Author's response to reviews

Title: Differences in characteristics between healthcare-associated and community-acquired infection in community-onset Klebsiella pneumoniae bacteremia in Korea

Authors:

Younghye Jung (jubaragiy@naver.com)
Myung Jin Lee (mjinnie@naver.com)
Hye-Yun Shin (angel-son@hanmial.net)
Nak-Hyun Kim (naks79@gmail.com)
Jeong-Hwan Hwang (smilehwang77@hanmail.com)
Jinyong Park (twsjy@hanmail.net)
Pyoeng Gyun Choe (pgchoe@gmail.com)
Wan Beom Park (wbpark1@snu.ac.kr)
Eu Suk Kim (yonathan@hanafos.com)
Sang-Won Park (hswon1@snu.ac.kr)
Kyoung Un Park (m91w95pf@snu.ac.kr)
Hong Bin Kim (ksbkhb@chollian.net)
Nam-Joong Kim (molder@unitel.co.kr)
Eui-Chong Kim (euichong@snu.ac.kr)
Kyoung-Ho Song (khsongmd@gmail.com)
Myoung-don Oh (mdohmd@snu.ac.kr)

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Differences in characteristics between healthcare-associated and community-acquired infection in community-onset *Klebsiella pneumoniae* bacteremia in Korea

**Editor’s Comment**

It is an interesting article aiming to assess differences between HCA and CA infections by *Klebsiella pneumonia*. The article is well-written. However, it fails to answer a clearly stated hypotheses. Although there are many useful and interesting data, they should be interpreted in a more explicit and lucid way to let the paper unfold its whole potential.

A> Thank you for the helpful comments on our manuscript. We believe that all the suggested issues and concerns have been appropriately addressed and that the revised manuscript is improved. The following is our response to your comments.

**Reviewer #1**

**Reviewer's report:**

This is a retrospective study on community-onset *Klebsiella* bacteremia and differences between healthcare-associated (HCA) and community-acquired (CA) types of infection. The aim was to elicit clinical differences, presumably with the long-term goal of
improving management based on identifying the epidemiological difference between HCA and CA bacteremias. The authors enrolled >500 patients with Klebsiella pneumonia bacteremia during 6 years and identified HCA episodes based on Friedman’s criteria. A significant proportion (>50%) had criteria for HCA. HCA bacteremia was more commonly associated with peritonitis or an unknown focus, whereas CA bacteremia was more often due to liver abscesses. Klebsiella causing HCA bacteremias were more resistant than those causing CA bacteremia. In multivariate analysis, HCA infection was not a predictor of 30-day mortality.

MAJOR
1. This is a well executed study that is carefully described in this well written manuscript. My main concern is that is does not do a good job at clarifying what it adds to the current literature or how it is different from previous studies. The objective as declared by the authors was to compare HCA to CA bacteremias, however, no clear, testable hypothesis is presented to us. The results simply add to the body of literature showing that there are certain differences in what we used to perceive as homogeneous, community-onset bacteremia (before Friedman et al first applied their new classification in 2002). However, this is not really novel. To improve the manuscript, the authors should better highlight why their study is important.

A> As the reviewer indicated, the differences between HCA-bloodstream infection (BSI) and CA-BSI have been known since the last decade. However, we do not know about the impact of HCA infection on mortality or treatment outcome exactly. There are studies reporting that HCA infection itself is an independent risk factor for mortality (Shorr et al. Crit Care Med. 2006 Oct;34(10):2588-95; Valles et al. J Infect. 2008 Jan;56(1):27-34; Kollef et al. J Infect.

Based on these discrepancies, we aimed to study the impact of HCA infection on mortality in K. pneumoniae bacteremia which has been well known about its community-acquired infection. As the reviewer and the Editor recommended, we have explained the need for our study in terms of its impact on the HCA infection field by rephrasing the purpose and significance of our study in the Abstract and Introduction sections. In addition, we have added several new references to the revised manuscript.

Abstract, line (25)-(32):
Abstract

Background: Healthcare-associated (HCA) infection has emerged as a new epidemiological category. The aim of this study was to evaluate the impact of HCA infection on mortality in community-onset *Klebsiella pneumoniae* bloodstream infection (*KpBSI*).

Methods: We conducted a retrospective study in two tertiary-care hospitals over a 6-year period. All adult patients with *KpBSI* within 48 hours of admission were enrolled. We compared the clinical characteristics of HCA and community-acquired (CA) infection, and analyzed risk factors for mortality in patients with community-onset *KpBSI*.

Introduction, line (47)-(70):

Introduction

Within the last decade, the concept of healthcare-associated (HCA) infection has been introduced, and HCA infection has been described as an epidemiological category different from both community-acquired (CA) and nosocomial infection [1, 2]. Most importantly, mortality in HCA infection seems to be generally higher than that in CA infection, and similar to that in nosocomial infection [2-4]. However, there are conflicting results regarding whether HCA infection is an independent risk factor for mortality in bloodstream infection [1-5]. A few pathogens have been studied in terms of HCA infection with *S. aureus* dominating the research, and these studies reported inconsistent data concerning the impact of HCA infection on mortality [6-13]. For gram-negative bacteria, the data on the impact of HCA infection on mortality were conflicting, as well [9-12].

*Klebsiella pneumoniae* is one of the most important gram-negative bacteria clinically, and *K. pneumoniae* bloodstream infection (*KpBSI*) has a mortality rate of about 20% [11, 14-
Classically, $KpBSI$ was simply classified into CA and nosocomial infections depending on bacteremia onset time: within 48 hours and after 48 hours of admission, respectively, and the different characteristics of CA-$KpBSI$ versus nosocomial $KpBSI$ have been well evaluated [11, 14, 15, 17, 18]. CA-$KpBSI$ is usually associated with liver abscesses in patients with diabetes in East Asian countries, such as Korea and Taiwan [19-22]. On the other hand, nosocomial $KpBSI$ presents as primary bacteremia and/or pneumonia in patients with severe underlying diseases like malignancies. Thus, nosocomial infection has a higher mortality than CA infection [11, 14, 15, 17, 18]. However, there have been few studies of HCA-$KpBSI$ [11-13]. Therefore, we aimed to evaluate the impact of HCA infection on mortality and to compare the clinical characteristics of HCA and CA infection in patients with community-onset $KpBSI$.

2. Regarding empiric treatment, the proportion of inadequately treated patients is surprisingly low at 7%. See for comparison other studies that reported much higher rates. For instance, McDonald et al (Arch Intern Med 2005) found 8% (CA), 25% (HCA), and 32% (nosocomial) bacteremias, respectively, to be treated inadequately in the beginning. I think this should be discussed as well.

A> We agree with the reviewer’s comment regarding the low proportion of inadequately treated patients in the present study. As the reviewer stated (McDonald et al. Arch Intern Med. 2005 Feb 14;165(3):308-13), 7% is low compared to the proportions reported in other studies examining bloodstream infection (Marschall et al. Infect Control Hosp Epidemiol. 2009 Nov;30(11):1050-56; Son et al. J Korean Med Sci. 2010 Jul;25(7):992-8; Kollef et al. J Infect. 2011 Feb;62(2):130-5).

In our opinion, there are several factors that help to explain this difference. First, the
definition of ‘appropriate empirical treatment’ in our study was different from that in other studies, including the study mentioned by the reviewer. In our manuscript, we stated that “the empirical antimicrobial therapy was defined as the initial antibiotic choice before the results of blood culture and antimicrobial susceptibility tests were available” (Ibrahim et al. Chest 2000 Jul;118(1)146-55; Zaragoza et al. Clin Microbiol Infect. 2003 May;9(5):412-8; Song et al. BMC Infect Dis. 2009 Apr;9:41), which does not indicate a precise time period. Other studies usually defined ‘adequate empirical treatment’ as the initiation of susceptible antibiotics within 24 hours after the blood sample was obtained. According to our definition, starting susceptible antibiotics anytime before the culture results turned out (identification and susceptibility test), even outside of the 24 hours window, could be classified as ‘adequate empirical treatment’.

A second factor that accounts for our low frequency of inadequately treated patients is the specific pathogens under investigation. As McDonald et al. showed (McDonald et al. Arch Intern Med. 2005 Feb 14;165(3):308-13), gram-positive organisms such as methicillin-resistant \textit{S. aureus} or Enterococcus turned out to risk factors for the ineffective initial therapy. Seven percent is a still low incidence of inadequate treatment, even though considering the relationship between infections with gram-positive organism and the ineffectiveness of empirical antimicrobial therapy; studies considering only gram-negative pathogens also showed a higher proportion of inadequate empirical therapy compared to our study (Marschall et al. Infect Control Hosp Epidemiol. 2009 Nov;30(11):1050-56). However, upon reviewing other studies that specifically focused on \textit{K. pneumoniae} bacteremia, we found that our data were in line with previously published results. Tsay et al. reported that 5.1% of total patients were treated inadequately, although they used more strict criteria of appropriateness (Tsay et al. Arch Intern Med. 2002 May 13;162(9):1021-7), and Kang et al. reported 2.1% in
community-acquired *K. pneumoniae* bacteremia (Kang et al. J Korean Med Sci. 2006 Oct;21(5):816-22). In addition, a recent study performed in Taiwan also reported a low proportion of patients treated with inappropriate empirical therapy (1.9 % in CA infection, 5.5% in HCA infection) (Wu et al. J Infect. 2012 Feb;64(2):162-8).

Finally, upon looking into the antimicrobial regimens that we started, we found that broad-spectrum antimicrobial agents such as 3rd generation cephalosporin or carbapenem accounted for 84.6 % of CA infections and 74.7% of HCA infections, even though only 3.3% of the organisms in CA infections and 9.3% of the organisms in HCA infections were non-susceptible to extended-spectrum cephalosporin. This practice might result from a concern for increasing the resistance of organisms.

In short, differences in the definition, organism and empirical antimicrobial regimen attributed to the relatively low proportion of inadequate empirical therapy in our study, but our data are similar to those of other *K. pneumoniae* studies.

To clarify this matter within the manuscript, we have mentioned the low percentage of patients treated inadequately, and we have explained the relevant factors in the Discussion section, as follows, and we have added new references in the revised manuscript.

**Discussion, line (236)-(248):**

Regarding empirical treatment, the proportion of patients treated inappropriately (7.2% of total patients) was much lower than was observed in other studies, which showed that over 20% of patients were treated inappropriately [9, 29, 30]. This discrepancy might have been the result of differences in the definition of ‘appropriate empirical treatment’, because the definition we used was less strict than those in other studies. In addition, broad-spectrum
antimicrobial agents, such as 3\textsuperscript{rd} generation cephalosporins or carbapenems, were frequently used empirically in our study (84.6\% in CA infection, 74.7\% in HCA infection). Considering that only 3.3\% of organisms in CA infection and 9.3\% of organisms in HCA infection were non-susceptible to extended-spectrum cephalosporins, the use of broad-spectrum antimicrobial agents also might have influenced the lower proportion of patients with treated inappropriately. However, other East Asian studies of \textit{K. pneumoniae} bacteremia also demonstrated a similar proportion of patients treated with inappropriate empirical therapy [12, 14, 18].

3. A cursory literature search in Pubmed (with the key words “klebsiella”, “bacteremia”, “community”, and “healthcare”) reveals at least one other study that could be discussed in the results. Marschall et al. (Infect Control Hosp Epi 2009) compared HCA to CA and nosocomial Gram-negative bacteremias and also failed to see differences in outcomes between these types of bacteremias.

A> As the reviewer noted, the study comparing HCA and CA gram-negative bacteremia also failed to find differences in treatment outcomes (Marschall et al. Infect Control Hosp Epidemiol. 2009 Nov;30(11):1050-56). Shorr et al., in contrast showed higher mortality in HCA infection than in CA infection and hypothesized that the difference might be due to the frequency of \textit{S. aureus} in their report. However, we cannot directly compare the study of Shorr et al. with that of Marschall et al. because Shorr et al. did not study subgroup analyses (Shorr et al. Crit Care Med. 2006 Oct;34(10):2588-95). In addition, there are other reports that could show differences in outcomes between these types of bacteremia (Friedman et al. Ann Intern Med. 2002 Nov 19;137(10):791-7; Lesens et al. Infect Control Hosp Epidemiol. 2005 Feb;26(2):204-9; Liao et al. Diagn Microbiol Infect Dis. 2005 Oct;53(2):85-92; Lenz et

As we described in the Discussion section, we believe that studies failing to demonstrate the impact of HCA infection on treatment outcome also have clinical implications. First, well-known risk factors such as the severity of underlying disease and acute illness in bacteremia are still important for predicting treatment outcome, even in the era of HCA infection as a new epidemiological category. Second, specific characteristics of each pathogen may be more influential in treatment outcome than is HCA infection. To emphasize those aspects of HCA infection, we have added the following highlighted sentences in the Discussion section.

**Discussion, line (254)-(255):**

This finding is consistent with the recent report from Taiwan [12] and a bloodstream infection study dealing with gram-negative bacteria [9].

**Discussion, line (306)-(310):**

Finally, even though we showed many differences between HCA infection and CA infection, we did not find HCA infection to be an independent risk factor for mortality in *Kp*BSI, which confirmed that the already known risk factors for mortality (severity of underlying disease, inadequate empirical therapy and severity of acute illness) are still important risk factors predicting mortality in *Kp*BSI [12, 14].

4. An important point in Jung et al.’s analysis is that the variation of treatment (drug, duration, dosage) was not taken into account when they did the multivariate analysis of mortality predictors. This should be discussed as a limitation.
Unfortunately, we could not collect data on the variation of treatment. However, the mortality rate in other studies on *Kp*BSI, is similar to ours, so the regimen and duration of therapy we used may not be out of the standard practice that could change the data shown in the present study (Tsay et al. Arch Intern Med. 2002 May 13;162(9):1021-7; Wu et al. J Infect. 2012 Feb;64(2):162-8). We have discussed this as a limitation in the Discussion section, as follows.

Discussion, line (282)-(289):

Fourth, because we did not review the patients’ previous exposure to antimicrobial agents, we could not determine the influence of that factor on the acquiring resistant organisms and treatment outcome. Additionally, we did not collect data on the variation of antimicrobial therapy, such as duration or dosage; therefore, we could not take into account these issues, which could affect the analysis of risk factors for mortality. However, upon examining the mortality rate in other studies, our data are comparable; therefore, the regimen and duration of therapy we used might not be out of the standard practice that could significantly change the results of our study [12, 14].

5. After all, what providers would really want to know is whether a specific management is better suited for HCA or CA bacteremia, respectively.

We absolutely agree with the reviewer’s comment. What clinicians actually want to know is the specific work-up process or treatment effective for HCA infection. Accordingly, our study would serve as a useful guide for clinicians. First, our report showed that HCA infection was more commonly associated with peritonitis or primary bacteremia than CA infection in *Kp*BSI. The frequency of peritonitis in CA infection was relatively high (20.4%)
and was not different from that observed in nosocomial infection in the previous report (Kang et al. J Korean Med Sci. 2006 Oct;21(5):816-22), but when we classified more precisely we could see that peritonitis occurred in much lower incidence in true CA infection. Furthermore, only 8.8% of patients could not be identified for infection focus in true CA infection, while 25.7% patients were not identified for infection focus in previously defined CA infection. In the previous report, only 11% of patients had liver abscesses in CA-KpBSI. However, after excluding patients with HCA infection, we could see that 27.9% patients had liver abscesses in true CA infection. Considering these results, we think that identifying HCA infection in K. pneumoniae bacteremia can be helpful for searching the infection source.

Second, we showed that, the resistance rate to antimicrobial agents is higher in HCA infection than in CA infection. This data can help clinicians choose an effective empirical antimicrobial agent, which means we should not only consider broad-spectrum antimicrobial agents in HCA infection, but additionally, we should not start the broad-spectrum antimicrobial agents, such as extended-spectrum cephalosporin or carbapenem, in CA infection. Actually, quinolone can be a drug of choice in treating true CA-KpBSI based on our data. Selecting patients with HCA infection does not always lead to easy use of broad-spectrum antimicrobial agents; this approach can also narrow the spectrum of antimicrobial agents clinicians start in treating CA infection. More accurate therapy can be given to a more accurate subset of patients through classifying HCA infection from the community-onset infection.

Finally, our study did not find HCA infection to be an independent risk factor for mortality in K. pneumoniae bacteremia and showed that other risk factors such as severity of underlying disease, acute illness and inappropriate empirical antimicrobial therapy still are important risk factors for mortality.
Discussion, line (290)-(310):

What clinicians actually want to know is that HCA infection needs a specific work-up process or treatment. Accordingly, our study can provide useful information. First, we could see the difference of infection focus according to the epidemiological category more clearly by separating HCA infection and CA infection in comparison to our previous report [18]. Peritonitis is more commonly associated with HCA infection than with CA infection in the present study, while the frequency of peritonitis in CA infection was relatively high (20.4%) and was not different from that observed in nosocomial infection in the previous study [18]. However, when we classified more precisely we could see that peritonitis occurred in much lower frequency in true CA infection. In addition, we could identify the infection focus of all but 8.8% of the patients with true CA infection (in previously defined CA infection, 25.7% patients were unidentified for infection focus) [18]. Second, comparing the resistance rate to antimicrobial agents in HCA infection with CA infection can help clinicians choose an initial antimicrobial agent in treating patients of each subset, which means not only should we consider broad-spectrum antimicrobial agents in HCA infection but also that we should not start broad-spectrum antimicrobial agents, such as extended-spectrum cephalosporins or carbapenems, in CA infection. Based on our data, quinolone can be a drug of choice in treating true CA- KpBSI. Finally, even though we showed many differences between HCA infection and CA infection, we did not find HCA infection to be an independent risk factor for mortality in KpBSI, which confirmed that the already known risk factors for mortality (severity of underlying disease, inadequate empirical therapy and severity of acute illness) are
still important risk factors predicting mortality in KpBSI [12, 14].
MINOR

Abstract:

1. Line 3: KpB is not an established abbreviation for Klebsiella pneumoniae bacteremia. Would suggest “Kp-BSI”.
A> We have changed all KpB to KpBSI as suggested

2. Line 6: “clinical characteristics OF HCA and CA infections”
A> We have added ‘of’ in the sentence as the reviewer noted.

Introduction:

3. Line 6: “associated with liver abscessES”
A> We have changed to the plural form

4. Line 7: would add “EAST Asian countries”
A> We agree with that comment. We have added ‘East’.

Methods:

5. Line 11: “Helsinki” instead of “Helsiniki”
A> We misspelled this name. We have corrected the misspelling.

6. I could not find “prior antibiotic exposure” as a variable that was collected in this study. Antibiotic exposure may have had a significant impact on resistance levels and the likelihood of starting an adequate empiric antibiotic. If it was not collected then this should be mentioned under limitations.
A> We fully agree with reviewer’s comment. We have discussed this point in the Discussion section as follows, as already mentioned in response to reviewer’s number 4 comment.

**Discussion, line (282)-(284):**

Fourth, because we did not review the patients’ previous exposure to antimicrobial agents, we could not determine the influence of that factor on the acquiring resistant organisms and treatment outcome.

Results:

**7. Risk factors for 30-day mortality: would give Odds Ratios here so that the reader does not have to flip to the tables.**

A> To help readers to understand the data quickly, we have added odds ratios and numbers in the Results section, as follows

**Results, line (173)-(197):**

**Risk factors for 30-day mortality**

The results of the univariate analyses of risk factors for 30-day mortality are shown in Table 3. High Charlson’s weighted index of co-morbidity was a risk factor (odds ratio [OR], 2.86; 95% confidence interval [CI], 1.83-4.48) and, when we analyzed each underlying disease, solid tumor (OR, 3.32; 95% CI, 2.09-5.28) and hematologic malignancy (OR, 3.52; 95% CI, 1.58-7.84) also turned out to be significant risk factors. Infections of unknown origin (OR, 3.71; 95% CI, 2.17-6.34) and respiratory infections (OR, 3.38; 95% CI, 1.76-6.48) developed more frequently in non-survivors than in survivors. In contrast, liver abscess (OR, 0.11; 95% CI, 0.03-0.35) and pancreatobiliary infection (OR, 0.50; 95% CI, 0.30-0.84) were
more common in survivors than in non-survivors. In addition, high Pitt bacteremia score (OR, 8.04; 95% CI, 4.87-13.28), neutropenia at initial presentation (OR, 4.48; 95% CI, 2.37-8.46), inappropriate empirical antimicrobial therapy (OR, 2.46; 95% CI, 1.22-4.96), polymicrobial infection (OR, 2.30; 95% CI, 1.34-3.94) and healthcare-associated infection (OR, 2.27; 95% CI, 1.41-3.68) were risk factors in univariate analyses. There was no significant difference in rates of antimicrobial resistance to ciprofloxacin (7.0% in survivors vs. 9.3% in non-survivors; \( p = 0.440 \)) and extended-spectrum cephalosporin (6.4% in survivors vs. 8.2% in non-survivors; \( p = 0.499 \)) between survivors and non-survivors.

From the multivariate logistic regression analysis, significant risk factors for 30-day mortality were high (≥3) Charlson’s weighted index of co-morbidity (OR, 3.23; 95% CI, 1.88-5.57), high (≥4) Pitt bacteremia score (OR, 8.43; 95% CI, 4.70-15.11), neutropenia (OR, 2.60; 95% CI, 1.24-5.48), polymicrobial infection (OR, 2.36; 95% CI, 1.21-4.60) and inappropriate empirical antimicrobial therapy (OR, 2.43; 95% CI, 1.07-5.52). Liver abscess (OR, 0.17; 95% CI, 0.05-0.58) and pancreatobiliary tract infection (OR, 0.42; 95% CI, 0.23-0.79) were found to be protective factors (Table 4). HCA infection was not an independent risk factor for mortality in multivariate analysis.

8. Line 15: would say “…although in THE TAIWANESE study…”
A> We have changed the word, as recommended.

9. Page 2, line 8: Appropriateness suggests that an option could be no antibiotics at all. Would prefer to use the term “inadequacy”.
A> As recommended, we have changed the word and deleted ‘adversely’, as follows.
Discussion, line (229):
Although frequent antimicrobial resistance could affect the inadequacy of the initial choice of antimicrobial agent, there was no difference in rate of inappropriate empirical antimicrobial therapy between the HCA-\textit{KpBSI} and the CA-\textit{KpBSI} (6\% vs. 8\%; \textit{p} = 0.266).

10. Page 3, line 7: would say: “Unlike THE U.S., South Korea has \textbf{STARTED} a national health insurance system \textbf{IN} 1977 and…”
A> We have made the recommended corrections, as follows.

Discussion, line (268)-(270):
Unlike the U.S., South Korea has \textbf{started} a national health insurance system \textbf{in} 1977 and extended it nationwide in 1982.

11. References:
Reference #21: there are no volume and page number given for this article.
A> We have added the volume and page number of the reference and changed the year of the reference as follows because 2011 was a e-publication year.

This manuscript is new, is not being considered elsewhere, and will not be republished in any other journal in the same or similar form without the written consent of the copyright holder if it is accepted. All authors have seen and approved the content and have contributed significantly to the work. There are no potential conflicts of interest for all authors.

We believe we have addressed all the questions and comments in a suitable fashion, but we would be happy to provide further information or revision if necessary.

Thank you for your consideration of the revised manuscript.

Sincerely yours,

Kyoung-Ho Song M.D.
Assistant Professor
Division of Infectious Diseases
Seoul National University Bundang Hospital
300 Gumi-dong, Bundang-gu, Seongnam-si
Gyeonggi-do 463-707, Republic of Korea
Tel: +82-31-787-7044, Fax: +82-31-787-4052
E-mail: khsongmd@snu.ac.kr or khsongmd@gmail.com