUB-Réa Study Group. Incidence and impact of organ dysfunctions associated with sepsis. Chest 2005;127:942-51.
24. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, Oh MD, Choe KW. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. Antimicrob Agents Chemother 2005;49:760-6.
25. Vallés J, Rello J, Ochagavía A, Garnacho J, Alcalá MA. Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival. Chest 2003;123:1615-24.
26. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 2000;118:146-55.